2018

CHICAGO ESSENTIAL EVIDENCE UPDATE CONFERENCE

MARCH 2-3

UNIVERSITY OF ILLINOIS AT CHICAGO
MOLECULAR BIOLOGY RESEARCH BUILDING
901 S MARSHFIELD, CHICAGO, IL

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UIC UNIVERSITY OF ILLINOIS AT CHICAGO Department of Family Medicine COLLEGE OF MEDICINE

ILLINOIS ACADEMY OF FAMILY PHYSICIANS
Devoted to Advocacy, Education & Action

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Illinois Academy of Family Physicians (IAFP) and University of Illinois at Chicago, Department of Family Medicine. The Illinois Academy of Family Physicians / Family Practice Education Network is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. AMA PRA Category 1 - The Illinois Academy of Family Physicians/Family Practice Education Network designates this live activity, Chicago Essential Evidence Topics for a maximum of 12.00 AMA PRA Category 1 credits™.

Chicago Essential Evidence March 2018
Illinois Academy of Family Physicians

Learning Objectives

Discuss recent research critical to family physicians for updating their diagnostic and treatment approaches to common medical conditions cared for in primary care. Objectives for each presentation are listed at the beginning of each talk. Each talk is based on a literature review of recent research studies. Evidence sources include PubMed, InfoPoems and Cochrane systematic reviews.

Accreditation

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Credit Designation

AMA PRA Category 1 - The Illinois Academy of Family Physicians designates this live activity, Chicago Essential Evidence Topics for a maximum of **12.00 AMA PRA Category 1 credits™**.

Prescribed - Application for CME credit has been filed with the American Academy of Family Physicians. Determination of credit is pending

Faculty Disclosure Statement

The Illinois Academy of Family Physicians adheres to the conflict of interest policy of the ACCME and the AMA. It is the policy of Illinois AFP to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All individuals in a position to control the content in our programs are expected to disclose any relationships they may have with commercial companies whose products or Services may be mentioned so that participants may evaluate the objectivity of the presentations. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty. Only those participants who have no conflict of interest or who agree to an identified resolution process prior to their participation were involved in the CME activity.

Dr. Hickner, Dr. Ebell, Dr. Ferenchick, Dr. Rowland, Dr. Hall, & Dr. Guthmann disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

Faculty

***Mark H. Ebell MD, MS*.** is a Professor in the College of Public Health at The University of Georgia. Dr. Ebell is Deputy Editor of *American Family Physician* and Editor-in-Chief of *Essential Evidence*. He is a graduate of the University of Michigan School of Medicine, a former RWJ Generalist Physician Faculty Scholar, and is former editor of the *Journal of Family Practice*. Dr. Ebell is author of 7 books and over 300 peer reviewed articles. From 2012 to 2016 he was a member of the USPSTF.

Gary Ferenchick, MD, MS. is Professor of Medicine at Michigan State University College of Human Medicine, where he practices general internal medicine and is deeply involved in MSU-CHM major curriculum renovation. He earned his master's degree in human nutrition and medical degree from Michigan State University and completed his residency training in internal medicine at Michigan State University College of Human Medicine, where he has been a faculty member for over 25 year. Dr. Ferenchick is a Past-President of the Clerkship Directors in Internal Medicine. His research interest is the interface between medical education and information technology.

Rick Guthmann, MD, MPH, a faculty member of the UIC/ Advocate Illinois Masonic Family Medicine Residency, began writing and editing evidence based reviews for the Family Practice Inquiries Network in 2003. He has contributed to Clinical Inquiries, Help Desk Answer, and PURLs. He is now the editor-in-chief for the Clinical Inquiries series which appears in the Journal of Family Practice and the American Family Physician. As the Medical Director for the Advocate Illinois Masonic PHO, he works on quality and utilization improvement. Dr. Guthmann graduated from Northwestern University Medical School, MacNeal Family Medicine residency, and the UIC School of Public Health.

Emily Hall, MD, is an assistant clinical professor of family medicine and the co-director of Family Centered Maternity Care at the University of Illinois at Chicago. She attended medical school at Columbia University's College of Physicians & Surgeons and completed her family medicine residency training at the University of Illinois at Chicago. At UIC, Dr. Hall was a chief resident as well as a recipient of the STFM Resident Teacher award. She also completed a faculty development fellowship at UIC. She is a full-spectrum family physician with clinical emphases on maternity care, maternal-child health, reproductive health, and procedures in the primary care setting. She is currently in the Masters in Health Professional Education (MHPE) program at UIC. Her medical-education research focuses on the teaching of procedural skills as well as narrative medicine. Prior to medical school, Dr. Hall was a senior mutual fund analyst at Morningstar, Inc., where she was a leading commentator in the fields of investor education, socially responsible investing, and health-care funds.

John Hickner, MD, MS. is Professor and Head of Family Medicine at the University of Illinois at Chicago and Editor-in-Chief of the *Journal of Family Practice*. After receiving his medical degree from Indiana University School of Medicine, Dr. Hickner completed his residency in family medicine at the Medical University of South Carolina and received a master's degree in Biostatistics and Research Design from the University of Michigan School of Public Health. His main research focus is patient safety, especially testing safety and medication safety in primary care practice.

Kate Rowland, MD, MS is core faculty at the Rush-Copley Family Medicine Residency and an assistant professor at Rush University. Since 2013, she has been editor-in-chief of the Priority Updates from the Research Literature (PURLs) series, produced by FPIN and published in the *Journal of Family Practice*. She is also an associate medical editor for the American Academy of Family Physician's *FP Essentials* series. She is a graduate of Rush Medical College and completed

post-graduate training at the Advocate Illinois Masonic Family Medicine residency and the University of Chicago primary care research fellowship.

William (Bill) Wadland, MD, MS. is Professor, former Chair of Family Medicine, and Senior Associate Dean Emeritus in the College of Human Medicine at Michigan State University. He received his MD from the University of Michigan School of Medicine and completed family medicine training at the Medical University of South Carolina. He was co-founder of the original Primary Care Medical Abstracts Courses on which the current Essentials Update Courses are modelled. His research focus is health promotion and disease prevention, especially tobacco control. He is the Deputy Editor of the *American Journal of Preventive Medicine* (AJPM).

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Chicago Essential Evidence 2018 Schedule

Friday, March 2

7:30-8:00	Registration and Continental Breakfast		**Page**
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9:30-10:00	Break		
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11:00-11:30	Help Desk Answers	Guthmann	43
11:30-12:00	PURLS 1	Rowland	50
12:00-12:45	Lunch		
12:45-1:15	Hyperlipidemia	Ferenchick	71
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1:45-2:15	PURLS 2	Rowland	90
2:15-2:45	Liver and GI Update	Ebell	113
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Saturday March 3

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11:30-12:00	Men's Health	Hickner	198
12:00-12:30	Editor's Choice 2	Ebell, Ferenchick, Hickner	208
12:30-12:45	Closing and Complete Evaluations	Hickner	

Information Mastery and Searching for Evidence: Key Points **Mark Ebell**

Objectives

1. Learn the importance of patient oriented evidence for interpreting medical studies
2. Learn an efficient way to search PubMed for clinically relevant information

Usefulness of medical information = (relevance x validity) / work

Relevance is a continuum:

Rat studies Surrogates Disease-specific All-cause mortality/QOL

Validity is a continuum:

Case study Case-control Cohort RCT Systematic review

Patient oriented evidence: anything that helps patients live a longer or better life.

Disease oriented evidence: everything else; surrogate or physiologic markers

POEM (Patient Oriented Evidence that Matters): a study that addresses a common or important condition, demonstrates improved patient oriented outcomes, and matters because it would change what we do.

Evidence-based sources to explore:

- Essential Evidence: www.essentialevidence.com
- Clinical Evidence: www.clinicalevidence.com
- Cochrane Library: www.cochrane.org
- DynaMed: www.dynamicmedical.com
- TRIP Database: www.tripdatabase.com
- Bandolier: www.medicine.ox.ac.uk/bandolier/
- National Guidelines Clearinghouse: www.guidelines.gov

Search hints

- Use Clinical Queries at the PubMed site
- Select “Narrow” filter
- Use quotes to narrow search to only those words appearing next to each other, i.e. “acute bronchitis” eliminates “acute exacerbation of chronic bronchitis”
- Combination of drug and disease is useful: “acute bronchitis” azithromycin; “infectious mononucleosis” corticosteroid; influenza osletamivir
- Optionally, “See all” and then add additional limits (English, abstract, human)
- Use “Not” terms to exclude groups of articles
- Then, select “Related articles” once you have a good hit.

Learning objectives | Understand and apply:

1. The various recommendations and changes in BP management recommendations over the past 4 years
2. The results of the Systolic Blood Pressure Intervention Trial (SPRINT) trial compared to the ACCORD BP Trial, and its relevance to cardiovascular disease prevention.
3. The results of the HOPE – 3 hypertension trial and its relevance to cardiovascular disease prevention.
4. Recent AAFP and ACP guidelines on intensive BP treatment for those > 60
5. Recent 2017 AHA ACC guideline on HTN
6. The AAFP and ACP's retort to the AHA ACC guideline

Be honest, how confident are you now in the management of HTN in light of the 2017 ACC/AHA guidelines published in November of 2017? If you feel like you have a good handle on the rapidly changing landscape of hypertension management you are doing extremely well.

This chapter is/was meant to be an update on CV medicine in the last year, as last year I did a chapter on HTN management specifically; however, the new ACC/AHA guidelines were released in late 2017 and have the potential to radically change how we approach HTN. Instead of glossing over this, I thought I would repeat some of the key elements of last year's talk, and attempt to tie into this the new much publicized HTN guidelines.

This is a PowerPoint heavy talk, as I could not think of a way to do this more efficiently. The first several sides are on the

#1: JNC 8

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes. There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes. Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.
REFERENCE: James PA et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311 (5):507-20.

#2: The SPRINT Trial

BACKGROUND: The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.
METHODS: We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of

less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.
RESULTS: At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.
CONCLUSIONS: Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.
REFERENCE: *SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.*

#3: The ACCORD BP Trial

BACKGROUND: There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants
with type 2 diabetes at high risk for cardiovascular events.
METHODS: A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.
RESULTS: After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).
CONCLUSIONS: In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)
Reference*: ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1575-85. PMID: 20228401*

#4: The Hope-3 Trial

BACKGROUND: Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.
METHODS: In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.
RESULTS: The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI,0.81 to 1.11; P=0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes).
CONCLUSIONS: Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.).
REFERENCE: *Lonn EM, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016 May 26;374(21):2009-20.*

Blood pressure recommendations in the post–SPRINT era

In January of 2017, the AAFP and the ACP jointly published a guideline based upon a systematic review of published randomized, controlled trials and observation studies (articles published through September of 2016 in Medline and January 2015 for other databases). There conclusions closely

reflected the recommendations of the JNC 8. Importantly this means they has the results of the SPRINT Trial for this review.

#5: AAFP/ACP: Practice guideline hypertensive treatment for patients > 60

Description: The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) jointly developed this guideline to present the evidence and provide clinical recommendations based on the benefits and harms of higher versus lower blood pressure targets for the treatment of hypertension in adults aged 60 years or older.
Methods: This guideline is based on a systematic review of published randomized, controlled trials for primary outcomes and observational studies for harms only (identified through EMBASE, the Cochrane Database of Systematic Reviews, MEDLINE,and ClinicalTrials.gov), from database inception through January 2015. The MEDLINE search was updated through September2016. Evaluated outcomes included all-cause mortality, morbidity and mortality related to stroke, major cardiac events (fatal and nonfatal myocardial infarction and sudden cardiac death), and harms. This guideline grades the evidence and recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method.
Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes all adults aged 60 years or older with hypertension.
Recommendation 1: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Reference: *Qaseen A et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017 Mar 21;166(6):430-437.*

ACC AHA Guideline Rating

The following is a quick review of the ACC AHA Class of Recommendation (COR) and Level of evidence (LOE) that is now used for all ACC/AHA Guidelines. They are meant of assist us and our patients in decision-making. Note the primary differences from the previous paradigm is separating Level B and Level C evidence based upon the quality of the underlying data.

Class (Strength) of Recommendation (COR) Table

- **Class I (Benefit >>> Risk):** **Should be done | *Is* useful | (Strong)**
- Class IIa (Benefit >> Risk): Reasonable to do | *Can* be useful | (Moderate)
- Class IIb (Benefit ≥ Risk): May be considered | *Unknown* usefulness (Weak)
- Class III (No benefit or harm): Not helpful or harmful

Level (Quality) of Evidence (LOE)

- Level A:
  - High quality evidence from ≥ 1 RCT
  - Meta-analysis of high-quality RCTs
  - ≥ 1 RCT corroborated by high-quality registry studies
- Level B-R (Randomized):
  - Moderate quality evidence from ≥ 1 RCT
  - Meta-analyses of moderate quality RCTs
- Level B-NR (Non-randomized):

    - Moderate quality evidence from ≥ 1 high-quality nonrandomized/observational or registry studies
    - Meta-analyses of such studies
- Level C-LD
    - Randomized or nonrandomized/observational or registry studies with limitations of design or execution
    - Meta-analyses of such studies
    - Physiological or mechanistic studies in humans
- Level C-EO
    - Consensus opinion based upon clinical experience

The COR and LOE are determined independent of each other. Any COR can be paired with any LOE (notably LOE C does not imply the COR is weak)

#6 ACC/AHA guidelines take more aggressive, less evidence-based approach to hypertension management

Clinical Question: What changes to hypertension management are proposed by the 2017 guideline from the American College of Cardiology and the American Heart Association?
Bottom Line: This guideline from the American College of Cardiology and the American Heart Association (ACC/AHA) labels all patients with a blood pressure greater than 130/80 as hypertensive, and methodologically takes a step back from the 2014 Joint National Committee 8 guidelines by focusing more on observational studies and disease-oriented outcomes to support their recommendations, and by extending the Systolic Blood Pressure Intervention Trial (SPRINT) findings to patients with diabetes, lower cardiovascular risk, and chronic kidney disease. The United States is in the midst of a "society war," pitting primary care professional societies against subspecialty societies regarding the definition of hypertension, when to begin treatment, and blood pressure treatment goals. In fact, this guideline was explicitly not endorsed by the American Academy of Family Physicians (AAFP). This conflict illustrates the problem with practice guidelines: Who is on the committee, how they assess the studies, and the types of outcomes they consider can result in different recommendations. If you choose to use a blood pressure target of 130/80 mmHg for your patients with diabetes, chronic kidney disease, or a greater than 10% 10-year risk of a cardiovascular event, it is critical that you measure blood pressure the same way that it was measured in the SPRINT trial (have the patient sit in a quiet room for 5 minutes before testing, then use the average of 3 mechanically measured blood pressures). (LOE = 5)
Reference: Whelton PK, Carey RM, Aronow AS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2017; doi: 10.1016/j.jacc.2017.11.006 [Epub ahead of print].
Study Design: Practice guideline **Funding:** Foundation
Setting: Various (guideline) **Allocation:** Unknown
Synopsis: The most recent US national hypertension guideline was originally developed by National Heart, Lung, and Blood Institute, and when it was proposed that its home move to the AHA/ACC, the members of the panel objected and published their "guideline formerly known as JNC 8" separately from either organization. That guideline endorsed a blood pressure target of 140/90 for most adults, with 150/90 acceptable for those older than 60 years. Similar targets have been endorsed by the AAFP and the American College of Physicians (ACP). The AHA/ACC have now released a new guideline in conjunction with a number of specialty societies, but notably without participation from the societies of physicians who take care of most hypertensive patients in the United States: the AAFP and ACP. The change that has received the most coverage is a target blood pressure of 130/80 for everyone, with drug therapy recommended for persons with known cardiovascular disease, diabetes, chronic kidney disease, or who have a 10-year risk of a cardiovascular event greater than 10%. This revised blood pressure target is based largely on the results of the recent, and controversial, SPRINT trial (http://www.essentialevidenceplus.com/content/poem/180101). This trial enrolled hypertensive patients without diabetes who had at least a 15% 10-year risk of cardiovascular event. However, evidence of similar benefit for patients with diabetes or those at lower risk is lacking or was not found in other trials. The guideline authors state that this new target would only lead to a relatively small increase in the percentage of persons requiring drug therapy compared with current goals, but it is not hard to imagine that it will become the new de facto standard for all patients, regardless of risk. The guideline recommends use of the pooled cohort equations to estimate risk, which are also used to guide decisions about statin and aspirin use. However, there is evidence that these equations somewhat overestimate risk (http://www.essentialevidenceplus.com/content/poem/180707), which could also lead to overtreatment. The SPRINT trial also measured blood pressure very differently than do most offices: patients sat alone in a quiet room for 5 minutes, and then the average of 3 measurements was used as the final reading. Sound like your office? A SPRINT blood pressure of 130/80 is probably closer to a typical office blood pressure of 140/90 or higher, again potentially leading to overtreatment. The actual absolute benefit of achieving a target of 120/80 instead of 140/90 (measured the SPRINT way) was modest, with an absolute reduction of 0.54% per year in cardiovascular events and 0.37% per year in all-cause mortality. And, of course, there were harms associated with a more aggressive blood pressure target, including higher risks of a greater than 30% reduction in glomerular filtration rate (0.86% per year), more episodes of hypotension, and the need to take one additional medication. The current guidelines extends the 130/80 target to patients with chronic kidney disease and diabetes, as well, despite inconsistent evidence of benefit from other trials such as ACCORD and HOPE-3 of more intensive blood pressure targets in these patients (http://www.essentialevidenceplus.com/content/poem/120502). There is a clear bias toward avoiding undertreatment, rather than

avoiding the harms of overtreatment. The guideline also recommends chlorthalidone 12.5 mg to 25 mg over hydrochlorothiazide 25 mg to 50 mg as the diuretic of choice. These doses are higher than those currently used by many patients, and are based on the doses used in trials like ALLHAT; however, they also carry a higher risk of hypokalemia. Consistent with the US Preventive Services Task Force, the guidelines recommend out-of-office blood pressure measurements to guide care. An important question is whether physicians will actually use the pooled cohort equations, or whether they will take the simpler approach of just using a target of 130/80 for all adults, resulting in overtreatment.

2107 ACC AHA Guidelines on HTN

In November of 2017, the American College of Cardiology/American Heart Association published a new guideline on the prevention, detection, evaluation, and management of high blood pressure in adults. The article was published online and is 41 pages, 106 recommendations and 23 tables; however, the "meat" of the guideline was covered in only ~ 89 pages. Also the COI declarations covered 22 pages (on a quick review however, most authors had no COI with industry). Articles published through August of 2015 were included. This guideline was heavily influenced by results of the SPRINT study.

Broad sections included the following:

- BP and CVD risk
- Classification of the BP
- Measurement of BP
- Causes of HTN
- Patient Evaluation
- Treatment of High BP
- Hypertension in patients with comorbidities
- Special patient groups
- Other considerations (e.g. resistant HTN, hypertensive crises etc)

I'm including my determination of the items that are most relevant for primary care providers. *My Summary* of key aspects of the New BP guidelines are below the numbering and emphases are mine

The New Normal

1. BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 6) (COR I | LOE B-NR)

The new normal is < 120 / < 80. In addition, a new category of "Elevated Blood Pressure" is included (i.e. 120 – 129 / < 80; and if present, non-pharmacological therapy is recommended).

Hypertension is defined now as > 130 / > 80. Also returned from previous guidelines are stages of hypertension (Stage 1 and Stage 2). Note the checklist for accurate BP measurement from this guideline is in the appendix

BP Category	SBP		DBP
Normal	< 120	and	< 80
Elevated	120-129	and	< 80
Hypertension			
• Stage 1	130-139	or	80 - 89
• Stage 2	> 140	or	> 90

Out-of-office BP measurements recommended

2. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions. (COR I | LOE A)

Take at least two readings 1 min apart in morning before taking medications and in evening before supper. Optimally, measure and record BP daily. Ideally, obtain weekly BP readings beginning 2 weeks after a change in the treatment regimen and during the week before a clinic visit. BP should be based on an average of readings on ≥2 occasions for clinical decision-making.

Also note that the UPSTF "recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment".

- "The USPSTF found convincing evidence that ABPM is the best method (i.e. reference standard) for diagnosing hypertension."
- "Good-quality evidence suggests that confirmation of hypertension with HBPM (with appropriate protocols) may be acceptable."
    - However the evidence is not as substantial as it is for ABPM

The information above may be reinforced with videos available online: Monitoring Your Blood Pressure at Home.

Treatment recommendations are a bit more nuanced

3. Use of BP-lowering medications is recommended for **secondary prevention** of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for **primary prevention** in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher. (COR I | LOE A for SBP)
4. Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. (COR I | LOE C-LD)

Use the ACC/AHA Pooled Cohort Equation to estimate 10-year risk of atherosclerotic CVD. However – with one exception (as noted in the blue cell below) treatment should be initiated with a confirmed BP of ≥ 130 / ≥ 80. You will note that for most patients we are asked to calculated the 10-year ASCVD risk (much like we are asked to do for determining candidacy for statin therapy) to determine if the patients 10-year risk is > or < 10%

Summary of BP Thresholds and Goals for Pharmacologic Treatment		
Clinical Condition(s)	**BP Threshold, mm**	**Hg BP Goal, mm Hg**
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized,	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥130/80	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

5. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. (COR I | LOE A)
6. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. (COR I | LOE C-EO)

Special Circumstances

Stable ischemic Heart Dz (SIHD)

7. Adults with SIHD and hypertension (BP ≥130/80 mm Hg) should be treated with medications (e.g., GDMT beta blockers, ACE inhibitors, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension

Heart Failure with Preserved Ejection Fraction

8. Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta blockers titrated to attain SBP of less than 130 mm Hg. (COR I | C-LD)

Note that GDMT beta-blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta-blockers with intrinsic sympathomimetic activity (e.g. pindolol, acebutolol). The beta-blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

Diabetes

9. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (COR I | LOE A)
10. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (COR IIb | LOE B-NR)

African-Americans

11. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (COR I | B-R)
12. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension. (COR I | C-LD)

Elderly (> 65)

13. Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher (COR I | LOE A)
14. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. (COR IIa | LOE C-EO)

According to data from NHANEs published in the guideline, the prevalence of HTN will triple for men and double for women under the age of 45 (a group of patients not well represented in trials of aggressive BP lowering). (Ann Intern Med 2017); Recall that the average of the participants in the SPRINT trial was 50.

It is now commonplace to recommend that lipid-lowering treatment be primarily based upon a patients' predicted cardiovascular disease risk rather than just the LDL cholesterol concentrations, thus essentially eliminating treatment thresholds that are based only on LDL cholesterol concentrations. This approach recognizes that the patient's baseline risk "is a major determinant of the absolute benefits of statin treatment". This reflects a classic example of understanding how to apply baseline risk assessments in helping patients make treatment decisions.

As a theoretical example: if a given treatment reduces the risk of an event by 50%, an individual with a low baseline risk (e.g. 2%) has almost nothing to gain (this 50% decrease translates into a post treatment risk of 1% | NNT = 100). However an individual with a moderate-high baseline risk (e.g. 20%) has more to gain (this 50% decrease translates into a post treatment risk of 10% | NNT = 10). Also, note that in each instance the relative risk reduction is the same.

Whether these levels of risk reduction are meaningful to the patient is where, of course, shared decision-making comes in.

In the new AHA/ACC guidelines, we are asked to use the 10-year cohort risk calculator much like we do for determining statin eligibility, to make therapeutic decisions for primary prevention in HTN. Abstract 6 support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.

#7: 13.7% more people in the US are now classified as having HTN

BACKGROUND: The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults provides recommendations for the definition of hypertension, systolic and diastolic blood pressure (BP) thresholds for initiation of antihypertensive medication and BP target goals.
OBJECTIVE: Determine the prevalence of hypertension, implications of recommendations for antihypertensive medication and prevalence of BP above the treatment goal among US adults using criteria from the 2017 ACC/AHA and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines.
METHODS: We analyzed data from the 2011-2014 National Health and Nutrition Examination Survey (N=9,623). **NHANES** participants completed study interviews and an examination. For each participant, blood pressure was measured three times following a standardized protocol and averaged. Results were weighted to produce
US population estimates.
RESULTS: According to the 2017 ACC/AHA and JNC7 guidelines, the overall crude prevalence of hypertension among US adults was 45.6% (95% confidence interval [CI] 43.6%,47.6%) and 31.9% (95%CI 30.1%, 33.7%), respectively, and antihypertensive medication was recommended for 36.2% (95%CI 34.2%, 38.2%) and 34.3% (32.5%, 36.2%) of US adults, respectively. Compared to US adults recommended antihypertensive medication by JNC7, those recommended treatment by the 2017 ACC/AHA guideline but not JNC7 had higher CVD risk. Non-pharmacological intervention is advised for the 9.4% of US adults with hypertension according to the 2017 ACC/AHA guideline who are not recommended antihypertensive medication. Among US adults taking antihypertensive medication, 53.4% (95%CI 49.9%, 56.8%) and 39.0% (95%CI 36.4%, 41.6%) had BP above the treatment goal according to the 2017 ACC/AHA and JNC7 guidelines, respectively. Overall, 103.3 (95%CI 92.7,114.0) million US adults had hypertension according to the 2017 ACC/AHA guideline of whom 81.9 (95%CI 73.8, 90.1) million were recommended antihypertensive medication.
CONCLUSION: Compared with the JNC 7 guideline, the 2017 ACC/AHA guideline results in a substantial increase in the prevalence of hypertension but a small increase in the percentage of U.S. adults recommended antihypertensive medication. A substantial proportion of US adults taking antihypertensive medication is recommended more intensive BP lowering under the 2017 ACC/AHA guideline.
***REFERENCE**: Muntner P et al. Potential U.S. Population Impact of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline.J Am Coll Cardiol. 2017 Nov 6.(PMID: 29146532)*

#8: Baseline predicted CV risk equations for DP lowering decisions

BACKGROUND: We aimed to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for blood pressure-lowering therapy, as is recommended for lipid-lowering therapy.
METHODS: This meta-analysis included individual participant data from trials that randomly assigned patients to either blood pressure-lowering drugs or placebo, or to more intensive or less intensive blood pressure-lowering regimens. The primary outcome was total major cardiovascular events, consisting of stroke, heart attack, heart failure, or cardiovascular death. Participants were separated into four categories of baseline 5-year major cardiovascular risk using a risk prediction equation developed from the placebo groups of the included trials (<11%, 11-15%, 15-21%, >21%).
FINDINGS: 11 trials and 26 randomised groups met the inclusion criteria, and included 67,475 individuals, of whom 51,917 had available data for the calculation of the risk equations. 4167 (8%) had a cardiovascular event during a median of 4·0 years (IQR 3·4-4·4) of follow-up. The mean estimated baseline levels of 5-year cardiovascular risk for each of the four risk groups were 6·0% (SD 2·0), 12·1% (1·5), 17·7% (1·7), and 26·8% (5·4). In each consecutive higher risk group, blood pressure-lowering treatment reduced the risk of cardiovascular events relatively by 18% (95% CI 7-27), 15% (4-25), 13% (2-22), and 15% (5-24), respectively (p=0·30 for trend). However, in absolute terms, treating 1000 patients in each group with blood pressure-lowering treatment for 5 years would prevent 14 (95% CI 8-21), 20 (8-31), 24 (8-40), and 38 (16-61) cardiovascular events, respectively (p=0·04 for trend).
INTERPRETATION: Lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.
REFERENCE: Blood Pressure Lowering Treatment Trialists' Collaboration, Sundström J, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014 Aug 16;384(9943):591-8.

2017 Cochrane Reviews

The following abstracts were published in the Cochrane reviews in 2017, for brevity purposes I included only the conclusions, which were a combination of the authors, published conclusions with my additions from the results section.

#9: In healthy adults a small net benefit of treating BP > 140 / > 90

CONCLUSIONS: In 7 studies (17,327 patients, mean age of 50 and mean BP of 160/98, 5 years of follow up) antihypertensive drugs (compared to placebo or no therapy) used to treat predominantly healthy adults aged 18 to 59 years with mild to moderate primary hypertension (SBP > 140 OR DBP >90) have a small absolute effect to reduce cardiovascular mortality and morbidity primarily due to reduction in cerebrovascular mortality and morbidity (0.6% vs 1.3%). All-cause mortality (2.3 vs 2.4%) and coronary heart disease were not reduced. There is lack of good evidence on withdrawal due to adverse events. Future trials in this age group should be at least 10 years in duration and should compare different first-line drug classes and strategies.
REERENCE: Musini VM et al. Pharmacotherapy for hypertension in adults aged 18 to 59 years. Cochrane Database Syst Rev. 2017 Aug 16;8:CD008276.

#10: In adults with CV Dz, no benefit in lower (<135/<85) vs higher BP targets

CONCLUSIONS: In 6 RCTs (9,795 patients with a history of CV Dz {including MI, angina, CVA or PAD}, mean age of 50 and mead BP of 160/98, 3.7 years of follow up), no evidence of a difference in total mortality (RR 1.05) or CV mortality (RR 0.96) and serious adverse events (RR 1.02) was found between treating to a lower (<135/85) or to a standard blood pressure target (<140-160/90-100) in people with hypertension and cardiovascular disease. This suggests no net health benefit from a lower systolic blood pressure target despite the small absolute reduction in total cardiovascular serious adverse events (RR 0.87). There was very limited evidence on adverse events (RR 8.16 for more participant withdrawals), which lead to high uncertainty. At present there is insufficient evidence to justify lower blood pressure targets (≤ 135/85 mmHg) in people with hypertension and established cardiovascular disease. More trials are needed to answer this question.
REFERENCE: Saiz LC, et al. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database Syst Rev. 2017 Oct 11;10:CD010315.

#11: In older adults, BP target of < 140/ <90 of uncertain benefit

CONCLUSIONS: In 3 unblinded randomized trials of 8221 hypertensive adults mean ag 74.8, higher BP targets 150-160/90 compared to lower targets of 140/90 followed for 2 - 4 years demonstrated a no significant difference in all-cause mortality (RR 1,24) stroke (RR 1.25) total CV serious events (RR 1.19). However, the 95% confidence intervals of these outcomes suggest the lower BP target is probably not worse, and might offer a clinically important benefit. At the present time there is insufficient evidence to know whether a higher BP target (range 150 to 160 / 95 to 105 mmHg) or a lower BP target (less than 140/90 mmHg) is better for older adults with high BP. Data on adverse effects were not available from all trials and not different, including total serious adverse events, total minor adverse events, and withdrawals due to adverse effects. Additional good-quality trials assessing BP targets in this population are needed.
REFERENCE: Garrison SR et al. Blood pressure targets for hypertension in older adults. Cochrane Database Syst Rev. 2017 Aug 8;8:CD011575.

AAFP does not endorse the new AHA/ACC HTN guidelines

In Mid-December 2017, the AAFP decided to not endorse the AHA/ACC HTN guidelines, but to continue to endorse the 2014 JNC8 guideline. The AAFP was not involved in the development of the guidelines. The chair of the AAFP's Commission on Health of the Public and Science (CHPS), David O'Gurek, M.D. stated that the AAFP used the same process to review both the JNC 8 and the AHA/ACC Guidelines, and concluded that the 2017 guidelines "didn't meet the Academy's criteria for endorsement or affirmation of value," and that “JNC8 upheld the scientific rigor that provided strong recommendations to family physicians and patients on appropriate treatment of hypertension.” Reasons for non-endorsement included the contention that:

- The bulk of the guideline was not based on a systematic evidence review
    - A systematic review was performed for 4 key questions, although the guideline provided over 100 recommendations
    - Assessments of the quality of individual studies or systematic reviews weren't provided
    - Specifically “…the guideline offered a strong recommendation (COR: I) for using the unvalidated atherosclerotic cardiovascular disease risk assessment tool previously developed by AHA and ACC to determine whether medications should be initiated for

BP control. However, this recommendation wasn't based on evidence that using the tool in this way improves outcomes."

- Substantial weight was given to the SPRINT trial, while other trials were minimized
    - The AAFP "… commission said conflict of interest is a major concern in judging the trustworthiness of guidelines and plays a key role in the AAFP's assessment of guidelines. In the case of the AHA/ACC guideline, the guideline panel commissioned the chair of the SPRINT trial steering committee to chair its work, when, notably, the SPRINT trial served as the foundation for the guideline panel's recommendations to change BP treatment targets."
- Additionally "… several other AHA/ACC guideline panel members had intellectual conflicts of interest, which were not considered in the guideline's preparation."
    - "The AAFP chose not to participate in this guideline development given significant concerns about the guideline methodology, including the management of intellectual conflicts of interest of guideline participants"
- The harms of treating patients to a lower BP were not assessed in the systematic review.

"With competing guidelines and recommendations, family physicians, as bold champions of science, have an opportunity to be a guiding light in the darkness of confusion to deliver quality care that's grounded in science and is patient-centered," O'Gurek concluded.

AAFP News | Accessed Online December 26th 2017

The ACP does not endorse the new AHA/ACC HTN guidelines

Comments from Dr. Timothy Wilt writing for the Clinical Guidelines Committee of the American College of Physicians in an editorial published in January 2018:

- "... the (ACC/AHA) guideline falls short in weighing the potential benefits against potential harms, costs, and anticipated variation in individual patient preferences."

- "Are the harms, costs, and complexity of care associated with this new target justified by the presumed benefits of labeling nearly half the U.S. population as unwell and subjecting them to treatment? We think not and believe that many primary care providers and patients would agree.
- The ACC/AHA based the new definition primarily on selected observational studies showing an association between a BP above 130/80 mm Hg and elevated cardiovascular risk, but few empirical data show that treating to this target in the general population will improve outcomes."
- "It is important to consider the ramifications of labeling asymptomatic persons as unwell before expanding a disease definition"
- "We believe that initiation of pharmacologic therapy at or above a BP of 130/80 mm Hg and treatment to targets less than 130/80 mm Hg in a broad population of older adults are not supported by evidence and may result in low-value care for several reasons."
- "SPRINT provides the footing for an intensive treatment target in higher-risk populations, but the lack of consistent benefit across trials underscores the uncertainty about the actual benefit of aggressive control and highlights the need for targeted application of the SPRINT findings"
- "In addition, the assumption that data from trials in patients with established hypertension applies to newly diagnosed patients is flawed"
- "Third, there is no evidence from randomized controlled trials to support a DBP target less than 80 mm Hg."
- "Clinical policy focused on lower SBP targets should permit a choice based on a patient's risk profile, susceptibility to harms, and treatment preferences."

REFERENCE: Wilt T et al, for the Clinical Guidelines Committee of the American College of Physicians. Hypertension Limbo: Balancing Benefits, Harms, and Patient Preferences Before We Lower the Bar on Blood Pressure. Annals of Internal Medicine 2018;168:

Conclusions:

- The JNC 8 (published in 2014) recommends treatment for BP when it is > 140/>90 in patients < 60 and >150/>90 in patients over 60.
- The SPRNT trial demonstrated that in a select group of high-risk hypertensive patients, treating to a BP target of ~ 120/80 is associated with fewer adverse CV event and mortality (NNT ~ 90) but more harm (NNH -=45) and higher medication burden, but did not include diabetics or patients with cerebrovascular disease
- The AAFP and ACP jointly published a guideline in 2017 essentially endorsing the JNC 8 recommendations of treating a blood pressure of >150/>90 for those over the age of 60The AHA ACC guideline published in late 2017 recommended treatment at a threshold of 130/80 for almost all adult patients (the exception is a treatment threshold of 140/90 for lower risk patients
- The AAFP and the ACP have not endorsed the AHA ACC guideline

Asthma and COPD Update — John Hickner, MD, MSc

Objectives

1. Know recent new developments in the diagnosis and treatment of asthma
2. Know recent developments in the diagnosis and treatment of COPD
3. Understand the benefits of newer therapies for asthma and COPD

There remains a high level of research in asthma and COPD, and some studies are pertinent to primary care. Following are new research studies and meta-analyses published in the past 2 years that will have an impact on our practices. The first abstract may contain the most important finding.

1. One third of adults with diagnosed asthma can be weaned off all asthma meds

Clinical question: How many adults with physician-diagnosed asthma can safely taper off their asthma medications?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: These investigators randomly dialed both landline and cellular phones in Canada to identify a true cohort of adults, 18 years or older, with physician-diagnosed asthma within the previous 5 years. Exclusion criteria included pregnancy, smoking history greater than 10 pack-years, or the use of long-term oral steroids. Review of medical records allowed collection of data on the determination of the original diagnosis of asthma. All participants (N = 701) underwent assessment with baseline spirometry and continued symptom monitoring using standard tools, as well as serial bronchial challenge testing. Patients using daily medications and not confirmed to have asthma with either baseline spirometry or serial bronchial challenge testing had their medications gradually tapered off over 4 study visits. Patients with continued negative test results for asthma were followed up clinically and with repeated bronchial challenges over 1 year. Two pulmonologists independently reviewed all medical records to determine agreement with the final diagnosis for all participants. Discrepancies were resolved by consensus agreement with a third reviewer. A total of 613 patients (87.4%) completed the study assessment procedures. Of these, 203 (33.1%) had a diagnosis of current asthma ruled out. Patients ruled out for current asthma were less likely to be using asthma medications or daily asthma-controlling medications and less likely to have spirometry or bronchial challenge testing performed at the initial time of initial diagnosis. After 1 year of follow-up, 6 patients (2.9%) in the group who were ruled out for current asthma and tapered off their asthma medications presented with respiratory symptoms and resumed treatment. In 12 patients, a serious alternative respiratory diagnosis—including ischemic heart disease, subglottic stenosis, and bronchiectasis—was diagnosed.
Bottom line: This study found that current asthma was ruled out after repeated testing in one third of adults with physician-diagnosed asthma. Patients ruled out for current asthma were less likely to be using asthma medications or daily-controlling medications and less likely to have undergone testing for airflow limitation at the time of initial diagnosis. After 1 year of follow-up, 2.9% of the patients who tapered off their asthma medications presented with respiratory symptoms and resumed treatment.
Aaron SD, Vandemheen KL, FitzGerald JM, et al, for the Canadian Respiratory Research Network. Reevaluation of diagnosis in adults with physician-diagnosed asthma. JAMA 2017:317(3):269-279.

Asthma in Children

Reducing environmental exposure is one of the pillars of asthma treatment. Mite-impermeable covers provide benefits, but reducing mouse infestation in housing does not. A comprehensive community based intervention including allergy testing and environmental control was somewhat effective in reducing asthma symptom days in high risk low income children. Consider a single dose of dexamethasone instead of 3 days of prednisone for asthma exacerbations in children and adults.

2. Mite-impermeable covers decreases hospital visits in kids with asthma

Clinical question: Can mite-impermeable bedding decrease asthma exacerbations in children with asthma who are sensitive to mites?
Study design: Randomized controlled trial (double-blinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: House dust mites are a common allergen associated with asthma. This United Kingdom study included children with physician-diagnosed asthma who visited the hospital for an exacerbation (emergency department or admission). After the exacerbation had cleared, the researchers skin tested the children for house dust mite, cat, dog, pollen, and other allergens. They randomized children who had a wheal at least 3 mm larger than the negative control to receive mite-impermeable bedding covers (n = 146) or identical but non-impermeable bedding covers (n = 138) to use at home. The researchers gave all participants the same instructions on the care of the bedding covers and none were given instructions on mite avoidance. In the event that a second child from the same family entered the study, the researchers assigned them to the same intervention. Interviewers unaware of group assignment interviewed the child's primary caregiver 1, 4, 8, and 12 months after enrollment to ascertain exacerbations, unscheduled medical care, medication use, and quality of life. Additionally, the researchers vacuumed the child's bedroom floor at baseline and at the end of the study to estimate the mite load in the room. At the end of 1 year, 23 children in the mite-impermeable bedding group dropped out compared with 20 in the control group. Although this 15% drop-out rate is not a major problem, it is still a bit worrisome. At the end of a year, 29% of children in the mite-impermeable bedding group had exacerbations leading to a hospital visit compared with 42% of the

control group (number needed to treat = 9; 95% CI 5 - 512). However, approximately half the children in each group used oral corticosteroids during the year. Approximately 25% of the children complained that the special bedding covers were uncomfortable and thought about removing them, as did fewer than 3% of the children with the regular covers. These mite-impermeable bedding covers cost approximately US$200.
Bottom line: In children with house dust mite allergies and asthma, the use of mite-impermeable bedding decreases the frequency of asthma exacerbations.
Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children. A randomized trial of mite-impermeable bedcovers. Am J Respir Crit Care Med 2017;196(2):150-158.

3. Intensive intervention to reduce mouse infestation does not improve asthma morbidity in children

Clinical question: Does a professionally delivered pest management intervention reduce asthma morbidity among mouse-sensitized and exposed children and adolescents with asthma?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: It is currently unknown if reducing mouse allergen exposure reduces asthma morbidity among mouse-sensitized children and adolescents. These investigators enrolled children and adolescents, aged 5 to 17 years, with persistent asthma and known mouse sensitization based on either a positive skin test result or an elevated mouse urine–specific IgE level. After a home visit, those patients with an elevated mouse allergen concentration on their bed or bedroom floor (N = 361) randomly received assignment (uncertain allocation concealment) to either a professionally delivered integrated pest management (IPM) intervention plus pest management education (PME) or PME alone. The IPM intervention was performed by licensed pest management experts and included cleaning to remove allergen reservoirs, placement of traps and rodenticide, sealing holes and cracks, installation of allergen-proof mattresses and pillow encasements, and placement of portable air purifiers. PME included written materials about setting mouse traps, sealing holes and cracks, and housekeeping practices. Infestation was assessed every 3 months and additional IPM was delivered as needed up to a total of 4 treatments. Asthma-related outcomes were assessed at clinic visits and via telephone calls every 3 months for a total of 12 months. The authors do not state whether the individuals who assessed outcomes remained masked to treatment group assignments. Complete follow-up occurred for 88% of participants at 12 months. Using intention-to-treat analyses, the authors found no significant difference between the 2 groups in the primary outcome of maximal number of days with symptoms in the 2 weeks prior to a clinical visit or telephone call. Similarly, they found no significant group differences in measured secondary outcomes, including rescue medication use, urgent health care clinic visits, emergency department use, hospitalizations, or reductions of 75% or 90% of mouse allergen levels. A decrease of at least 50% of mouse allergen levels was significantly associated with reduced asthma morbidity in both groups. The study was 90% powered to detect a predetermined clinically significant group difference.
Bottom line: An intensive year-long professionally delivered pest management intervention in the homes of mouse-sensitized and exposed children and adolescents with asthma was no more effective than written pest management education alone for reducing asthma morbidity.
Matsui EC, Perzanowski M, Peng R, et al. Effect of an integrated pest management intervention on asthma symptoms among mouse-sensitized children and adolescents with asthma. A randomized clinical trial. JAMA 2017;317(10):1027-1036.

4. Effectiveness of evidence-based asthma Interventions in high risk, low income children

BACKGROUND AND OBJECTIVES: Researchers often struggle with the gap between efficacy and effectiveness in clinical research. To bridge this gap, the Community Healthcare for Asthma Management and Prevention of Symptoms (CHAMPS) study adapted an efficacious, randomized controlled trial that resulted in evidence-based asthma interventions in community health centers.
METHODS: Children (aged 5-12 years; *N* = 590) with moderate to severe asthma were enrolled from 3 intervention and 3 geographically/capacity-matched control sites in high-risk, low-income communities located in Arizona, Michigan, and Puerto Rico. The asthma intervention was tailored to the participant's allergen sensitivity and exposure, and it comprised 4 visits over the course of 1 year. Study visits were documented and monitored prospectively via electronic data capture. Asthma symptoms and health care utilization were evaluated at baseline, and at 6 and 12 months.
RESULTS: A total of 314 intervention children and 276 control children were enrolled in the study. Allergen sensitivity testing (96%) and home environmental assessments (89%) were performed on the majority of intervention children. Overall study activity completion (eg, intervention visits, clinical assessments) was 70%. Overall and individual site participant symptom days in the previous 4 weeks were significantly reduced compared with control findings (control, change of -2.28; intervention, change of -3.27; difference, -0.99; $P < .001$), and this result was consistent with changes found in the rigorous evidence-based interventions.
CONCLUSIONS: Evidence-based interventions can be successfully adapted into primary care settings that serve impoverished, high-risk populations, reducing the morbidity of asthma in these high-need populations.
Pediatrics. 2017 Jun;139(6).

5. Salmeterol appears safe in children, but no benefit regarding exacerbations

Clinical question: Does adding salmeterol to fluticasone increase the likelihood of serious asthma related events or reduce the likelihood of exacerbations?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: This is another in a series of FDA-mandated, industry-sponsored trials to sort out the pros and cons of using a long-acting beta agonist (LABA) in addition to an inhaled corticosteroid in people with persistent asthma and frequent exacerbations. In this case, the drug is salmeterol and the population is children aged 4 to 11 years with a history of an asthma exacerbation in the past 1 to 12 months. The mean age was 7.6 years, 62% were boys, and 65% were white. A total of 6250 children were randomized to receive either fluticasone plus salmeterol or fluticasone alone; the dose of the fluticasone was either 100 mcg or 250 mcg, depending on disease

severity. The groups were balanced at the start of the study, analysis was by intention to treat, and both patients and outcome assessors were masked to treatment assignment during the 6-month trial period. The authors designed this is a noninferiority trial with regard to serious asthma-related events (hospitalization, intubation, or asthma death), with a fairly generous margin. Basically, if the upper bound for the 95% confidence interval of the hazard ratio was less than 2.675, everything was just fine. They found 27 asthma-related hospitalizations in the combination therapy group and 21 in the fluticasone-only group, which met their criteria for noninferiority. There was no difference in the likelihood of experiencing a severe exacerbation (8.5% vs 10.0%; hazard ratio 0.86; 95% CI 0.73-1.01). They also examined the likelihood of exacerbations stratified by the previous therapy, and found a small benefit only for those who had originally been taking the combination of a glucocorticoid and a LABA (7.5% vs 9.9%; P < .05; number needed to treat = 42).
Bottom line: The addition of salmeterol to fluticasone was found to be safe in terms of serious asthma-related events (in this study, that meant hospitalizations) when using generous margins for "noninferiority." There was no significant difference in the number of severe exacerbations, though.
Stempel DA, Szefler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. N Engl J Med 2016; 375: 840-9.

6. Inhaled steroids are effective prevention for wheezing preschoolers

Clinical question: In preschoolers with recurrent wheeze, do "controller" treatments decrease recurrences?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The researchers searched 3 databases, including Cochrane CENTRAL, to identify randomized studies of children 6 years or younger with asthma or recurrent wheeze (at least 2 episodes in the past year) that compared inhaled corticosteroids, given daily or intermittently, with placebo or montelukast to prevent exacerbations requiring systematic steroids. The studies were selected and the data abstracted independently by 2 researchers. They found 22 studies enrolling a total of 4550 patients. The studies for the most part were of high quality, and heterogeneity was not significant. Most of the studies (n = 15, 3278 patients) compared daily inhaled corticosteroids with placebo. On average, the exacerbations were decreased by 30% (risk ratio [RR] = .70; 95% CI .61 - .79), with one fewer exacerbation for every 9 children treated. Results were better in patients with persistent asthma. In a single study of 202 patients, treatment with daily inhaled corticosteroids was more effective than with montelukast at preventing exacerbation (RR = .59; .38 - .92). Daily versus intermittent inhaled corticosteroids were found to be equal in 2 studies, but the number of patients (and events) was too small to draw firm conclusions. Though not formally a part of this analysis, height was slightly (.7 - 1.1 cm) affected by treatment with inhaled corticosteroids but growth differences resolved following discontinuation.
Bottom line: Daily moderate-dose inhaled corticosteroids can decrease episodes of wheezing that require oral corticosteroid treatment in kids 6 years or younger, especially if they have persistent asthma. Intermittent treatment is likely effective, too, and reduces the total inhaled steroid dose. Inhaled corticosteroid treatment is more effective than montelukast (Singulair).
Kaiser SV, Huynh T, Bacharier LB, et al. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. Pediatrics. 2016;137(6):e20154496.

7. Single-dose dexamethasone = 3 days of steroids in children with acute asthma

Clinical question: In children with acute exacerbation of asthma, is a single dose of corticosteroid as effective as 3 days of treatment?
Study design: Randomized controlled trial (nonblinded)
Setting: Emergency department
Synopsis: These Irish investigators enrolled 226 children (for a total of 245 enrollments; some were enrolled twice) between the ages of 2 and 16 years with an acute exacerbation of asthma. The children were randomized (concealed allocation unknown) to receive either a single dose of oral dexamethasone (0.3 mg/kg) or 3 days of oral prednisolone (1 mg/kg/day) in addition to usual therapy. None of the patients, their parents, or the investigators were masked to treatment assignment, though the outcome assessor was unaware of treatment at the time of evaluation, which was 4 days after presentation. The Pediatric Respiratory Assessment Measure (PRAM) was used to measure symptoms. It consists of measuring suprasternal and scalene muscle contraction, air entry, wheezing, and oxygen saturation, with a maximum score of 12. At 4 days, PRAM scores were similar among the 2 groups (0.91 vs 0.91). Hospital admission rates were also similar between the 2 groups, as were days lost from school and parental workdays missed. Return visits were similar between the 2 groups, though more children receiving the single dose required further steroid treatment within the following 2 weeks (13% vs 4%). Vomiting occurred more often with prednisolone.
Bottom line: In addition to usual beta-agonist treatment, a single dose of oral dexamethasone is as effective as 3 days of prednisolone (with less vomiting) in decreasing respiratory symptoms without increasing hospitalizations, follow-up visits, and days lost from school. Additional treatment with a steroid was more common in the group receiving the single dose of dexamethasone.
Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. Ann Emerg Med. 2016;67(5):593-601.

Asthma in Adults

Single dose dexamethasone is about as effective as 5 days of prednisone for adults with asthma exacerbations. Although azithromycin 3 times a week reduces the frequency of asthma exacerbations, a short course for exacerbations is not helpful. Adding LABAs to inhaled steroids provides modest benefit in reducing exacerbations. Anti-IL5 monoclonal antibody therapies for asthma are somewhat effective in reducing prednisone dose and exacerbations in patients with severe asthma and are very expensive.

8. Single-dose dexamethasone: an option for acute adult asthma

Clinical question: Is a single dose of dexamethasone as effective as 5 days of prednisone for acute exacerbations of asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Emergency department
Synopsis: These investigators enrolled 456 adults younger than 56 years who presented with acute asthma to an emergency department and required at least one treatment with a beta-agonist. The patients were randomly assigned, using concealed allocation, to receive treatment with prednisone 60 mg daily for 5 days or a single dose of dexamethasone 12 mg followed by 4 days of placebo. Treatment was started in the emergency department. Of the 456 people initially enrolled, 376 could be evaluated; 16 were admitted before leaving the emergency department and 73 could not be contacted (more in the dexamethasone group). Over the subsequent 2 weeks, 12.1% of the dexamethasone group and 9.8% of prednisone group had a relapse that required additional treatment (difference 2.3%; 95% CI -4.1% to 8.6%). This difference did not meet the researcher's threshold for noninferiority of 8%, meaning that treatment with dexamethasone was slightly less effective. The hospitalization rate was low (3%) and did not differ between treatment groups. Side effects were more common in the prednisone group.
Bottom line: A single dose of 12 mg dexamethasone, which has a longer duration of action than prednisone, is almost as effective as 5 days of 60 mg prednisone for the prevention of relapse in adults with acute asthma treated in an emergency department. It is a reasonable option for treatment in the emergency department, given its fewer side effects. In this study, patients who received the single dose also took placebo for 4 days; further research is needed to determine whether patients are comfortable with taking just a single dose.
Rehrer MW, Liu B, Rodriguez M, Lam J, Alter HJ. A randomized controlled noninferiority trial of single dose of oral dexamethasone versus 5 days of oral prednisone in acute adult asthma. Ann Emerg Med 2016;68(5):608-613.

9. Azithromycin reduces frequency of exacerbations in adults with persistent asthma

Clinical question: Does the regular use of azithromycin decrease the frequency of exacerbations in adults with persistent asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Uncertain
Synopsis: In this multicenter study, after a 2-week run-in period to establish stability and general adherence to an asthma care regimen, the researchers randomly assigned adults with symptomatic persistent asthma despite the use of inhaled corticosteroids and long-acting beta-agonists to receive azithromycin (500 mg 3 times per week; n = 213) or placebo (n = 207) for 48 weeks. The research team frequently evaluated the participants' exacerbations, medication use, adherence, and adverse events through office visits and telephone calls. The researchers evaluated the 2 primary end points (exacerbations and quality of life) using intention to treat. Unlike many studies that don't include the patients who withdraw, these authors conducted a true intention-to-treat analysis. The patients treated with azithromycin had fewer exacerbations (1.07 per year; 95% CI 0.85 - 1.29) than those treated with placebo (1.86; 1.54 - 2.18). Additionally, 44% of azithromycin-treated patients had at least one exacerbation compared with 61% of the placebo-treated patients (number needed to treat = 6; I 4 - 13). Azithromycin was effective in reducing the frequency of exacerbations in several planned subgroups of patients: those with sputum eosinophilia, frequent exacerbations, chronic cough, or bacterial pathogens on baseline sputum. There was no difference in the rate of severe adverse events or withdrawals due to side effects. More azithromycin-treated patients experienced diarrhea (34%) than placebo-treated patients (19%; number needed to treat to harm = 7; 5 - 16).
Bottom line: In this well-done government-funded study of adults with persistent asthma who use inhaled corticosteroids and long-acting beta-agonists, adding 500 mg azithromycin 3 times a week reduced the frequency of exacerbations. For every one exacerbation avoided, however, one patient will experience diarrhea.
Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017;390(10095):659-668.

10. No benefit to azithromycin for acute asthma exacerbations

Clinical question: For patients with acute asthma exacerbations, does the addition of azithromycin improve the resolution of symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Along with its antimicrobial activity, azithromycin may have anti-inflammatory and antiviral properties that could potentially help resolve an acute asthma exacerbation. To test this theory, investigators in the United Kingdom enrolled adult patients who presented with symptoms and signs of acute asthma exacerbation that required systemic steroids. This was done in order to exclude patients with mild exacerbations. Of the 4582 eligible patients, 4383 were excluded (!), mainly because they were currently taking antibiotics or had taken antibiotics within 28 days of enrollment. The remaining 199 patients were randomized to receive either azithromycin 500 mg daily or matching placebo for 3 days along with standard care. The 2 groups were balanced at baseline: mean age was 40 years, two thirds were women, and baseline asthma symptom scores were similar. Patients recorded their symptoms in a diary and were assessed at days 5 and 10 after the initiation of treatment. For the primary outcome of mean asthma symptom scores at day 10, no difference was detected between the 2 groups. Additionally, there were no differences in quality-of-life scores or on any measure of lung function during the entire study. Of note, patients in this study had a low likelihood of concurrent respiratory infections; sputum samples and nasal/throat swabs indicated only 10% had bacterial infections and 18% had viral infections.
Bottom line: These data show no improved outcomes with the addition of azithromycin to standard treatment for patients with acute asthma exacerbations requiring systemic steroids. However, the recruitment for this study was difficult, as half the eligible patients were excluded because of current or recent use of antibiotics, which resulted in a very underpowered study that only reached half its recruitment target. For each person included, more than 10 were excluded. Beyond its impact on the study results, the recruitment difficulty suggests that antibiotic use for asthma exacerbation is widespread despite current treatment guidelines that recommend otherwise.

Johnston SL, Szigeti M, Cross M, et al, for the AZALEA Trial Team. Azithromycin for acute exacerbations of asthma: the AZALEA randomized clinical trial. JAMA Intern Med 2016 Sep 19.

11. Adding formoterol to budesonide for asthma: no significantly increased harms; minimal benefits

Clinical question: Does adding the long-acting beta agonist formoterol to budesonide increase the risk of serious adverse events in persons with persistent asthma?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: This is one of several studies mandated by the FDA to assess the safety of LABAs in persons with asthma. This trial, sponsored by AstraZeneca, identified patients 12 years and older with persistent asthma (between 1 and 4 exacerbations in the previous year) who were taking a daily asthma medication, and had no previous life-threatening exacerbations. Their mean age was 43 years, 15% were current or former smokers, and 82% had experienced only 1 exacerbation in the previous year. A daily inhaled glucocorticoid was used by 90% at the time of recruitment, with half using a moderate dose. Based on the severity of their asthma, each patients was assigned to either a low dose of budesonide (160 mcg daily) or high dose of budesonide (320 mcg daily). They were then randomized to receive that dose of budesonide with or without formoterol in open-label fashion. A total of 11,693 persons were randomized, with approximately 80% receiving the high-dose budesonide. Patients were followed up for 26 weeks, with approximately 12% dropping out during that time (kind of a large number for such a short trial). Groups were balanced at the start of the study, and the primary analysis was by intention to treat. There was no significant difference between groups regarding serious asthma-related events, defined as hospitalization, intubation, or death. In the high-dose budesonide group, there were 37 serious asthma-related events in the formoterol group, including 2 deaths, compared with 32 events and no deaths in the budesonide-only group. The percentage of participants who experienced at least one exacerbation was slightly reduced in the combination therapy group (9.2 vs 10.8%; P = .002; number needed to treat = 63). However, the open-label design and apparent failure to mask the outcome assessors could easily bias the results.
Bottom line: I'm not convinced that adding formoterol will result in significant benefits, given its modest impact on exacerbations and the open-label design of this study. Formoterol appears to be safe, though the most important safety events (death or intubation) were very rare in this short trial, so it is important to combine these results with those from other trials of long-acting beta agonists (LABAs) in a meta-analysis.
Peters SP, Bleecker ER, Canonica GW, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med 2016;375(9):850-860.

12. Inhaled fluticasone-salmeterol better than fluticasone alone for moderate to severe asthma

Clinical question: Is the combination of a long-acting beta-agonist and an inhaled corticosteroid as safe and effective as an inhaled corticosteroid alone?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: This study was performed by GlaxoSmithKline at the behest of the FDA because of enduring concerns about the safety of long-acting beta-agonists. The authors identified patients with moderate to severe asthma who had experienced at least one exacerbation in the previous year that required systemic steroids or hospitalization (but no such episode in the previous month). The 11,751 included patients from 694 centers were randomized to receive fluticasone-salmeterol or fluticasone alone. The dose of fluticasone alone was stratified into 3 subgroups based on disease severity: 100 mcg, 250 mcg, and 500 mcg. In the combination treatment group, salmeterol 50 mcg was combined with fluticasone at 100 mcg, 250 mcg, and 500 mcg, again according to disease severity. All medications were given twice daily. Patients were 12 years and older (mean age = 43 years) and most patients were from North America or Europe. Groups were balanced at the beginning of the study and analysis was by intention to treat. Outcomes were adjudicated by members of the research team who were masked to treatment assignment. The primary efficacy endpoint was the first severe asthma exacerbation, defined as the use of systemic steroids for at least 3 days, asthma-related hospitalization, or an emergency department visit resulting in systemic steroid administration. There were fewer severe asthma exacerbations in the fluticasone-salmeterol group than in the group that received fluticasone alone (8% vs 10%; P < .001; NNT = 50 over 26 weeks). The primary safety outcome (a composite of asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations) was similar between groups: 36 events in the fluticasone-salmeterol group and 38 events in the fluticasone-only group. There were 3 deaths in the fluticasone-salmeterol group and 6 in the fluticasone-only group, none of which were adjudicated as being related to asthma.
Bottom line: The combination of fluticasone and salmeterol, with the steroid dose adjusted for disease severity, reduces the number of severe asthma exacerbations more than fluticasone alone (number needed to treat [NNT] = 50 over 26 weeks), with no difference in terms of potential harms such as intubation or asthma-related death.
Stempel DA, Raphiou I, Kral KM, et al, for the AUSTRI Investigators. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med 2016;374(19):1822-1830.

13. Benralizumab reduces daily oral prednisone dose for severe asthma from 10 mg to 5 mg

Clinical question: Does benralizumab improve outcomes in patients with severe asthma who are receiving long-term systemic glucocorticoids?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Benralizumab is a human monoclonal antibody against the interleukin-5 receptor that gives it anti-inflammatory properties. This trial enrolled patients with severe asthma and an elevated blood eosinophil count who were taking a moderate-dose to high-dose inhaled steroid, a long-acting beta-agonist, and a daily dose of an oral steroid for at least 6 months. They initially recruited 369 patients, of whom 220 ultimately met the eligibility criteria after a run-in period during which their oral glucocorticoid dose was reduced to the minimum effective dose and at least 70% compliance with their current medications was ensured. These 220 were then randomized to

receive either (1) benralizumab 30 mg by subcutaneous injection every 4 weeks for 28 weeks, (2) benralizumab 30 mg subcutaneously every 4 weeks for 3 months, and then every 8 weeks for the remaining 16 weeks, or (3) placebo injection every 4 weeks. All patients underwent a concerted effort during the 28-week study period to reduce their oral steroid dose, and the primary outcome was how much the steroid could be reduced. Groups were balanced at the start of the study, and analysis was by intention to treat. The mean age of participants was 50 years, with a median prednisone dose of 10 mg at baseline, and a forced expiratory volume in 1 second of approximately 60% of predicted. Asthma exacerbations were defined as requiring an increase in the steroid dose for 3 or more days, a visit to the emergency department (ED), or hospitalization. Patients in both of the active treatment groups saw a statistically significant reduction in the median daily oral dose of prednisone—from 10 mg to 5 mg—compared with no change in the placebo group. Approximately half the patients in the active treatment group were able to discontinue using their steroid. Patients in the active treatment groups were less likely to have any asthma exacerbation during the study period (17% to 19% vs 39%; P = .001; number needed to treat = 5 over 28 weeks). The annualized rate of exacerbations was lower for the active treatment groups (0.55 for benralizumab every 8 weeks, 0.82 for benralizumab every 4 weeks, 1.80 for placebo; P = .003). More serious exacerbations (resulting in a visit to the ED or hospitalization) were slightly less likely for the group dosed every 8 weeks (0.02 vs 0.32; P = 0.02), but not the group dosed every 4 weeks. There were small improvements in quality of life scores, but they were not clinically significant (eg, 0.45 points on a 12-point scale). Adverse events were similar between groups. In their article, the authors overemphasize the more dramatic-sounding relative reductions rather than the absolute reductions for all outcomes, something that the editors of the journal should not have tolerated.

Bottom line: The addition of the monoclonal antibody benralizumab reduced the median dose of prednisone from 10 mg to 5 mg, and resulted in a small decrease in serious exacerbations in one of the active treatment groups but not the other. Although this drug has not yet been approved by the US Food and Drug Administration, a similar drug, omalizumab (Zolair), is currently priced at approximately $1000 per month in the United States and $750 in Canada. It is unclear whether the modest benefits are worth the drug's high cost.

Nair P, Wenzel S, Rabe KF, et al, for the ZONDA Trial Investigators. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376(25):2448-2458.

14. Anti-IL5 therapies for asthma are somewhat effective

BACKGROUND: This review is the first update of a previously published review in The Cochrane Library (Issue 7, 2015). Interleukin-5 (IL-5) is the main cytokine involved in the activation of eosinophils, which cause airway inflammation and are a classic feature of asthma. Monoclonal antibodies targeting IL-5 or its receptor (IL-5R) have been developed, with recent studies suggesting that they reduce asthma exacerbations, improve health-related quality of life (HRQoL) and lung function. These are being incorporated into asthma guidelines.

OBJECTIVES: To compare the effects of therapies targeting IL-5 signaling (anti-IL-5 or anti-IL-5Rα) with placebo on exacerbations, health-related qualify of life (HRQoL) measures, and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments.

SEARCH METHODS: We searched the Cochrane Airways Trials Register, clinical trials registries, manufacturers' websites, and reference lists of included studies. The most recent search was March 2017.

SELECTION CRITERIA: We included randomised controlled trials comparing mepolizumab, reslizumab and benralizumab versus placebo in adults and children with asthma.

DATA COLLECTION AND ANALYSIS: Two authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by Cochrane.

MAIN RESULTS: Thirteen studies on 6000 participants met the inclusion criteria. Four used mepolizumab, four used reslizumab, and five used benralizumab. One study in benralizumab was terminated early due to sponsor decision and contributed no data. The studies were predominantly on people with severe eosinophilic asthma, which was similarly but variably defined. Eight included children over 12 years but these results were not reported separately. We deemed the risk of bias to be low, with all studies contributing data being of robust methodology. We considered the quality of the evidence for all comparisons to be high overall using the GRADE scheme, with the exception of intravenous mepolizumab because this is not currently a licensed delivery route. All of the anti-IL-5 treatments assessed reduced rates of 'clinically significant' asthma exacerbation (defined by treatment with systemic corticosteroids for three days or more) by approximately half in participants with severe eosinophilic asthma on standard of care (at least medium-dose inhaled corticosteroids (ICS)) with poorly controlled disease (either two or more exacerbations in the preceding year or Asthma Control Questionnaire (ACQ) 1.5 or more). Non-eosinophilic participants treated with benralizumab also showed a significant reduction in exacerbation rates, but no data were available for non-eosinophilic participants, and mepolizumab or reslizumab.

We saw modest improvements in validated HRQoL scores with all anti-IL-5 agents in severe eosinophilic asthma. However these did not exceed the minimum clinically important difference for ACQ and Asthma Quality of Life Questionnaire (AQLQ), with St. George's Respiratory Questionnaire (SGRQ) only assessed in two studies. The improvement in HRQoL scores in non-eosinophilic participants treated with benralizumab, the only intervention for which data were available in this subset, was not statistically significant, but the test for subgroup difference was negative. All anti-IL-5 treatments produced a small but statistically significant improvement in mean pre-bronchodilator forced expiratory flow in one second (FEV1) of between 0.08 L and 0.11 L.

There were no excess serious adverse events with any anti-IL-5 treatment, and indeed a reduction in favour of mepolizumab that could be due to a beneficial effect on asthma-related serious adverse events. There was no difference compared to placebo in adverse events leading to discontinuation with mepolizumab or reslizumab, but significantly more discontinued benralizumab than placebo, although the absolute numbers were small (36/1599 benralizumab versus 9/998 placebo).Mepolizumab, reslizumab and benralizumab all markedly reduced blood eosinophils, but benralizumab resulted in almost complete depletion, whereas a small number remained with mepolizumab and reslizumab. The implications for efficacy and/or adverse events are unclear.

AUTHORS' CONCLUSIONS: Overall our study supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control. These treatments roughly halve the rate of asthma exacerbations in this population. There is limited evidence for improved HRQoL scores and lung function, which may not meet clinically detectable levels. There were no safety concerns regarding mepolizumab or reslizumab, and no excess serious adverse events with benralizumab, although there remains a question over adverse events significant enough to prompt discontinuation. Further research is needed on biomarkers for assessing

treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal, non-eosinophilic patients, children (particularly under 12 years), and comparing anti-IL-5 treatments to each other and, in people eligible for both, to anti-immunoglobulin E. For benralizumab, future studies should closely monitor rates of adverse events prompting discontinuation.
Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev. 2017 Sep 21;9:CD010834.

15. Adjusting medications based on sputum eosinophils versus clinical symptoms reduces asthma exacerbations in adults

Background. Asthma severity and control can be measured both subjectively and objectively. Sputum analysis for evaluation of percentage of sputum eosinophilia directly measures airway inflammation, and is one method of objectively monitoring asthma. Using sputum analysis to adjust or tailor asthma medications is potentially superior to traditional methods based on symptoms and spirometry.
Objectives. To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to traditional methods (usually symptom-based with or without spirometry/peak flow) for asthma-related outcomes in children and adults.
Search methods. We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, trials' registries, and reference lists of articles. The last search was conducted in February 2017.
Selection criteria. All randomised controlled comparisons of adjustment of asthma therapy based on sputum eosinophils compared to traditional methods (primarily clinical symptoms and spirometry/peak flow).
Data collection and analysis. Results of searches were reviewed against pre-determined criteria for inclusion. In this update, two reviewers selected relevant studies, independently assessed trial quality and extracted the data. We contacted authors for further information when relevant. We analysed data as 'treatment received' and performed sensitivity analyses.
Main results. Three new studies were added in this update, resulting in a total of six included studies (five in adults and one involving children/adolescents). These six studies were clinically and methodologically heterogeneous (use of medications, cut-off for percentage of sputum eosinophils and definition of asthma exacerbation). Of 374 participants randomised, 333 completed the trials. In the meta-analysis, there was a significant reduction in the occurrence of any exacerbations when treatment was based on sputum eosinophil counts, compared to that based on clinical symptoms with or without lung function; pooled odds ratio (OR) was 0.57 (95% confidence interval (CI) 0.38 to 0.86). The risk of having one or more exacerbations over 16 months was 82% in the control arm and 62% (95% CI 49% to 74%) in the sputum strategy arm, resulting in a number needed to treat to benefit (NNTB) of 6 (95% CI 4 to 13).There were also differences between the groups in the rate of exacerbation (any exacerbation per year) and severity of exacerbations defined by requirement for use of oral corticosteroids and hospitalisations: the risk of one or more hospitalisations over 16 months was 24% in controls compared to 8% (95% CI 3% to 21%) in the sputum arm. Data for clinical symptoms, quality of life and spirometry were not significantly different between groups. The mean dose of inhaled corticosteroids per day was also similar in both groups. However sputum induction was not always possible. The included studies did not record any adverse events. One study was not blinded and thus was considered to have a high risk of bias. However, when this study was removed in a sensitivity analysis, the difference between the groups for the primary outcome (exacerbations) remained statistically significant between groups. The GRADE quality of the evidence ranged from moderate (for the outcomes 'Occurrence of any exacerbation' and 'Hospitalisation') to low (for the outcome 'Mean dose of inhaled corticosteroids per person per day') due to the inconsistency in defining exacerbations and the small number of hospital admissions.
Authors' conclusions. In this updated review, tailoring asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations in adults with asthma. Adults with frequent exacerbations and severe asthma may derive the greatest benefit from this additional monitoring test, although we were unable to confirm this through subgroup analysis. There is insufficient data available to assess tailoring asthma medications based on sputum eosinophilia in children. Further robust RCTs need to be undertaken and these should include participants with different underlying asthma severities and endotypes.
Reference. *Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD005603. DOI: 10.1002/14651858.CD005603.pub3.*

COPD

16. Screening for Chronic Obstructive Pulmonary Disease Not Recommended: Evidence Report and Systematic Review for the US Preventive Services Task Force

IMPORTANCE: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States.
OBJECTIVE: To systematically review literature on the accuracy of screening questionnaires and office-based screening pulmonary function testing and the efficacy and harms of treatment of screen-detected COPD.
DATA SOURCES: MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant English-language studies published through January 2015.
STUDY SELECTION: Two reviewers independently screened abstracts and studies. The search yielded 13,141 unique citations; 465 full-text articles were reviewed, and 33 studies met the inclusion criteria.
DATA EXTRACTION AND SYNTHESIS: Two reviewers rated the quality of each study using USPSTF criteria.
MAIN OUTCOMES AND MEASURES: Diagnostic accuracy (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]; treatment efficacy (COPD exacerbations, all-cause mortality, quality of life, and dyspnea); and treatment harms.
RESULTS: All screening questionnaires were based on symptoms as well as risk factors such as age and smoking history. The COPD Diagnostic Questionnaire was the most extensively studied (5 studies, n = 3048), with moderate overall performance for COPD detection: area under the receiver operating characteristic curve (AUC), 0.65 to 0.72; sensitivity, 80% to 93%; and specificity, 24% to

49%, at a threshold of greater than 16.5. Positive predictive value and NPV ranged from 17% to 45% and 76% to 98%, respectively. For pulmonary function-based screening tools, FEV1/FEV6 was the best studied (3 studies, n = 1587), with AUC ranging from 0.84 to 0.85. Sensitivity ranged from 51% to 80%. Specificity (range, 90%-95%) and PPV (range, 63%-75%) appeared better than questionnaires. There was not strong evidence to support that screening and supplying smokers with spirometry results improves smoking cessation rates. Treatment trials were unavailable for screen-detected patients. Trials that reported outcomes in patients with mild to moderate COPD included 2 trials of long-acting β-agonists (LABAs) (n = 3174), 1 RCT of LABAs and inhaled corticosteroids (ICS) (n = 1097), 5 RCTs of the long-acting muscarinic antagonist tiotropium (n = 4592), and 6 RCTs of ICS (n = 3983). They suggested no benefit in all-cause mortality, but a decrease in annual rates of exacerbations with pharmacologic treatments. Few trials reported harms for any individual drug class. Adverse effects were generally mild (eg, dry mouth and cough).
CONCLUSIONS AND RELEVANCE: There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations. Indirect evidence suggests that the COPD Diagnostic Questionnaire has moderate overall performance for COPD detection. Among patients with mild to moderate COPD, the benefit of pharmacotherapy for reducing exacerbations was modest.
Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP. Screening for Chronic Obstructive Pulmonary Disease: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016 Apr 5;315(13):1378-93

17. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease

BACKGROUND: Patients with mild or moderate chronic obstructive pulmonary disease (COPD) rarely receive medications, because they have few symptoms. We hypothesized that long-term use of tiotropium would improve lung function and ameliorate the decline in lung function in patients with mild or moderate COPD.
METHODS: In a multicenter, randomized, double-blind, placebo-controlled trial that was conducted in China, we randomly assigned 841 patients with COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or 2 (moderate) severity to receive a once-daily inhaled dose (18 μg) of tiotropium (419 patients) or matching placebo (422) for 2 years. The primary end point was the between-group difference in the change from baseline to 24 months in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use. Secondary end points included the between-group difference in the change from baseline to 24 months in the FEV_1 after bronchodilator use and the between-group difference in the annual decline in the FEV_1 before and after bronchodilator use from day 30 to month 24.
RESULTS: Of 841 patients who underwent randomization, 388 patients in the tiotropium group and 383 in the placebo group were included in the full analysis set. The FEV_1 in patients who received tiotropium was higher than in those who received placebo throughout the trial (ranges of mean differences, 127 to 169 ml before bronchodilator use and 71 to 133 ml after bronchodilator use; $P<0.001$ for all comparisons). There was no significant amelioration of the mean (±SE) annual decline in the FEV_1 before bronchodilator use: the decline was 38±6 ml per year in the tiotropium group and 53±6 ml per year in the placebo group (difference, 15 ml per year; 95% confidence interval [CI], -1 to 31; P=0.06). In contrast, the annual decline in the FEV_1 after bronchodilator use was significantly less in the tiotropium group than in the placebo group (29±5 ml per year vs. 51±6 ml per year; difference, 22 ml per year [95% CI, 6 to 37]; P=0.006). The incidence of adverse events was generally similar in the two groups.
CONCLUSIONS: Tiotropium resulted in a higher FEV1 than placebo at 24 months and ameliorated the annual decline in the FEV1 after bronchodilator use in patients with COPD of GOLD stage 1 or 2. (Funded by Boehringer Ingelheim and others; Tie-COPD ClinicalTrials.gov number, NCT01455129).
Zhou Y, Zhong NS, Li X, Chen S, Zheng J, Zhao D, Yao W, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017 Sep 7;377(10):923-935.

18. Physician assessment of COPD doesn't match spirometry results

Clinical question: How accurate are physician assessments of the severity of chronic obstructive pulmonary disease?
Study design: Cross-sectional
Setting: Outpatient (primary care)
Synopsis: The study included 899 patients with COPD who were randomly selected from the practices of 83 primary care physicians (63% family medicine docs and 37% general internists). The physicians had been in practice an average of 22 years and most had in-office spirometry available before this study. At one visit both the physician and the patient rated the patient's pulmonary disease severity at that time on a 5-point scale, ranging from 1 (no clinical symptoms or disease impact/mild symptoms) to 5 (very severe). Following this assessment the patient immediately underwent in-office spirometry, though only 75% were able to produce at least 1 high-quality result. Overall, there was poor correlation among physician assessment, patient assessment, and spirometry results. Physicians underestimated severity in 41% of patients and overestimated severity in 29% of patients using the spirometry results as the reference standard. Correlation wasn't much better with the patients' own estimates, with physicians underestimating severity in 42% of patients and overestimating severity in 18% as compared with those patients' self-assessments. Overall, physician ratings were accurate for only 30% of patients. More important, the physicians in this study recommended treatment changes for 37% of patients after reviewing spirometry results.
Bottom line: Using immediate, in-office spirometry results as the gold standard, seasoned physicians accurately identified chronic obstructive pulmonary disease (COPD) severity in approximately 1 in 3 patients, underestimating severity in 41% of patients and overestimating severity in 29% of patients. This mismatch seems to be important since the physicians participating in this study changed their treatment plans for 37% of patients after reviewing the spirometry results. A second issue in this study: Even though most of the physicians in the study had a spirometer in their office, they (or their staff) were unable to get usable spirometry results in 25% of their patients.
Mapel DW, Dalal AA, Johnson P, Becker L, Hunter AG. A clinical study of COPD severity assessment by primary care physicians and their patients compared with spirometry. Am J Med 2015;128(6):629-637.

19. Supplemental oxygen ineffective for COPD with moderate hypoxemia

Clinical question: Is long-term supplemental oxygen effective for patients with stable chronic obstructive pulmonary disease and moderate resting or exertional hypoxemia?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: Although there is good evidence that oxygen supplementation reduces mortality for patients with chronic obstructive pulmonary disease and severe resting hypoxemia, many patients are prescribed oxygen for moderate resting hypoxemia (a resting oxygen saturation of 89% to 93%) or moderate exertional hypoxemia (oxygen saturation of at least 80% for at least 5 minutes of a 6-minute walk test, but less than 90% for at least 10 seconds). Of the 738 patients in this study, 133 had moderate resting hypoxemia only, 319 had moderate exertional hypoxemia only, and 286 had both. Their mean age was 69 years, 73% were male, and their mean resting oxygen saturation on room air was 93%. Patients were randomized to receive oxygen supplementation or no oxygen supplementation. Of those randomized to receive oxygen supplementation, those with resting hypoxemia were told to use it 24 hours a day and those with exertional hypoxemia were told to use it during sleep and exercise. The "dose" was 2 liters of oxygen per minute, adjusted higher during exercise if necessary to maintain an oxygen saturation of at least 90%. Enrollment at the 42 participating centers was slow (it took 5 years). Patients were followed up for a median of 18 months (range 12 months to 6 years). Crossover rates were lower than expected: 12% to supplemental oxygen and 3% to no supplemental oxygen. Allocation was not concealed and the study was not masked, which would tend to bias in favor of the intervention. However, in the intention-to-treat analysis no difference was seen between groups with regard to death or first hospitalization; secondary outcomes, such as quality of life, psychological outcomes, and functional outcomes were also unaffected. There were 51 adverse events attributed to supplemental oxygen use, including 23 reports of tripping over equipment (2 that required hospitalization) and 5 reports of fires or burns (1 that required hospitalization).
Bottom line: In patients with moderate resting or exertional hypoxemia, supplemental oxygen does not reduce mortality or prevent hospitalizations. The groups were slightly imbalanced at the beginning of the study, with a lower BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index in the supplemental oxygen group, which is associated with lower mortality. However, this imbalance, as well as the failure to conceal allocation or mask the study, would bias the results in favor of supplemental oxygen, if bias occurred.
The Long Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med 2016;375(17):1617-1627.

20. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease improves outcomes

Background. Guidelines have provided positive recommendations for pulmonary rehabilitation after exacerbations of chronic obstructive pulmonary disease (COPD), but recent studies indicate that postexacerbation rehabilitation may not always be effective in patients with unstable COPD.
Objectives. To assess effects of pulmonary rehabilitation after COPD exacerbations on hospital admissions (primary outcome) and other patient-important outcomes (mortality, health-related quality of life (HRQL) and exercise capacity).
Search methods. We identified studies through searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PEDro (Physiotherapy Evidence Database) and the Cochrane Airways Review Group Register of Trials. Searches were current as of 20 October 2015, and handsearches were run up to 5 April 2016.
Selection criteria. Randomised controlled trials (RCTs) comparing pulmonary rehabilitation of any duration after exacerbation of COPD versus conventional care. Pulmonary rehabilitation programmes had to include at least physical exercise (endurance or strength exercise, or both). We did not apply a criterion for the minimum number of exercise sessions a rehabilitation programme had to offer to be included in the review. Control groups received conventional community care without rehabilitation.
Data collection and analysis. We expected substantial heterogeneity across trials in terms of how extensive rehabilitation programmes were (i.e. in terms of number of completed exercise sessions; type, intensity and supervision of exercise training; and patient education), duration of follow-up (< 3 months vs ≥ 3 months) and risk of bias (generation of random sequence, concealment of random allocation and blinding); therefore, we performed subgroup analyses that were defined before we carried them out. We used standard methods expected by Cochrane in preparing this update, and we used GRADE for assessing the quality of evidence.
Main results. For this update, we added 11 studies and included a total of 20 studies (1477 participants). Rehabilitation programmes showed great diversity in terms of exercise training (number of completed exercise sessions; type, intensity and supervision), patient education (from none to extensive self-management programmes) and how they were organised (within one setting, e.g. pulmonary rehabilitation, to across several settings, e.g. hospital, outpatient centre and home). In eight studies, participants completed extensive pulmonary rehabilitation, and in 12 studies, participants completed pulmonary rehabilitation ranging from not extensive to moderately extensive. Eight studies involving 810 participants contributed data on hospital readmissions. Moderate-quality evidence indicates that pulmonary rehabilitation reduced hospital readmissions (pooled odds ratio (OR) 0.44, 95% confidence interval (CI) 0.21 to 0.91), but results were heterogenous (I2 = 77%).

Extensiveness of rehabilitation programmes and risk of bias may offer an explanation for the heterogeneity, but subgroup analyses were not statistically significant (P values for subgroup effects were between 0.07 and 0.11). Six studies including 670 participants contributed data on mortality. The quality of evidence was low, and the meta-analysis did not show a statistically significant effect of rehabilitation on mortality (pooled OR 0.68, 95% CI 0.28 to 1.67). Again, results were heterogenous (I2 = 59%). Subgroup analyses showed statistically significant differences in subgroup effects between trials with more and less extensive rehabilitation programmes and between trials at low and high risk for bias, indicating possible explanations for the heterogeneity. Hospital readmissions and mortality studies newly included in this update showed, on average, significantly smaller effects of rehabilitation than were seen in earlier studies.

High-quality evidence suggests that pulmonary rehabilitation after an exacerbation improves health-related quality of life. The eight studies that used St George's Respiratory Questionnaire (SGRQ) reported a statistically significant effect on SGRQ total score, which was above the minimal important difference (MID) of four points (mean difference (MD) -7.80, 95% CI -12.12 to -3.47; I2 = 64%).

Investigators also noted statistically significant and important effects (greater than MID) for the impact and activities domains of the SGRQ. Effects were not statistically significant for the SGRQ symptoms domain.

Again, all of these analyses showed heterogeneity, but most studies showed positive effects of pulmonary rehabilitation, some studies showed large effects and others smaller but statistically significant effects. Trials at high risk of bias because of lack of concealment of random allocation showed statistically significantly larger effects on the SGRQ than trials at low risk of bias. High-quality evidence shows that six-minute walk distance (6MWD) improved, on average, by 62 meters (95% CI 38 to 86; I2 = 87%). Heterogeneity was driven particularly by differences between studies showing very large effects and studies showing smaller but statistically significant effects. For both health-related quality of life and exercise capacity, studies newly included in this update showed, on average, smaller effects of rehabilitation than were seen in earlier studies, but the overall results of this review have not changed to an important extent compared with results reported in the earlier version of this review.

Reference: *Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD005305. DOI: 10.1002/14651858.CD005305.pub4.*

21. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype may benefit from treatment with mepolizumab, a monoclonal antibody directed against interleukin-5.

METHODS: We performed two phase 3, randomized, placebo-controlled, double-blind, parallel-group trials comparing mepolizumab (100 mg in METREX, 100 or 300 mg in METREO) with placebo, given as a subcutaneous injection every 4 weeks for 52 weeks in patients with COPD who had a history of moderate or severe exacerbations while taking inhaled glucocorticoid-based triple maintenance therapy. In METREX, unselected patients in the modified intention-to-treat population with an eosinophilic phenotype were stratified according to blood eosinophil count (≥150 per cubic millimeter at screening or ≥300 per cubic millimeter during the previous year). In METREO, all patients had a blood eosinophil count of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter during the previous year. The primary end point was the annual rate of moderate or severe exacerbations. Safety was also assessed.

RESULTS: In METREX, the mean annual rate of moderate or severe exacerbations in the modified intention-to-treat population with an eosinophilic phenotype (462 patients) was 1.40 per year in the mepolizumab group versus 1.71 per year in the placebo group (rate ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.98; adjusted P=0.04); no significant between-group differences were found in the overall modified intention-to-treat population (836 patients) (rate ratio, 0.98; 95% CI, 0.85 to 1.12; adjusted P>0.99). In METREO, the mean annual rate of moderate or severe exacerbations was 1.19 per year in the 100-mg mepolizumab group, 1.27 per year in the 300-mg mepolizumab group, and 1.49 per year in the placebo group. The rate ratios for exacerbations in the 100-mg and 300-mg mepolizumab groups versus the placebo group were 0.80 (95% CI, 0.65 to 0.98; adjusted P=0.07) and 0.86 (95% CI, 0.70 to 1.05; adjusted P=0.14), respectively. A greater effect of mepolizumab, as compared with placebo, on the annual rate of moderate or severe exacerbations was found among patients with higher blood eosinophil counts at screening. The safety profile of mepolizumab was similar to that of placebo.

CONCLUSIONS: Mepolizumab at a dose of 100 mg was associated with a lower annual rate of moderate or severe exacerbations than placebo among patients with COPD and an eosinophilic phenotype. This finding suggests that eosinophilic airway inflammation contributes to COPD exacerbations. (Funded by GlaxoSmithKline; METREX and METREO ClinicalTrials.gov numbers, NCT02105948 and NCT02105961).

Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017 Oct 26;377(17):1613-1629.

Bottom Lines

1. Re-evaluate your asthma patients with spirometry. Many do not have asthma.
2. Dust mite impermeable mattress covers improve symptom control in children with asthma and dust mite sensitivity.
3. Consider using a single dose of dexamethasone in children and adults who have an asthma exacerbation requiring steroids.
4. Adding long acting beta agonists to inhaler corticosteroids appears to be safe and provides very modest benefit compared to the steroid alone for patients with asthma.
5. Supplemental oxygen does not prolong life or reduce hospitalizations in COPD patients with moderate hypoxia.
6. Pulmonary rehab improves outcomes for COPD patients.
7. Tiotropium may be useful in slowing the decline in lung function in COPD patients.
8. Physicians are not very accurate in predicting severity of COPD based on signs and symptoms.
9. Monoclonal antibody medications for asthma and COPD are proliferating, modestly effective and very expensive.

Acute Respiratory Tract Infections Mark H. Ebell MD, MS

Objectives

1. Summarize the latest evidence on sore throat, including use of steroids and ibuprofen lozenges.
2. Learn the latest information about more accurate diagnosis of bacterial sinusitis, mono, and pertussis.
3. Learn strategies for antibiotic stewardship

Sore throat

Here is a novel therapy that reduces sore throat pain.

1. POEM: Low-dose ibuprofen throat lozenge effective for sore throat pain

Clinical question: Is a 25-mg ibuprofen throat lozenge effective in reducing sore throat pain in adults?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (primary care)
Synopsis: Oral ibuprofen, 400 mg to 800 mg, is effective for sore throat pain, but the efficacy of a low-dose 25-mg ibuprofen throat lozenge was uncertain. These investigators identified adults, 18 years or older, who presented for an acute sore throat of 72 hours or less and a pain score on swallowing of at least 60 mm on a 0 to 100 mm visual analogue throat pain intensity scale. Eligible patients (N = 385) randomly received (uncertain allocation concealment) either ibuprofen 25 mg or matched placebo lozenge. Patients were instructed to suck one lozenge slowly until dissolution as needed for pain; up to six lozenges daily, with a minimal interval of at least 2 hours between lozenges. No other topical or systemic pain medications were allowed. Patients masked to treatment group assignment self-reported pain scores after every dose for up to 4 days. Complete follow-up occurred for 96.9% of patients for 4 days. Using intention-to-treat analysis, 33% and 50% pain-relief response rates up to 45 minutes after the first dose were significantly higher in the ibuprofen group than in the placebo group (number needed to treat = 8.0 and 11.5, respectively). Pain relief was also significantly higher for ibuprofen than placebo on the evening of the first day, but the differences in pain relief scores were no longer significant from day 2 onward.
Bottom line: Low-dose (25-mg) ibuprofen throat lozenges are more effective than placebo in reducing sore throat pain in adults for up to 24 hours.
Bouroubi A, Donazzolo Y, Donath F, et al. Pain relief of sore throat with a new anti-inflammatory throat lozenge, ibuprofen 25 mg: A randomised, double-blind, placebo-controlled, international phase III study. Int J Clin Pract 2017;71:e12961.

What about steroids? Some conflicting evidence from a positive Cochrane review and a large and less favorable randomized trial. Cochrane review including studies of varying quality, while trial excluded patients with most severe sore throat who are most likely to benefit.

2. POEM: Single-dose oral dexamethasone decreases sore throat pain (Cochrane review)

Clinical question: Do oral corticosteroids relieve pain in patients with acute sore throat?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: To determine whether an oral corticosteroid aids in symptom resolution, these researchers searched 4 databases, including Cochrane CENTRAL, trial registries, and reference lists of retrieved studies, and identified 10 studies of 1426 patients 5 years or older. Two reviewers independently selected the studies for inclusion and abstracted the data, selecting randomized controlled trials that compared 1 or 2 daily doses of corticosteroid with standard treatment or placebo in patients who presented to an emergency department or primary care office with clinical sore throat. Five studies evaluated oral dexamethasone and 3 studies evaluated a single intramuscular dose of dexamethasone, in addition to antibiotic treatment and analgesic treatment. Onset of pain relief was 4.8 hours faster with the steroid (7.4 vs 12.3 hours), with more than twice as many patients reporting complete resolution at 24 hours (relative risk 2.24; 95% CI 1.17 - 4.29). There was no demonstrated difference in days missed from school or work, and no difference in adverse effect rates between groups.
Bottom line: Sore throats are rarely fatal any more, but there is really no such thing as "just a sore throat." Whereas antibiotics have no analgesic activity, a single low-dose of a corticosteroid such as oral dexamethasone—0.6 mg per kg for children at least 5 years of age and up to 10 mg for adults—is effective in decreasing pain in the first 24 hours.
Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. BMJ 2017;Sep 20;358:j3887.

3. POEM: Dexamethasone may reduce sore throat symptoms in adults at 48 hours

Clinical question: Are oral steroids effective in the treatment of acute sore throat in adults?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)

Synopsis: These investigators identified adults, 18 years or older, who presented to primary care offices in England with acute symptoms of sore throat and odynophagia for which the treating clinician did not prescribe immediate antibiotic therapy. Exclusion criteria included the recent use of inhaled or oral corticosteroids, recent adenotonsillectomy, recent use of antibiotics, or a clear alternative diagnosis such as pneumonia. Eligible participants (N = 565) randomly received (concealed allocation assignment) a single dose of dexamethasone (10 mg) or matching placebo. Treating clinicians could decide to offer no antibiotics (n = 349) or a delayed antibiotic (n = 227). Patients unaware of group assignment self-assessed outcomes including the primary outcome of complete resolution of sore throat symptoms at 24 hours. Secondary exploratory outcomes included complete resolution of sore throat at 48 hours, duration of moderately bad symptoms, time to onset of pain relief and time to complete resolution of symptoms, consumption of delayed antibiotic prescription, time missed from work or education, attendance at or telephone contact with any heath care facility because of the sore throat, and use of over-the-counter medications and/or other prescription medications in the first 7 days. Complete follow-up occurred for 94% of participants at 1 month. Using intention-to-treat analysis, no significant difference occurred among the steroid group and the placebo group in achieving complete resolution of symptoms at 24 hours. Results were similar between patients who were and were not offered a delayed antibiotic prescription. At 48 hours significantly more participants who received dexamethasone reported complete resolution of symptoms compared with those who received the placebo (35.4% vs 27.1%, respectively; NNT = 12; 7 - 146). Neither severity of sore throat at baseline nor a positive throat culture for Streptococcus bacteria on throat swab were related to group differences. No significant differences occurred between the treatment group and the placebo group in other secondary outcomes or serious adverse events.
Bottom line: A single dose of oral dexamethasone is no more effective than placebo in resolving acute sore throat symptoms at 24 hours in adults who do not receive immediate antibiotic therapy. However, among a multitude of exploratory secondary outcomes, the authors found that dexamethasone compared with placebo did increase the proportion of patients with symptom resolution at 48 hours (number needed to treat [NNT] = 12; 95% CI 7 - 146).
Hayward GN, Hay AD, Moore MV, et al. Effect of oral dexamethasone without immediate antibiotics vs placebo on acute sore throat in adults. A randomized clinical trial. JAMA 2017;317(15):1535-1543.

No need for back-up throat cultures, and signs and symptoms aren't a lot of help with infectious mono.

4. POEM: Back-up culture not needed for negative rapid strep test results

Clinical question: Do negative "rapid strep" test results need to be confirmed by culture?
Study design: Meta-analysis (other)
Setting: Various (meta-analysis)
Synopsis: The investigators searched MEDLINE and EMBASE to identify 48 studies that compared rapid antigen tests for group A streptococcus with throat culture, the gold standard. They limited their search to English-language studies, but searched bibliographies of identified studies and previous reviews. Two investigators assessed all studies for quality. Studies were performed throughout the world and used 6 different testing methods (latex agglutination, ELISA, and so forth). Overall, the sensitivity of all rapid antigen tests was 86% (95% CI 83% - 88%) and specificity was 96% (94% - 97%). Results were similar when limited to studies performed in children. Molecular techniques (DNA probes, polymerase chain reaction methods) were slightly better, though these tests have a turnaround time of 1 hour to 3 hours.
Bottom line: Although rheumatic heart disease due to group A streptococcal infection has all but disappeared in wealthy countries (Lancet 2012;379:953-964), some countries still go to great lengths to test for Streptococcal throat infections -- I'm talking to you, United States. As a result, we spend more than $8 million per each additional case of rheumatic heart disease prevented (Prev Med 2002;35(3):250 -257).This meta-analysis found that the rapid antigen tests widely in use are very effective in both identifying and excluding strep. Overall, the sensitivity of these tests is 86% and specificity is 96%, both overall and in children. The authors of this analysis argue that this sensitivity is high enough -- and the likelihood of rheumatic heart disease is low enough -- to drop the long-held practice of confirming negative antigen test results with culture. Maybe one day we'll retire strep testing; until then, maybe we can get rid of cultures. Show this paper to your local micro lab director.
Lean WL, Arnup S, Canchin M, Steer AC. Rapid diagnostic tests for group A streptococcal pharyngitis: a meta-analysis. Pediatrics 2014;134(4);771-781.

5. POEM: Accurate signs, symptoms, and labs for diagnosing mononucleosis

Clinical question: Are there accurate signs, symptoms, and laboratory data for diagnosing infectious mononucleosis?
Study design: Diagnostic test evaluation
Setting: Population-based
Synopsis: These investigators systematically searched multiple sources including the Database of Abstracts of Review of Effectiveness, PubMed, EMBASE and bibliographies of relevant studies reporting data on the accuracy of symptoms, signs, and laboratory studies among patients with either a sore throat or who underwent testing for infectious mononucleosis. Inclusion criteria were consecutive enrollment or a convenience sample (no case-control studies); sufficient data to calculate sensitivity, specificity, and likelihood ratios; and a comparison of the index test with an adequate reference standard (eg, Epstein-Barr virus immunoglobulin test or heterophile antibody test). At least 2 individuals reviewed each study for inclusion and quality using a standard diagnostic studies scoring tool. Any discrepancies were resolved if needed by discussion with a third author. Three studies (n = 1388) included patients prospectively presenting with a sore throat, 3 retrospective studies (n = 2088) used laboratory data for patients suspected of mononucleosis, and 5 case series studies (n = 1293) enrolled patients with serologically confirmed mononucleosis. The absence of sore throat or headache (negative likelihood ratio [LR-] ranges = 0.51 - 0.62 and 0.63 - 0.73, respectively) were the most useful symptoms to reduce the likelihood of mononucleosis. Useful clinical signs for increasing the likelihood of the diagnosis included the presence of palatine petechiae (positive likelihood ratio [LR+] = 5.3; 95% CI 2.1-13), posterior cervical adenopathy (LR+ = 3.1; 1.6-5.9), and axillary or inguinal adenopathy (LR+ range = 3.0 - 3.1). The absence of any lymphadenopathy was most useful for reducing the

likelihood of mononucleosis (LR- range = 0.23 - 0.44). Splenomegaly occurred in 7% to 53% of patients with mononucleosis (LR+ range = 1.9 - 6.6). Useful laboratory data included the presence of atypical lymphocytosis greater than or equal to 10% (LR+ = 11), with increasing likelihood with a greater percentage of atypical lymphocytes (LR+ = 26 for at least 20%, and LR+ = 50 for at least 40%). The presence of monocytosis also increased the likelihood of mononucleosis (LR+ range = 2.9 -14). The likelihood of mononucleosis was decreased with the presence of less than 10% atypical lymphocytes (LR- = 0.37; 0.26-0.51) and less than 35% lymphocytes overall (LR- = 0.22; 0.18-0.27).
Bottom line: Symptoms that reduce the likelihood of infectious mononucleosis include the absence of sore throat or headache. Clinical findings that increase the likelihood of infectious mononucleosis include palatine petechiae; splenomegaly; and posterior cervical, axillary, or inguinal adenopathy. Laboratory data that increase the likelihood of the diagnosis include an increasing percentage of lymphocytes with atypical lymphocytosis and monocytosis.
Ebell MH, Call M, Shinholser J, Gardner J. Does this patient have infectious mononucleosis? The rational clinical examination systematic review. JAMA 2016;315(14):1502-1509

Most useful are posterior cervical, axillary, or inguinal adenopahy (LR+ 3) and either lymphocytosis and/or atypical lymphocytosis (LR 11 to 50).

Sinusitis

Here is a clinical decision rule (Ebell. Ann Fam Med 2017; 15(4)), although it requires CRP. Another simple rule of thumb from the same study is that the risk of bacterial infection is low in patients with no unilateral maxillary sinus tenderness and no maxillary toothache.

CT as Reference Standard			Bacterial culture as reference standard	
Finding	**Points**		**Finding**	**Points**
Preceding upper RTI	2		Preceding upper RTI	1
Previous sinus infection	-2		Previous sinus infection	-1
Tender maxillary sinus (unilateral)	2		Tender maxillary sinus (unilateral)	2
Anosmia	1		Maxillary toothache	2
CRP > 15 mg/L	4		Purulent nasal discharge	1
			CRP > 15 mg/L	2
Total:				

CT as Reference Standard			Bacterial culture as reference standard	
Finding	**Points**		**Finding**	**Points**
Low risk (-2 to 1)	13/42 (31%)		Low risk (-1 to 3)	13/77 (17%)
Mod risk (2 to 4)	42/60 (70%)		Mod risk (4 to 6)	33/74 (44%)
High risk (5 to 9)	65/73 (89%)		High risk (7 to 8)	15/23 (65%)

Is there any role for radiographs and ultrasound? They are actually reasonably sensitive (80% to 90%) so may be helpful in ruling out. But overall, not recommended and lots of false positives. Some promising approaches include point of care CRP and using a urine dipstick to test the snot for blood and leukocyte (one unvalidated study).

6. POEM: Tests not very helpful in diagnosing acute rhinosinusitis

Clinical question: How useful are diagnostic tests in evaluating patients with suspected acute rhinosinusitis?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: The authors (one of whom is a POET) performed a limited systematic review; they searched MEDLINE then supplemented the search by looking at the reference lists of previous meta-analyses, review articles, and guidelines. They included studies that compared at least one diagnostic modality (blood tests, imaging) for patients with suspected acute rhinosinusitis against one of several possible reference standards: radiography, ultrasound, computed tomography, magnetic resonance imaging, or the findings on antral puncture. Two authors independently evaluated each candidate article for inclusion, extracted data, and assessed the quality of each included study. They resolved discrepancies through consensus. The main limitation of the authors' methods is their acceptance of low-quality reference standards. (I assume they were being generous because they knew overall study quality was low; if they were too rigorous they might not have been able to get their paper published.) Antral puncture is probably the best reference standard, although most of our patients with colds would not like to go through this! The authors included 30 studies, 16 of which enrolled adults only, 8 enrolled adults and children, and 4 enrolled children only (2 studies didn't mention the age of the patients). Only 4 of the studies were at low risk of bias. Eleven studies used antral puncture as the gold standard. The overall prevalence of acute rhinosinusitis ranged from 41% to 49%. Although the authors pooled the data and calculated the diagnostic accuracy of various diagnostic modalities, these

calculations are likely to be biased and unreliable. The authors make an interesting suggestion to to assign low-, medium-, and high-risk thresholds based on the results of erythrocyte sedimentation rates or C-reactive protein levels that can be factored into a risk stratification tool, but this suggestion is based on low-quality evidence and should be independently validated.
Bottom line: The research on diagnostic tests is generally poor and often compares various tests against low-quality reference standards. We need better research!
Ebell MH, McKay B, Guilbault R, Ermias Y. Diagnosis of acute rhinosinusitis in primary care: a systematic review of test accuracy. Br J Gen Pract 2016;66(650):e612-632.

7. Cochrane: Antibiotics for acute maxillary sinusitis in adults

Background: Sinusitis is one of the most common diagnoses among adults in ambulatory care, accounting for 15% to 21% of all adult outpatient antibiotic prescriptions. However, the role of antibiotics for sinusitis is controversial.
Objectives: To assess the effects of antibiotics in adults with acute maxillary sinusitis by comparing antibiotics with placebo, antibiotics from different classes and the side effects of different treatments.
Search methods: We searched CENTRAL 2013, Issue 2, MEDLINE (1946 to March week 3, 2013), EMBASE (1974 to March 2013), SIGLE (OpenSIGLE, later OpenGrey (accessed 15 January 2013)), reference lists of the identified trials and systematic reviews of placebo-controlled studies. We also searched for ongoing trials via ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). We imposed no language or publication restrictions.
Selection criteria: Randomised controlled trials (RCTs) comparing antibiotics with placebo or antibiotics from different classes for acute maxillary sinusitis in adults. We included trials with clinically diagnosed acute sinusitis, confirmed or not by imaging or bacterial culture.
Data collection and analysis: Two review authors independently screened search results, extracted data and assessed trial quality. We calculated risk ratios (RRs) for differences between intervention and control groups in whether the treatment failed or not. All measures are presented with 95% confidence intervals (CIs). We conducted the meta-analyses using either the fixed-effect or random-effects model. In meta-analyses of the placebo-controlled studies, we combined data across antibiotic classes. Primary outcomes were clinical failure rates at 7 to 15 days and 16 to 60 days follow-up. We used GRADEpro to assess the quality of the evidence.
Main results: We included 63 studies in this updated review; nine placebo-controlled studies involving 1915 participants (seven of the studies clearly conducted in primary care settings) and 54 studies comparing different classes of antibiotics (10 different comparisons). Five studies at low risk of bias comparing penicillin or amoxicillin to placebo provided information on the main outcome: clinical failure rate at 7 to 15 days follow-up, defined as a lack of full recovery or improvement, for participants with symptoms lasting at least seven days. In these studies antibiotics decreased the risk of clinical failure (pooled RR of 0.66, 95% CI 0.47 to 0.94, 1084 participants randomised, 1058 evaluated, moderate quality evidence). However, the clinical benefit was small. Cure or improvement rates were high in both the placebo group (86%) and the antibiotic group (91%) in these five studies. When clinical failure was defined as a lack of full recovery (n = five studies), results were similar: antibiotics decreased the risk of failure (pooled RR of 0.73, 95% CI 0.63 to 0.85, high quality evidence) at 7 to 15 days follow-up. Adverse effects in seven of the nine placebo-controlled studies (comparing penicillin, amoxicillin, azithromycin or moxicillin to placebo) were more common in antibiotic than in placebo groups (median of difference between groups 10.5%, range 2% to 23%). However, drop-outs due to adverse effects were rare in both groups: 1.5% in antibiotic groups and 1% in control groups. In the 10 head-to-head comparisons, none of the antibiotic preparations were superior to another. However, amoxicillin-clavulanate had significantly more drop-outs due to adverse effects than cephalosporins and macrolides.
Author's Conclusions: There is moderate evidence that antibiotics provide a small benefit in immunocompetent primary care patients with uncomplicated acute sinusitis. However, about 80% of participants treated without antibiotics improved within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population levels.
Reference: Ahovuo-Saloranta A, Rautakorpi U, Borisenko OV, Liira H, Williams Jr JW, Mäkelä M. Antibiotics for acute maxillary sinusitis in adults. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD000243. DOI: 10.1002/14651858.CD000243.pub4.

Cough, chest cold, and "acute bronchitis"

Among outpatients with cough for more than a week or two, about 12% in primary care and 18% of children had pertussis. In patients with community acquired pneumonia, about 10% had mycoplasma and 3% legionella (Marchello C. Ann Fam Med 2016;14:552– 66). As with mono, clinical diagnosis of pertussis is of limited value. The most valuable "test"? Your gut (LR+ 3.3, LR- 0.63).

8. POEM: Typical signs and symptoms minimally effective for the diagnosis of pertussis infection

Clinical question: Are the typical signs and/or symptoms useful to accurately diagnose Bordetella pertussis infections in children and adults?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: Pertussis is much more common than many clinicians realize, with an overall prevalence of 12.4% (1 in 8) and 18% (1 in 5.5) among adults and children, respectively, with prolonged cough (greater than one week) seen in primary care settings. These investigators, including that Georgian Demon, thoroughly searched MEDLINE and reference lists of pertinent studies for prospective cohort studies of patients presenting with acute cough, prolonged cough, or clinically suspected pertussis. Inclusion criteria included the use of an acceptable reference test on all patients (e.g. PCR, culture, or serology). No restrictions applied to language, age, or immunization status. Two investigators independently evaluated all studies for inclusion criteria and methodologic quality using standard scoring tools. Discrepancies were resolved by consensus discussion with a third investigator. Studies using only single, non-

paired, serology were considered to have a high risk of bias. A total of 22 studies (n=15,909) met inclusion criteria, including 14 judged at low risk, 4 at moderate risk, and 4 at high risk of bias. The overall clinical assessment by the evaluating clinician was most useful at ruling in pertussis (LR+ = 3.3; LR- = 0.63). Other typical symptoms including whooping cough, posttussive vomiting, paroxysmal cough, sputum, and disturbed sleep all had likelihood ratios of minimal, if any, diagnostic value (between 2.1 and 0.58). In children, whooping cough was more accurate for diagnosing pertussis than in adults (LR+ = 2.9 vs 1.9, respectively).
Bottom line: Bordetella pertussis (BP) is often the cause of cough lasting longer than 1 week in primary care settings. The overall clinical assessment by the evaluating clinician is most useful for accurately diagnosing BP infection. Other individual symptoms, including whooping cough, posttussive vomiting, and paroxysmal cough, are minimally, if at all, accurate for diagnosing BP.
Ebell MH, Marchello C, Callahan M. Clinical diagnosis of Bordetella pertussis infection: A systematic review. J Am Board Fam Med 2017;30(3):308-319.

What about steroids for patients with LRTI who do not have asthma? Don't you wish it worked and was safe?

9. POEM: Oral steroids not helpful for acute lower respiratory tract infection in nonasthmatic adults

Clinical question: Are steroids useful in the treatment of acute lower respiratory tract infection in adults without asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: Because symptoms of acute LRTI can mimic those of exacerbated asthma, steroids are commonly prescribed with or without antibiotics. These investigators enrolled adults, 18 years or older, presenting with an acute cough (lasting 28 days or less) as the main symptom and at least 1 other lower respiratory tract symptom (eg, phlegm, chest pain, wheezing, or shortness of breath). Exclusion criteria included evidence of chronic pulmonary disease, having received any asthma medication in the previous 5 years, or requiring same day hospitalization or urgent antibiotic treatment. Patients (N = 401) randomly received (concealed allocation assignment) either 40 mg prednisolone daily for 5 days or matched placebo. Those patients also receiving a nonurgent antibiotic prescription were asked to delay filling the prescription for at least 48 hours. Patients assessed outcomes using symptom diaries and remained masked to their treatment group assignment. Symptoms were measured daily, including twice-daily peak expiratory flow, for 28 days or until symptom resolution. Complete follow-up occurred for 94% of patients at 28 days. Using intention-treat analysis, no clinically significant group differences occurred in the median duration of cough or severity of symptoms, symptom duration, antibiotic use, peak flow, or patient satisfaction. There were also no significant subgroup effect differences (ie, smoking, wheezing, chest pain, or shortness of breath).
Bottom line: This study found no clinically significant benefit of steroids for the treatment of acute lower respiratory tract infection (LRTI) in adults without asthma, including those presenting with wheezing or shortness of breath.
Hay AD, Little P, Harnden A, et al. Effect of oral prednisolone on symptom duration and severity in nonasthmatic adults with acute lower respiratory tract infection. A randomized clinical trial. JAMA 2017;318(8):721-730.

So let's STOP giving steroids to everyone. They are appropriate with a history of asthma or COPD, but not for everyone who is coughing!

10. Cochrane: Antibiotics for acute bronchitis

Background: The benefits and risks of antibiotics for acute bronchitis remain unclear despite it being one of the most common illnesses seen in primary care.
Objectives: To assess the effects of antibiotics in improving outcomes and to assess adverse effects of antibiotic therapy for people with a clinical diagnosis of acute bronchitis.
Search methods: We searched CENTRAL 2016, Issue 11 (accessed 13 January 2017), MEDLINE (1966 to January week 1, 2017), Embase (1974 to 13 January 2017), and LILACS (1982 to 13 January 2017). We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 5 April 2017.
Selection criteria: Randomised controlled trials comparing any antibiotic therapy with placebo or no treatment in acute bronchitis or acute productive cough, in people without underlying pulmonary disease.
Data collection and analysis: At least two review authors extracted data and assessed trial quality.
Main results: We did not identify any new trials for inclusion in this 2017 update. We included 17 trials with 5099 participants in the primary analysis. The quality of trials was generally good. At follow-up there was no difference in participants described as being clinically improved between the antibiotic and placebo groups (11 studies with 3841 participants, risk ratio (RR) 1.07, 95% confidence interval (CI) 0.99 to 1.15). Participants given antibiotics were less likely to have a cough (4 studies with 275 participants, RR 0.64, 95% CI 0.49 to 0.85; number needed to treat for an additional beneficial outcome (NNTB) 6) and a night cough (4 studies with 538 participants, RR 0.67, 95% CI 0.54 to 0.83; NNTB 7). Participants given antibiotics had a shorter mean cough duration (7 studies with 2776 participants, mean difference (MD) -0.46 days, 95% CI -0.87 to -0.04). The differences in presence of a productive cough at follow-up and MD of productive cough did not reach statistical significance.
Antibiotic-treated participants were more likely to be improved according to clinician's global assessment (6 studies with 891 participants, RR 0.61, 95% CI 0.48 to 0.79; NNTB 11) and were less likely to have an abnormal lung exam (5 studies with 613 participants, RR 0.54, 95% CI 0.41 to 0.70; NNTB 6). Antibiotic-treated participants also had a reduction in days feeling ill (5 studies with 809 participants, MD -0.64 days, 95% CI -1.16 to -0.13) and days with impaired activity (6 studies with 767 participants, MD -0.49 days, 95% CI -0.94 to -0.04). The differences in proportions with activity limitations at follow-up did not reach statistical significance. There was a significant trend towards an increase in adverse effects in the antibiotic group (12 studies with 3496 participants, RR 1.20, 95% CI 1.05 to 1.36; NNT for an additional harmful outcome 24).

Authors' conclusions: There is limited evidence of clinical benefit to support the use of antibiotics in acute bronchitis. Antibiotics may have a modest beneficial effect in some patients such as frail, elderly people with multimorbidity who may not have been included in trials to date. However, the magnitude of this benefit needs to be considered in the broader context of potential side effects, medicalisation for a self limiting condition, increased resistance to respiratory pathogens, and cost of antibiotic treatment.
Reference: Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD000245. DOI: 10.1002/14651858.CD000245.pub4.

Recurrent respiratory infections

So how helpful are these (very) expensive new drugs for patients with asthma?

11. POEM: Omalizumab decreases respiratory viral infections in children with allergic asthma (PROSE)

Clinical question: Does omalizumab decrease respiratory viral infections in children with allergic asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: The Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study members randomized children from low-income cities to receive guideline-based asthma care plus placebo (n = 89) or add-on omalizumab (n = 348). The children were aged 6 to 17 years, had allergic asthma for at least one year, and had at least one exacerbation that required systemic corticosteroids or hospitalization within the preceding 19 months. The researchers administered omalizumab every 2 to 4 weeks according to the children's weight and IgE level. Every week for 90 days, the researchers collected nasal mucous samples to test for respiratory virus shedding. Additionally, the children and caregivers kept respiratory symptom diaries. The researchers enrolled the children in autumn to maximize the potential to be exposed to and develop respiratory infections. Slightly more than half of these little germ factories were already shedding viruses at the end of the first week! In addition to reporting that the omalizumab group had one fewer day of virus shedding than the control group and 0.4 fewer log units of peak shedding (who cares?), the researchers report that omalizumab decreased the frequency of illnesses (34% vs 58%; number needed to treat [NNT] = 5) and the frequency of viral illnesses AND overall illnesses (63% vs 71%; NNT = 13), but had no effect on the duration of symptomatic illness. The authors don't report on the adverse effects of omalizumab.
Bottom line: In children with allergic asthma, omalizumab (Xolair) decreases the frequency of symptomatic respiratory illnesses, but not their duration. It is expensive, however, and the authors don't report on its adverse effects or on how many asthma exacerbations or hospitalizations are prevented.
Esquivel A, Busse WW, Calatroni A, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. Am J Respir Crit Care Med 2017;196(8):985-992.

By the way, it costs $1100/month. To quote Senator Joseph Welch: “Sir, have you no sense of decency?” Giving parents azithromycin and having them give it at the first sign of lower RTI in kids with recurrent respiratory infections:

12. POEM: Early azithromycin prevents severe lower RTI in children with recurrent WARIs

Clinical question: Does early treatment with azithromycin prevent recurrent severe respiratory inflections in children with recurrent wheezing-associated respiratory illnesses?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: Many preschool children develop multiple episodes of WARI, with some episodes progressing to severe infections requiring systemic steroids and antibiotics. These investigators identified children, aged 12 months through 71 months, with recurrent severe wheezing in the context of lower RTIs who required systemic steroids, unscheduled clinic or urgent care visits, emergency department visits, or hospitalization. Exclusion criteria included more than 4 courses of steroids or more than 1 hospitalization in the past 12 months, or the use of long-term controllers for asthma for more than 8 months. Eligible patients (N = 607) randomly received (concealed allocation assignment) either oral azithromycin, 12 mg/kg once daily for 5 days, or matching placebo beginning as soon as parents or guardians noted the symptoms or signs of an RTI. Outcome assessors remained masked to treatment group assignment. Follow-up continued either for a total of 78 weeks, until an individual patient used the study treatment for a maximum of 4 treated RTIs not progressing to severe lower RTIs, or until early termination status was achieved (any child developing severe symptoms requiring emergent/urgent care prior to or on the same day as initiating study medication). Of the 607 children who initially underwent randomization, 164 did not experience a treated RTI. Early termination occurred for 109 participants and 105 withdrew for other reasons or were lost to follow-up. Therefore, complete data were available for 65% of study participants. Treatment occurred for a total of 937 RTIs (azithromycin group, 473; placebo group, 464) resulting in 92 severe lower RTIs (azithromycin group, 35; placebo group, 57). The risk of progressing to severe lower RTI occurred significantly less often in the azithromycin group than in the placebo group (hazard ratio = 0.64; 95% CI 0.41-0.98), with increasing benefit of active treatment in proportion to the number of RTIs experienced (numbers needed to treat for 1 RTI = 33, for 2 RTIs = 14, for 3 RTIs = 10, and for 4 RTIs = 7). However, no significant group differences occurred in the need for urgent care and emergency department visits or hospitalizations, nor in the risk of subsequent RTIs.
Bottom line: Early treatment with azithromycin (Zithromax) at the first signs or symptoms of a respiratory tract infection (RTI) in children with a history of recurrent wheezing-associated respiratory illnesses (WARIs) reduces the risk of a subsequent severe lower RTI. This study did not, however, find a significant effect of early azithromycin treatment on preventing subsequent urgent/emergent care or hospitalization.
Bacharier LB, Guilbert TW, Mauger DT, et al, for the National Heart, Lung, and Blood Institute's AsthmaNet. Early administration of

azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with history of such illnesses. A randomized clinical trial. JAMA 2015;314(19):2034-2044.

Antibiotic stewardship

We've been recommending delayed antibiotic prescriptions for a while now. Do they cause any harms, though? Turns out patients don't mind, and it might even reduce re-consultation.

13. POEM: Delayed Rx for respiratory infections produces similar results and satisfaction as immediate treatment

Clinical question: In patients with respiratory tract infections (bronchitis, sinusitis, pharyngitis), is a delayed prescription strategy as effective as immediate treatment and as accepted by patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: These researchers evaluated 398 adults with acute, uncomplicated respiratory infections from 23 primary care centers in Spain. The patients had acute pharyngitis (46%), acute bronchitis (32%), rhinosinusitis (20%), or exacerbation of mild-to-moderate chronic obstructive pulmonary disease (2%). The physicians had "reasonable doubt as to whether to treat with an antibiotic." Patients were, on average, on the younger side (mid-40s), half were smokers or former smokers, almost no patients (< 2%) were febrile, and they reported mild to moderate symptoms for an average of 6 days. Patients were randomized, using concealed allocation, to 1 of 4 potential prescription strategies. One group was given an antibiotic to begin at once; 2 groups were given a delayed prescription, either a "take and hold prescription" or a "come back and pick up, if necessary prescription"; and the final group was not given any prescription. The average duration of symptoms was significantly longer in patients not given a prescription as compared with patients given an immediate antibiotic, with the duration in patients given delayed prescriptions somewhere in between but not significantly different from the immediate prescription. The duration of moderate or severe symptoms was lessened significantly with immediate treatment as compared with delayed prescriptions, but the average difference in duration was 0.5 day to 1.0 day. Patients in the delayed prescription groups experienced fewer days absent from work or unable to do their daily activities. Patient satisfaction was similar across all groups. Prescription use was decreased by two-thirds with the delayed prescription approaches.
Bottom line: In almost 400 Spanish primary care patients with mild to moderate symptoms of respiratory infection of less than 1 week's duration, both a "take-and-hold" prescription and a "come back and pick up, if necessary" prescription produced a similar clinical response -- and similar patient satisfaction score -- as immediate antibiotic treatment, while decreasing overall antibiotic use. Other studies of this patient population have shown that patients prefer the security of a prescription, delayed or not, over withholding antibiotic treatment. The effect of legitimizing an illness by awarding a prescription should not be underestimated.
de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, et al, for the Delayed Antibiotic Prescription (DAP) Group. Prescription strategies in acute uncomplicated respiratory infections. A randomized clinical trial. JAMA Intern Med 2016;176(1):21-29.

14. POEM: Delayed antibiotic prescription for new-onset cough associated with decreased re-consultation

Clinical question: In adults with lower respiratory tract infection, what is the effect of different antibiotic prescribing strategies?
Study design: Cohort (prospective)
Setting: Outpatient (primary care)
Synopsis: This study included adult patients seen in United Kingdom primary care offices who had acute cough for 3 weeks or less that was judged by their physician to be due to infection. Follow-up was 99.6% of patients. Of the 28,779 patients not immediately referred for hospitalization or radiographic investigation, 25.5% were not treated with an antibiotic, 61.3% received a prescription for an antibiotic, and 13.3% received a prescription for delayed antibiotic (average advised delay was 3 days). This was not a randomized study and physicians were selective in their use of antibiotics, prescribing immediate antibiotic for patients who were older; had major comorbidities; reported more shortness of breath, fever, or purulent sputum; or had low oxygen saturation, higher severity, and crackles or wheeze. Subsequently, hospitalization or death occurred in 0.3% after no antibiotic, 0.9% after immediate antibiotic treatment, and 0.4% after delayed antibiotic (no statistically significant difference). Follow-up visits were common in all groups but were significantly reduced by delayed antibiotic treatment (14.1% with delayed antibiotic vs 19.7% with no antibiotic and 25.3% with immediate antibiotic).
Bottom line: Delayed antibiotic treatment (that is, giving a prescription with a suggestion to fill it only if symptoms are still present after 3 days) was associated with decreased revisits by adults with new-onset cough deemed to be infective. Neither immediate nor delayed antibiotic treatment altered hospitalization rates, but this lack of difference might be due to appropriately selective prescribing of antibiotics to more at-risk patients. In this study, 1 in 4 patients were not prescribed antibiotic treatment and they fared as well as the patients who received a prescription.
Little P, Stuart B, Smith S, et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. BMJ 2017;357:j2148.

The next study looked at 3 interventions: an automated alternative treatment suggestions when providers attempted to prescribe antibiotics for antibiotic-inappropriate diagnoses; requiring providers to text an "antibiotic justification note" that became a permanent part of the medical record; or distributing periodic emails to participating providers labeling them as either a "top performer" or "not a top performer" by comparing their antibiotic prescribing behavior with their peers'.

15. POEM: Behavioral interventions reduce inappropriate antibiotic prescribing for acute RTIs

Clinical question: Do behavioral interventions reduce rates of inappropriate antibiotic prescribing for acute respiratory tract infections in primary care?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: Clinical guidelines encourage avoiding antibiotics for infections when treatment is of minimal, if any, benefit. However, inappropriate antibiotic prescribing for acute respiratory tract infections persists. These investigators invited 49 practices in Massachusetts and California (N = 243 clinicians) to receive various combinations of behavioral interventions aimed at reducing inappropriate antibiotic prescribing. The first intervention used automated alternative treatment suggestions when providers attempted to prescribe antibiotics for antibiotic-inappropriate diagnoses. A second intervention required providers to text an "antibiotic justification note" that became a permanent part of the medical record. The third intervention distributed periodic emails to participating providers labeling them as either a "top performer" or "not a top performer" by comparing their antibiotic prescribing behavior with their peers'. Providers included internists (60%), nurse practitioners/physician assistants (19%), and family physicians (13%). The study excluded patients with chronic medical conditions that necessitate more frequent antibiotic prescriptions for acute respiratory tract infections (eg, emphysema). Practices were randomized to receive 0, 1, 2, or all 3 interventions for 18 months and no cases were lost to follow-up. Not surprisingly, the control group significantly decreased inappropriate antibiotic prescribing rates (11% absolute reduction) during the study period. This is known as the Hawthorne effect: changing your behavior simply because you know you're being observed. Both the accountable justification and peer comparison interventions significantly decreased antibiotic prescribing rates compared with the control group (-7.0% and -5.2%, respectively). However, the suggested alternatives intervention did not significantly reduce antibiotic prescribing rates compared with control. The latter result is disheartening but consistent with prior findings about influencing clinical decision making: Information alone rarely changes behavior. The most powerful influence continues to be peer pressure and the desire to conform. Please attribute the authorship of this POEM to Patrick L. Turner, MD, Fellow, Department of Family Medicine, The University of Virginia, Charlottesville, VA.
Bottom line: Requiring clinicians to justify antibiotic prescribing in the permanent electronic health record and to undergo periodic peer comparisons of prescribing rates are both effective interventions for reducing inappropriate antibiotic prescribing for acute respiratory tract infections. Helpful reminders and suggested treatment alternatives do not reduce inappropriate prescribing rates. Information alone rarely changes behavior, but the desire to conform with our peers can be very persuasive.
Meeker D, Linder JA, Fox CR, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices. JAMA 2016;315(6):562-570.

Take Home Points

1. New therapies such as anti-inflammatory lozenges and sprays may be helpful for sore throat
2. Dexamethasone is of limited benefit, if any, for sore throat.
3. Diagnosing acute bacterial rhinosinusitis is hard.
4. Steroids do nothing for acute bronchitis in patients without asthma, and antibiotics do almost nothing (and have harms).
5. Behavioral interventions and delayed prescriptions can reduce antibiotic use for RTI.

Musculoskeletal: Backs and Knees

John Hickner, MD, MSc

Objectives

1. Discuss the findings of recent studies of the effectiveness or lack of effectiveness for treatments of knee osteoarthritis and low back pain

Low Back Pain

I thought there was nothing more to say about low back pain. I was wrong. Here are some new studies that may help you manage patients with back pain.

1. Diazepam adds little to NSAID treatment for acute low back pain

Clinical question: In patients with acute low back pain, does the addition of diazepam to analgesic treatment improve symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Emergency department
Synopsis: These authors enrolled 114 patients who presented to an emergency department with uncomplicated low back pain that lasted less than 2 weeks and had a score of at least 5 (median = 18) on the Roland-Morris Low Back Pain and Disability Questionnaire. The 24-item disability questionnaire asked patients about daily activities that would be limited by back pain. The patients were randomized, allocation concealment uncertain, to receive naproxen 500 mg twice daily as needed for 1 week with either placebo or diazepam 5 mg, 1 or 2 tablets every 12 hours, as needed. Scores at 1 week by telephone interview had improved by an average 11 points on the disability scale in both groups. Moderate to severe pain was still reported in 32% of patients in the diazepam group and 22% of patients in the placebo group (P = NS) at 7 days. Other outcomes—length of time to return to work, desire to seek additional treatment, or desire to take the prescribed medicine (diazepam or placebo) again—were also not different. The study had 80% power to find a difference in scores of at least 5.
Bottom line: Diazepam (Valium) added to naproxen does not improve disability or pain scores in patients with acute low back pain more than naproxen alone. The dose was standard and most patients had significant relief regardless of whether they took diazepam or placebo in addition to analgesia.
Friedman BW, Irizarry E, Solorzano C, et al. Diazepam is no better than placebo when added to naproxen for acute low back pain. Ann Emerg Med 2017;70(2):169-176.

2. Lumbar fusion no better than exercise and therapy in the long term

Clinical question: Is lumbar fusion effective for patients with chronic low back pain?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: This is an important question; one not without controversy. This study reports a mean 12.8 years of follow-up from a trial that randomized 294 persons with severe chronic low back pain in a 3:1 ratio to lumbar fusion or physical therapy. This report provides almost no detail about their methods, but a look at their earlier publication reveals that outcome assessors (and, obviously, patients) were not masked to treatment assignment. The earlier report, after 2 years of follow-up, showed generally favorable results for surgery. Approximately 20% of patients in each group died or were lost to follow-up. In the long-term results, using intention-to-treat analysis, there is no difference between groups for any outcome, including the patient's Global Assessment (GA) of back pain score, the Oswestry Disability index score, a visual analog scale for pain score, pain medication use, pain frequency, or employment status. The authors also report an "as treated" analysis, which counts the 19 of 72 patients who crossed over to surgery as if they had originally been assigned to surgery (they were not!), and they report a per-protocol analysis, which ignores patients who crossed over or were lost to follow-up. Both of these analyses found an improvement in the patient's GA score with surgery, but failed to find improvement in any other outcomes. On the basis of the single outcome of GA score in the more biased analyses, the authors' conclusion is that surgery should be considered effective. An accompanying editorial, which strongly disagrees with the authors, begins with the snide headline: Consensus at last... fusion is no better than nonoperative care in improving pain and disability in chronic low back pain.
Bottom line: This trial is a good example of how to do just about everything wrong in order to get the results you want. The authors did not conceal allocation, did not mask anyone in the study, used an unvalidated and subjective primary outcome, and downplayed the intention-to-treat analysis. Funding for the original study came from industry, and the authors have numerous conflicts of interest. Two other trials in the United Kingdom and Norway found no benefit to lumbar fusion, and the results of this study are consistent with those findings, despite what the authors conclude.
Hedlund R, Johansson C, Hagg O, et al. The long-term outcome of lumbar fusion in the Swedish lumbar spine study. Spine 2016;16(5):579-587.

3. Adding spinal fusion to decompression does not improve outcomes for lumbar stenosis and has harms

Clinical question: Does the addition of spinal fusion in patients with lumbar stenosis (with or without evidence of spondylolisthesis) improve outcomes?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)

Synopsis: Almost all US patients with lumbar stenosis and spondylolisthesis, and many without spondylolisthesis, undergo spinal fusion as well as decompression. In this study, 247 patients aged 50 to 80 years with lumbar stenosis and neuroclaudication for at least 6 months were randomized to decompression only or decompression plus spinal fusion. Fourteen patients did not receive the assigned intervention, leaving 233 in the per-protocol population. The mean age was 67 years, 98 patients had no evidence of spondylolisthesis while 135 did, and the patients with spondylolisthesis were more likely to be women. The primary outcome was a per-protocol analysis, which is probably acceptable in this case since relatively few patients assigned to surgery did not undergo it. At 2 years, there was no difference between groups with regard to pain and function scores or overall assessment of decreased back or leg pain. Approximately half of the patients without spondylolisthesis and approximately two thirds of those with spondylolisthesis reported satisfaction with the surgery, with no difference between groups by type of surgery. Harms of adding spinal fusion included a longer length of stay (7.4 vs 4.1 days), higher cost ($12,200 vs $5,400), a longer operative time, and greater blood loss.
Bottom line: Adding spinal fusion does not improve outcomes among patients with lumbar stenosis.
Forsth P, Olafsson G, Carlsson T, et al. A randomized, controlled trial of fusion surgery for lumbar spinal stenosis. N Engl J Med 2016;374(15):1413-1423.

4. Spinal fusion does not significantly improve outcomes for patients with lumbar stenosis and grade I spondylolisthesis

Clinical question: Does the addition of spinal fusion to decompressive laminectomy improve outcomes in patients with grade I degenerative spondylolisthesis and spinal stenosis?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: Although lumbar decompression is often accompanied by spinal fusion in patients with spinal stenosis and degenerative spondylolisthesis, to date there have been no randomized controlled trials of this practice, only observational studies with conflicting results. In this study, 66 patients with grade I lumbar spondylolisthesis (3 mm to 14 mm of vertebral body displacement) and lumbar stenosis accompanied by symptoms of neurogenic claudication. Patients with instability or previous surgery, as well as those with major comorbidities, were excluded. A panel of 10 spine surgeons reviewed images and decided that each patient was suitable for randomization (clinical equipoise). This is good trial design and, according to the researchers, appeared to increase the likelihood that patients were willing to be included in the randomization, which was a problem in previous trials of spinal surgery. Approximately half the patients who were screened for inclusion agreed to be randomized to receive either decompression alone or decompression plus posterolateral-instrumented fusion at the level of the spondylolisthesis. The fusion is thought to stablize the spine and reduce the risk of recurrence. The patients had a mean age of 67 years, 80% were women, and they had a mean 6 mm of spondylolisthesis. Groups were balanced and analysis was by intention to treat. Patients were followed up for 4 years, and the primary outcome was the change in the physical component of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the change in the ODI. The surgical group had a slightly greater improvement on both scales, which was statistically significant for the SF-36 but not for the ODI. However, the changes were small and unlikely to be clinically noticeable (~ 4 to 9 points on a 100-point scale). The rate of re-operation was lower for the fusion group (14% vs 34%; P = .05; number needed to treat = 5), but this may reflect the fact that surgeons knew patients in the decompression-only group had not undergone fusion, which might make them more likely to offer surgery as an option if symptoms recurred or worsened. There was more blood loss and longer hospital stays for patients in the fusion group. Loss to follow-up was relatively high after the first year, so estimates based on longer follow-up are unreliable.
Bottom line: Adding spinal fusion to lumbar decompression provides an increase in the physical component of quality of life, but no significant improvement on the more sensitive Oswestry Disability Index (ODI). An editorial in the same journal concluded--and I agree--that the small benefits of routinely adding spinal fusion to decompression in patients with lumbar stenosis and spondylolisthesis are probably not worth the additional costs and risks.
Ghogawala Z, Dziura J, Butler WE, et al. Laminectomy plus fusion versus laminectomy alone for lumbar spondylolisthesis. N Engl J Med 2016;374:1424-1434.

5. Does Operative or Nonoperative Treatment Achieve Better Results in A3 and A4 Spinal Fractures Without Neurological Deficit? - Systematic Literature Review With Meta-Analysis

STUDY DESIGN: Systematic literature review with meta-analysis.
OBJECTIVE: Thoracolumbar (TL) fractures can be treated conservatively or surgically. Especially, the treatment strategy for incomplete and complete TL burst fractures (A3 and A4, AOSpine classification) in neurologically intact patients remains controversial. The aim of this work was to collate the clinical evidence on the respective treatment modalities.
METHODS: Searches were performed in PubMed and the Web of Science. Clinical and radiological outcome data were collected. For studies comparing operative with nonoperative treatment, the standardized mean differences (SMD) for disability and pain were calculated and methodological quality and risk of bias were assessed.
RESULTS: From 1929 initial matches, 12 were eligible. Four of these compared surgical with conservative treatment. A comparative analysis of radiological results was not possible due to a lack of uniform reporting. Differences in clinical outcomes at follow-up were small, both between studies and between treatment groups. The SMD was 0.00 (95% CI -0.072, 0.72) for disability and -0.05 (95% CI -0.91, 0.81) for pain. Methodological quality was high in most studies and no evidence of publication bias was revealed.
CONCLUSIONS: We did not find differences in disability or pain outcomes between operative and nonoperative treatment of A3 and A4 TL fractures in neurologically intact patients. Notwithstanding, the available scores have been developed and validated for degenerative diseases; thus, their suitability in trauma may be questionable. Specific and uniform outcome parameters need to be defined and enforced for the evaluation of TL trauma.
Rometsch E, Spruit M, Härtl R, McGuire RA, Gallo-Kopf BS, Kalampoki V, Kandziora F. Does Operative or Nonoperative Treatment Achieve Better Results in A3 and A4 Spinal Fractures Without Neurological Deficit? - Systematic Literature Review With Meta-Analysis. Global Spine J. 2017 Jun;7(4):350-372.

6. ACP Recommendations for Care of Low Back Pain

Clinical question: What are the roles of the various interventions in the treatment of acute and chronic low back pain?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This guideline is based on 2 systematic reviews, conducted by outside researchers, of drug and nondrug treatment of low back pain (doi: 10.7326/M16-2459 and doi: 10.7326/M16-2458). The guideline developers evaluated the effects of treatment on patient-oriented outcomes, graded the evidence, and minimized (but didn't eliminate) conflicts of interest. Their recommendations are as follows. For acute or subacute low back pain: Strong recommendation: Start with heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). Consider drug therapy with a nonsteroidal anti-inflammatory drug or skeletal muscle relaxant (moderate-quality evidence). For chronic low back pain: Strong recommendation: Start with any nondrug therapy that appeals to the patient exercise, rehabilitation, acupuncture, or mindfulness-based stress reduction (moderate-quality evidence); or tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). Drug therapy is largely not effective. In patients with an inadequate response to these treatments, consider a nonsteroidal anti-inflammatory drug as first-line therapy, and tramadol (Ultram) or duloxetine (Cymbalta) as second-line therapy. Weak recommendation: Opioid treatment should be reserved for patients for whom nothing else works and only after a discussion of benefits, risks, and realistic expectations (moderate-quality evidence).
Bottom line: These guidelines recommend starting with nondrug approaches to the treatment of both acute low back pain and chronic low back pain, given the low evidence of benefit and the risks associated with medication. See the synopsis: There is evidence of some benefit for a wide variety of nondrug approaches, which allows patients to choose the one that makes the most sense for them.
Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017 Feb 14. doi: 10.7326/M16-2367. [Epub ahead of print]

7. Placebo decreases chronic low back pain

Clinical question: Can simply telling patients that a medicine works, even if it is placebo, decrease pain and improve disability in patients with chronic low back pain?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: These investigators, who conducted the study in Portugal, enrolled 83 patients who'd had low back pain for at least 3 months and responded to an advertisement. Most (87%) were taking analgesia, approximately 40% were taking adjuvant medication (eg, gabapentin or a muscle relaxant), and approximately 20% were taking an antidepressant. The authors excluded patients with severe fibromyalgia or rheumatoid arthritis and those who had received opioid treatment in the past. For 3 weeks patients were asked to continue their usual treatment. Using concealed allocation, half of the patients were also given 2 placebo tablets twice a day. They were told that it was an inactive placebo, but: (1) it could still have a powerful effect; (2) the body can automatically respond to placebo; (3) a positive attitude is helpful but not necessary; and, (4) the placebo must be taken faithfully. Knowingly taking placebo significantly decreased maximum reported pain, minimum reported pain, and usual pain as compared with usual therapy only. Back pain–related disability was also decreased with placebo. There were several problems with the study, however: unbalanced baseline pain, small numbers in each group, and the lack of a commercially available placebo.
Bottom line: Building on the received wisdom of Sir William Osler that, "The desire to take medicine is perhaps the greatest feature which distinguishes man from animals," these investigators gave twice daily placebo to patients with chronic back pain and told them it was placebo. They also told them that placebos can have a pronounced effect (which is true). The addition of placebo to usual care improved patients' pain and disability scores over the 3 weeks of the study. Although we probably won't start prescribing placebo, this study emphasizes the great value of conveying one's confidence in the treatment to bolster its effect
Carvalho C, Caetano JM, Cunha L, et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain 2016;157(12):2766-2772.

Knees

I see patients with painful knee osteoarthritis in my office every day. After pain medication, exercise and physical therapy and perhaps acupuncture, it appears that we have to jump to joint replacement and skip other invasive treatments such as injections and arthroscopic whittling, which now have strong evidence against effectiveness.

8. OA shoes no better than walking shoes for knee OA pain and function

Clinical question: Are special shoes more effective than conventional walking shoes to decrease the pain of knee osteoarthritis and improve physical function?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Some shoes are specifically designed to "unload" knees through modified midsoles that have variable stiffness and a lateral wedge to decrease the biomechanical load on the medial aspect of the knee. This study, conducted in Australia, enrolled 164 patients recruited through advertising who were at least 50 years old, had knee pain of at least 4 on a scale of 0 to 10 for most days, and radiographic evidence of medial knee osteoarthritis. The participants were randomly assigned, using concealed allocation, to wear either unloading shoes (Asics GEL-Melbourne OA) or neutral walking shoes (Asics GEL-Odyssey) for at least 4 hours a day for 6 months. Shoes for both groups were provided by the researchers. Pain scores changed from an average 5.7 to 6.0 before the start of

the study to an average 4.2 in both groups on an 11-point scale (P = NS). Function also improved to a clinically significant degree (> 6 units on the Western Ontario and McMaster Universities Osteoarthritis Index) in both groups (function improved in 44% and 48% of patients in the unloading and neutral shoe groups, respectively).The study had 90% power to find a 2.5-unit difference in pain and a 10.5-unit difference in function. The results might be cause in part by an "acquiescence bias," in which people in both groups felt they needed to report improvement to researchers who gave them free shoes. It would have been great if this study had included a third group who stuck to their usual shoe-wearing habits.
Bottom line: A quick search of the Internet will yield many walking shoes targeted at the bad knees market. But specifically designed shoes with modified midsoles and a wedge to unload the medial aspect of the knee are no more effective than typical walking shoes at relieving pain and improving function in patients with documented knee osteoarthritis. In this study, patients in both groups improved, which either might be an artifact of the study or because any type of walking shoe improves pain and function.
Hinman RS, Wrigley TV, Metcalf BR, et al. Unloading shoes for self-management of knee osteoarthritis. A randomized trial. Ann Intern Med 2016;165(6):381-389.

9. Meta-analysis: acupuncture minimally decreases knee pain from DJD in the short term

Clinical question: Is acupuncture effective in alleviating knee pain in patients with degenerative joint disease?
Study design: Meta-analysis (randomized controlled trials)
Setting: Outpatient (any)
Synopsis: These researchers searched PubMed, EMBASE, and the Cochrane Registry of Controlled Trials to identify randomized trials that evaluated acupuncture in managing knee pain in patients with DJD. Two authors independently assessed studies for inclusion and resolved disagreements by discussion, reserving third-party consultation and voting for when discussion failed. They don't describe additional efforts to identify unpublished studies, but they report that they did not find evidence of significant publication bias. The authors evaluated the quality of each included study using the Cochrane Back Review Group criteria. Ultimately they included 10 studies (4 from the United States, 2 from the United Kingdom, and 1 each from Canada, Spain, Germany, and Australia) with 2007 patients (range 20 - 697). Most of the studies were of high quality. The studies assessed outcomes from 3 to 26 weeks after treatment. Seven used sham acupuncture. The researchers identified modest amounts of heterogeneity among the study results. In the short term, patients treated with acupuncture had an average improvement of 1.2 weighted mean difference in pain measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (range 0 - 20 points). Additionally, patients treated with acupuncture had an average improvement in the WOMAC function score of 4.6 (range 0 - 68). Sensitivity analysis did not change results. Although these results are statistically significant, they are probably not clinically meaningful. The authors don't report on the proportion of patients experiencing the minimal clinically important difference in pain or function. Finally, long-term pain scores were comparable among the different treatment groups.
Bottom line: In this meta-analysis, patients with knee pain from degenerative joint disease (DJD) treated with acupuncture experienced minimal improvement in short-term pain and function compared with those who received sham acupuncture or usual care. The improvements are not likely to be clinically important.
Lin X, Huang K, Zhu G, Huang Z, Qin A, Fan S. The effects of acupuncture on chronic knee pain due to osteoarthritis: a meta-analysis. J Bone Joint Surg Am 2016;98(18):1578-1585.

10. Bone marrow aspirate injections equal saline in patients with knee DJD

Clinical question: Do injections of bone marrow aspirate concentrate improve pain in patients with mild to moderate knee degenerative joint disease?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (specialty)
Synopsis: The authors describe this as a pilot study comparing a novel therapy (bone marrow aspirate concentrate) with saline in 25 patients with bilateral knee DJD. They enrolled patients with 2 bad knees so that patients could serve as their own internal control and, of course, to spare control patients from sham bone marrow aspiration. Statistically, this means they didn't need as many patients. To be included, the patients had to have longstanding bilateral knee pain from mild to moderate bilateral osteoarthritis despite conventional treatments such as activity modification, weight loss, physical therapy, analgesics, nonsteroidal anti-inflammatory drugs, or injection therapy. The study staff concentrated patients' own bone marrow and then re-suspended it with platelet-poor plasma. Each patient's right knee received an injection of either bone marrow aspirate concentrate or saline and the left received the other therapy (the knees were randomized to avoid the possibility of differential treatment allocation based on severity). Patients experienced improved pain scores in both knees 1 week, 3 months, and 6 months after treatment. However, there was no differences in the degree of relief between the knees.
Bottom line: In this study, patients with bilateral knee degenerative joint disease (DJD) experience comparable degrees of pain relief with saline injections or bone marrow aspirate concentrate injections.
Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. Am J Sports Med 2017;45(1):82-90.

11. Steroid injection does not improve response to exercise therapy for knee OA

Clinical question: Does a steroid injection before the start of exercise therapy improve the response in patients with knee osteoarthritis?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: The Danish researchers enrolled 100 patients with knee osteoarthritis (confirmed by radiography) and knee pain while walking who were not morbidly obese. The patients were randomized, using concealed allocation, to receive an injection of methylprednisolone 40 mg or saline (both with lidocaine). Two weeks later all participants started a 12-week supervised exercise program. At the 2-week visit (before starting exercise), pain scores had improved slightly in both groups. By the end of 3 months of

exercise therapy, scores had improved significantly and similarly in both groups.
Bottom line: Unlike other study results, in this study a steroid injection given 2 weeks before the start of supervised exercise was no more effective than a placebo injection at improving pain scores 2 weeks later in patients with knee osteoarthritis. It also did not cause a greater improvement after 3 months of exercise.
Henriksen M, Christensen R, Klokker L, et al. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee: A randomized clinical trial. JAMA Intern Med 2015;175(6):923-930.

12. Steroid injections ineffective for knee osteoarthritis

Clinical question: Do intra-articular corticosteroids improve pain and function and decrease cartilage loss in adults with osteoarthritis of the knee?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Although intra-articular corticosteroids are commonly used for the treatment of knee osteoarthritis, data are limited in terms of benefits and safety. The most recent Cochrane Review on this topic evaluated 27 randomized controlled trials (26 with a high risk of bias) and found minimal improvement in pain and function in the short-term with steroids compared with placebo. The only study with low risk of bias found no benefit from steroids (Jüni P, et al. Cochrane Database Syst Rev 2015;(10):CD005328). These investigators recruited 140 adults, 45 years or older, with knee osteoarthritis diagnosed using standard national criteria. Eligible patients randomly received (concealed allocation assignment) either ultrasound-guided intra-articular triamcinolone (40 mg) or saline injections every 3 months for 2 years. Patients, clinicians administering the injections, and outcome assessors remained masked to treatment group assignment. Pain and function assessments based on validated questionnaires and physical examination occurred regularly throughout the study. Periodic magnetic resonance imaging occurred at 0, 12, and 24 months to evaluate changes in knee cartilage volume over the 2-year period. Complete follow-up occurred for 95% of patients at 2 years. Using intention-to-treat analysis, pain and function scores did not significantly differ between the 2 groups. However, the rate of cartilage loss and damage was significantly greater in the triamcinolone treatment group. There were no significant group differences in serious adverse events. The authorship of this POEM is attributed to Emma J. Pace, MD, Fellow and Instructor, Department of Family Medicine, University of Virginia, Charlottesville, VA.
Bottom line: This well-done study found that regular three-month intra-articular injections of triamcinolone for two years resulted in no significant difference in pain and function assessments compared to saline. However, a significant increase in cartilage loss and damage did occur in patients receiving steroids compared to saline. This study confirms the findings of the only other published study with a low risk of bias (see Synopsis).
McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 2017;317(19):1967-1975.

13. Exercise = knee surgery for degenerative meniscal tear

Clinical question: Is arthroscopic surgery better than exercise therapy to treat symptoms associated with degenerative meniscal tears in middle-aged patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: The researchers (orthopedists practicing in Norway) enrolled 140 patients (between the ages of 35 and 60 years) who were referred for care for unilateral knee pain with medial degenerative meniscal tear confirmed by magnetic resonance imaging. Most (96%) had no or minimal radiographic changes associated with osteoarthritis. Pain had to be present for at least 2 months without a history of major knee trauma. The patients were randomized, using concealed allocation, to receive either exercise therapy 2 or 3 times weekly for 3 months or arthroscopic meniscectomy. There were no sham treatments; patients assigned to exercise did not get arthroscopy without meniscal repair and patients undergoing surgery did not have additional sham or actual exercise. Patients reported on pain, function, knee-related quality of life, and other symptoms using the knee injury and osteoarthritis outcome score. Using intention-to-treat analysis at 2 years, there was no difference between the 2 groups. Approximately 1 in 5 (19%) patients who received exercise therapy eventually underwent arthroscopic surgery without any additional benefit.
Bottom line: Despite a significant initial bump in benefit due to the placebo effect, arthroscopic meniscectomy in patients without a history of acute trauma and without a history of knee locking does not reduce pain and improve function after 2 years as compared with 3 months of exercise therapy. This study did not evaluate surgery with exercise versus exercise alone, but other studies have done so and found no additional benefit.
Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ 2016 July 20;354:i3740.

14. Arthroscopic meniscal surgery = nonoperative management

Clinical question: Is arthroscopy better than nonsurgical treatment for patients with meniscal tears?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: These authors searched multiple databases, including registries of clinical trials and the reference lists of retrieved studies, to identify randomized trials of systematic reviews published in English. Two authors independently decided which studies to include and determined the risk of bias in the included studies. They resolved disagreements through conversation and, when necessary, through third-party adjudication. Ultimately, they included 9 randomized trials and 8 systematic reviews. The clinical trials included 68 to 351 patients and the systematic reviews included 98 to 1374 patients. All the systematic reviews were published after 2012, so the variation in sample size is rather striking and reflects the inclusion criteria. For example, the largest systematic review evaluated case series, only slightly less biased than expert opinion in determining the effectiveness of an intervention. The main recurring problems with the randomized trials were the lack of adequate masking and the selective outcome reporting. Only 2 of the trials compared arthroscopy with sham surgery. The others used active comparisons (for example, resection, exercise, physical therapy, steroid

injections, and bioabsorbable arrows). The follow-up duration for the studies ranged from 6 months to 5 years. The studies also used several different outcome assessments: repeat tear, radiographic findings, pain on a visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index score, Knee Injury and Osteoarthritis Outcome Score, and so forth. The authors, appropriately, decided not to pool the data and just summarize the findings. Most of the systematic reviews failed to identify clinically meaningful improvements and only one of the randomized trials found "marginal benefit" in patients treated arthroscopically. Since the systematic reviews included cohort and case-control study designs and the randomized trial flaws all tend to be biased in favor of intervention, the existing data strongly suggest that arthroscopy for meniscal injuries is ineffective. I find it remarkable that so many systematic reviews exist with only 9 clinical trials. This seems like overanalyzing the existing data. The authors seem disappointed, and no matter how many times the data demonstrate no advantage to arthroscopy they will likely call for more clinical trials. No, we do not have an urgent need for evidence—the existing evidence is plenty.
Bottom line: The existing research base, with biases that typically make interventions look better, is unable to demonstrate that arthroscopy for meniscal injuries is any better than nonoperative approaches. Since this is a costly intervention, and is being used more frequently, perhaps insurance companies should re-evaluate whether to continue paying for it.
Monk P, Garfjeld Roberts P, Palmer AJ, et al. The urgent need for evidence in arthroscopic meniscal surgery. Am J Sports Med 2017;45(4):965-973.

15. Knee surgery does not reduce knee catching or locking in patients with meniscal tear (FIDELITY)

Clinical question: Does partial meniscectomy fix mechanical symptoms -- knee catching or locking -- better than sham surgery?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: This report is a substudy of a larger study investigating the effect of arthroscopic surgery on (relatively) young patients with meniscal tear but without signs of osteoarthritis. These Finnish investigators enrolled 146 patients, aged 35 to 65 years, who had knee pain for at least 3 months and evidence of a degenerative meniscal tear but did not respond to conservative treatment. They excluded patients with a verified locked knee (unable to straighten), though they included patients (n = 69) who had symptoms of "catching" or occasional or frequent locking. All patients underwent arthroscopic surgery, though slightly more than half were randomly assigned, using concealed allocation, to a group that did not have the tear addressed (sham surgery). In the surgery group, damaged and loose parts were removed; in the sham surgery group, diagnostic arthroscopy was performed and the surgeon simulated actual surgery (since patients were awake) without removing anything. In the subsequent 12 months, 23 (72%) in the surgery group and 22 (59%) in the sham surgery group with preoperative mechanical symptoms reported symptoms at least once. Only 9 of 32 patients (28%) in the surgery subgroup and 15 of 37 (41%) in the sham surgery subgroup reported complete resolution of their symptoms.
Bottom line: I guess it's time to stop the knee-jerk reaction of sending patients with occasional catches and locking to ortho for meniscal resection. Removing the torn bits of meniscus in middle-aged patients who have intermittent knee catches or locking does not decrease their likelihood of experiencing symptoms in the following year as compared with diagnostic arthroscopy (ie, looking but not touching). In general, meniscectomy does not improve knee pain, regardless of the symptoms (N Engl J Med 2013;369(26):2515-24).
Sihvonen R, Englund M, Turkiewicz A, Jarvinen TL, for the Finnish Degenerative Meniscal Lesion Study Group. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative meniscus tear: A secondary analysis of a randomized trial. Ann Intern Med. 2016;164(7):449-455.

16. Total knee replacement more effective for pain and function than nonsurgical treatment

Clinical question: Is total knee replacement better than nonsurgical treatment for patients with moderate to severe osteoarthritis?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (any)
Synopsis: It's about time. This is the first good-quality randomized controlled trial comparing total knee replacement with nonsurgical treatment of osteoarthritis. All patients had radiographically confirmed knee osteoarthritis classified as moderate to severe and were candidates for unilateral total knee replacement. Patients with previous knee replacement or pain worse than 60 on a 100-point visual analog scale were excluded. The patients' mean age was 66 years; 31% were women. Of the 127 who met the inclusion criteria, an impressive 100 were randomized (50 to each group). Half of the patients underwent total knee replacement, which was followed by 12 weeks of nonsurgical treatment that included education, exercise, dietary advice, custom insoles, and pain medications; the other half received only the 12 weeks of nonsurgical therapy. The authors reported both intention-to-treat and per-protocol analyses, with the latter including only patients who participated in at least 75% of the exercise sessions and who underwent the assigned treatment (ie, did not cross over). The primary outcomes—the total score and subscores for pain, symptoms, function, and quality of life on the Knee Injury and Osteoarthritis Outcome Scale (KOOS) at 12 months—were evaluated by a masked outcome assessor. Approximately 25% of the nonsurgical group crossed over to surgery before the 12 months were up, and overall only about half of the patients in each group met the criteria for the per-protocol analysis. At 12 months, the intention-to-treat analysis found that outcomes had improved significantly more in the surgical treatment group, and the differences were both clinically and statistically significant. Serious adverse events were more common in the surgery group (24 vs 6; P = .005) and in the affected knee, including 3 episodes of deep vein thrombosis, 3 of stiffness requiring mobilization under anesthesia, and 1 each of deep infection and supracondylar femur fracture. Unfortunately, the authors didn't ask the participants who had now been through surgery whether they would have chosen it, all things considered.
Bottom line: In patients with moderate to severe osteoarthritis, total knee replacement provides better symptomatic and functional improvement than nonsurgical care, but approximately half of the surgical patients experienced a serious adverse event, including 8 of 50 who had a serious adverse event that involved the affected limb.
Skou ST, Roos EM, Laursen M, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015;373(17):1597-1606.

Diagnosis of Gout

17. Clinical diagnosis of gout okay unless you suspect septic joint

Clinical question: How should gout be diagnosed?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This guideline is based on a systematic review and meta-analysis of various approaches to diagnosing gout, including various clinical criteria (eg, Rome Criteria), imaging, and aspiration of one or more joints. The authors found moderate-quality evidence that several clinical algorithms have good specificity and sensitivity (> 80%) for diagnosing gout compared with assessment of synovial fluid. The accompanying review has specifics for each set of diagnostic criteria (Ann Intern Med 2017;166:27-36). The authors found low-quality evidence that the use of either dual-energy computed tomography or ultrasound slightly improved diagnostic accuracy. The guideline development group consisted only of internal medicine physicians, included a methodologist, and they were all free of relevant conflicts of interest.
Bottom line: To aspirate or not to aspirate—that is the question. From the American College of Physicians: ". . . use synovial fluid analysis when clinical judgment indicates that diagnostic testing is necessary in patients with possible acute gout." Reading between the lines, it seems to me the common primary care practice of treating gout on the basis of clinical findings and elevated serum uric acid is just fine unless intuition makes you worry about a septic joint.
Qaseem A, McLean RM, Starkey M, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Diagnosis of acute gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:52-57.

Bottom lines

1. Don’t prescribe valium for acute low back pain.
2. Lumbar fusion does not appear to benefit patients with chronic low back pain.
3. Spinal stenosis decompression surgery is not better when lumber fusion is added.
4. Surgical management of spinal compression fracture does not lead to better outcomes than non-operative management.
5. Placebos can be effective for treating low back pain.
6. Special walking shoes for knee arthritis are no better than regular walking shoes.
7. Acupuncture may have a very small benefit for knee osteoarthritis (or may not) compared to sham acupuncture.
8. Steroid injections are not effective for chronic knee arthritis
9. Arthroscopic procedures are not effective for symptoms of knee osteoarthritis.
10. Joint replacement is, but about 15% of patients have complications.

EVIDENCE-BASED PRACTICE Vol 21 | No. 1 | January 2018

1. Is ondansetron safe to use during pregnancy?
2. Is cannabis an effective treatment for chronic pain?
3. What is the prevalence of vitamin D deficiency in the United States?
4. Is doxycycline more likely to result in teeth staining than tetracycline?
5. Which adult patients with asymptomatic microscopic hematuria require further evaluation to rule out occult malignancy?
6. Is combination doxylamine and pyridoxine effective and safe for nausea and vomiting of pregnancy?
7. Is valproate use during pregnancy associated with an increased risk of developmental delays in childhood?
8. What physical examination findings are most predictive of a diagnosis of obstructive sleep apnea?
9. How effective are the first and second doses of HPV vaccine in providing protection against cervical dysplasia?
10. Does daily caffeine intake increase the risk of anxiety?
11. Is T-SPOT.TB (tuberculosis-specific ELISPOT assay) useful for diagnosing tuberculosis in high-risk populations?
12. What are the most effective office-based psychological interventions for patients with panic disorder?
13. Does omega-3 supplementation reduce cardiac mortality?
14. Is sleep-disordered-breathing associated with poor maternal-fetal outcomes?
15. Do metabolically healthy obese individuals have the same mortality and morbidity risks as normal-weight metabolically healthy individuals?
16. When is a CT scan necessary in children and adolescents with cervical spine injury?
17. Is potassium citrate effective for preventing kidney stone recurrence in patients with calcium-containing stones?
18. What methods are effective to reduce operative interventions and maternal morbidity in women during the second stage of labor?
19. In patients with significant acute muscle strain, is heat or cold more effective for reducing symptoms?
20. What is the best treatment for seizures in patients with hyponatremia?
21. Can ESR and CRP be used interchangeably in the management of rheumatoid arthritis?
22. For patients with COPD, does pneumococcal vaccination reduce the incidence of pneumococcal pneumonia?
23. For female athletes, what sports are at high risk for concussion?
24. Before urinalysis and culture, in which patients would starting empiric antibiotics be appropriate?
25. Is psychotherapy effective in decreasing chronic low back pain?
26. What are the benefits of folate consumption during pregnancy?
27. What are the risks of using donor breast milk in preterm or low-birth-weight neonates?

1. Is ondansetron safe to use during pregnancy?

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EVIDENCE-BASED ANSWER

Ondansetron use in pregnancy is associated with a small increase in risk of renal and cardiac birth defects, but no increase in risk of major malformations. Evidence is conflicting on risk of cleft palate (SOR: B, systematic review of observational studies). However, for patients with hyperemesis, ondansetron use is also associated with a lower risk of miscarriage during the first trimester and a higher live birth rate. There is no association with other adverse outcomes (stillbirth, preterm delivery, low birthweight, and small-for-gestational age [SGA]) (SOR: B, retrospective cohort studies).

1. Carstairs S. Ondansetron use in pregnancy and birth defects. Obstet Gynecol. 2016; 127(5):878–883. [STEP 2]
2. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med. 2013; 368(9):814–823. [STEP 3]
3. Fejzo MS, MacGibbon KW, Mullin PM. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. Reprod Toxicol. 2016; 62:87–91. [STEP 3]

2. Is cannabis an effective treatment for chronic pain?

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EVIDENCE-BASED ANSWER

Inhaled and ingested cannabis formulations are somewhat effective in reducing chronic neuropathic or cancer-related pain compared with placebo; the numbers needed to treat (NNT) are 4 to 17 patients to result in 1 more patient achieving at least a 30% reduction in pain. Inhaled cannabis may be more effective than ingested cannabis, and pain relief may be dose dependent (SOR: B, meta-analyses of lower quality RCTs and 1 small RCT).

1. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015; 313(24):2456–2473. [STEP 1]
2. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain. 2015; 16(12):1221–1232.
[STEP 1]
3. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015; 16(7):616–627. [STEP 2]

3. What is the prevalence of vitamin D deficiency in the United States?

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EVIDENCE-BASED ANSWER

The overall prevalence of vitamin D deficiency (25-hydroxyvitamin D levels <30 nmol/L) in the United States is 8.1% and is slightly higher in females (9.9%) than males (6.3%). Mexican Americans (11%), and non-Hispanic blacks (31%) have a higher prevalence than whites (3.6%). In adolescents, the prevalence is 8.5% to 24.1% using 30 to 37.5 nmol/L cutoffs. Breastfed infants not receiving vitamin supplements have a prevalence of 64%. The data on children are inconsistent, with rates ranging from 0.7% to 40% (SOR: C, cross-sectional studies of diseaseoriented data).

1. Centers for Disease Control and Prevention (CDC). Second national report on biochemical indicators of diet and nutrition in the U.S. population. Hyattsville, MD: CDC; 2012. http://www.cdc.gov/nutritionreport/pdf/Nutrition_Book_complete508_final.pdf. Accessed December 21, 2017. [STEP 1]
2. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med. 2004; 158(6):531–537. [STEP 3]
3. Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med. 2008; 162(6):505–512. [STEP 3]

4. Is doxycycline more likely to result in teeth staining than tetracycline?

Gina Ayers, PharmD Winfred Frazier, MD Gretchen Shelesky, MD, MS UPMC St. Margaret Pittsburgh, PA

EVIDENCE-BASED ANSWER

Although no studies have been published that directly compare the effects of doxycycline and tetracycline on teeth staining, doxycycline exposure before 8 years of age is not associated with teeth staining in children 8 to 16 years old (SOR: B, retrospective cohort, prospective cohort). Conversely, tetracycline exposure during anterior permanent teeth formation is associated with teeth staining in children 8 to 11 years old, especially if the treatment course is longer than 10 days or a dose of more than 3 g is given (SOR: B, retrospective cohort).

1. Todd SR, Dahlgren FS, Traeger MS, Beltrán-Aguilar ED, Marianos DW, Hamilton C, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain Spotted Fever. J Pediatr. 2015; 166(5):1246–1251. [STEP 3]
2. Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. Clin Pediatr (Phila). 2007; 46(2):121–126. [STEP 3]
3. Conchie JM, Munroe JD, Anderson DO. The incidence of staining of permanent teeth by the tetracyclines. Can Med Assoc J. 1970; 103(4):351–356. [STEP 3]

5. Which adult patients with asymptomatic microscopic hematuria require further evaluation to rule out occult malignancy?

Violeta Barroso, MD Elise Nissen, MD Julia Shaver, MD Kaiser Napa-Solano FMR Vallejo, CA

EVIDENCE-BASED ANSWER

A validated risk index for asymptomatic microscopic hematuria (AMH) that incorporates age, sex, history
of gross hematuria, history of smoking, and degree of hematuria (<25 or >25 red blood cells per high-power field [RBC/HPF]) can identify a low-risk group of patients with a 0.2% risk of urinary tract malignancy, suggesting that these low-risk patients may not benefit from further evaluation (SOR: B, prospective cohort study). The American Urological Association (AUA) recommends computed tomography (CT) urography as the imaging test of choice, but also acknowledges that serious causes of AMH in younger patients (<35 years) without risk factors are rare, and so suggests ultrasound with or without intravenous urography as an alternative (SOR: C, expert opinion).

1. Loo RK, Lieberman SF, Slezak JM, Landa HM, Mariani AJ, Nicolaisen G, et al. Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. Mayo Clin Proc. 2013; 88(2):129–138. [STEP 2]
2. Davis JR, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol. 2012; 188(6 suppl):2473–2481. [STEP 5]

6. Is combination doxylamine and pyridoxine effective and safe for nausea and vomiting of pregnancy?

David A. Moss, MD Michael J. Kim, MD Nellis AFB FMR Las Vegas, NV

EVIDENCE-BASED ANSWER

Combination therapy with doxylamine and pyridoxine is somewhat effective treating nausea and vomiting of early pregnancy, improving well-being by about 10%. Combination therapy also appears safe for both mother and infant (SOR: B, RCT and cohort studies).

1. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayedrelease doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010; 203(6):571.e1–e7. [STEP 2]
2. Koren G, Clark S, Hankins GD, Caritis SN, Umans JG, Miodovnik M, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. BMC Pregnancy Childbirth. 2015; 15:59. [STEP 2]
3. Ashkenazi-Hoffnung L, Merlob P, Stahl B, Klinger G. Evaluation of the efficacy and safety of bi-daily combination therapy with pyridoxine and doxylamine for nausea and vomiting of pregnancy. Isr Med Assoc J. 2013; 15(1):23–26. [STEP 3]
4. Boskovic R, Rudic N, Danieliewska-Nikiel B, Navioz Y, Koren G. Is lack of morning sickness teratogenic? A prospective controlled study. Birth Defects Res A Clin Mol Teratol. 2004; 70(8):528–530. [STEP 3]

7. Is valproate use during pregnancy associated with an increased risk of developmental delays in childhood?

Kristin Sundy, BS Anne Mounsey, MD University of North Carolina Chapel Hill Chapel Hill, NC

EVIDENCE-BASED ANSWER

Yes, depending on dose. Compared with untreated controls, carbamazepine, lamotrigine, levetiracetam, and phenytoin, higher doses of valproate (≥800 mg/d) are associated with lower IQ scores at age 6 and delays in cognitive development at age 2 (SOR: B, based on prospective cohort studies).

1. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013; 12(3):244–252. [STEP 2]
2. Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, García-Fiñana M, et al; for the Liverpool and Manchester Neurodevelopment Group. IQ at 6 years after in utero exposure to antiepileptic
drugs: a controlled cohort study. Neurology. 2015; 84(4):382–390. [STEP 2]
3. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: levetiracetam vs sodium valproate. Neurology. 2011; 76(4):383–389. [STEP 2]

8. What physical examination findings are most predictive of a diagnosis of obstructive sleep apnea?

Paula Mackrides, DO Ben Panbehi, MD Jennifer Shaw, MD Greg Havermale, DO Aurora Bell, DO SIU Quincy FMRP Quincy, IL

EVIDENCE-BASED ANSWER

In patients referred for a sleep study, Mallampati class and pharyngeal narrowing are slightly predictive of obstructive sleep apnea (OSA) (SOR: B, systematic review of observational studies). A 4-item score using neck circumference plus clinical features is moderately predictive of OSA (SOR: C, cohort studies). Neck circumference, body mass index (BMI), and waist circumference are all moderately associated with OSA in a high-risk referral group (SOR: C, cross sectional study).

1. Myers K, Mrkobrada M, Simel D. Does this patient have obstructive sleep apnea? The Rational Clinical Examination systematic review. JAMA. 2013; 310(7):731–741. [STEP 1]
2. Flemons WW, Whitelaw WA, Brant R, Remmers J. Likelihood ratios for a sleep apnea clinical prediction rule. Am J Respir Crit Care Med. 1994; 150(5 pt 1):1279–1285. [STEP 2]
3. Grover M, Mookadam M, Chang Y, Parish J. Validating the diagnostic accuracy of the Sleep Apnea Clinical Score for use in primary care populations. Mayo Clin Proc. 2016; 91(4):469–476. [STEP 2]
4. Kang HH, Kang JY, Ha JH, Lee J, Kim SK, Moon HS, et al. The associations between anthropometric indices and obstructive sleep apnea in a Korean population. PloS One. 2014; 9(12):e114463.[STEP 2]

9. How effective are the first and second doses of HPV vaccine in providing protection against cervical dysplasia?

Megha Manek, MD, FAAFP Elaina Truax, BS Daniel Russo, BS Guthrie Clinic Sayre, PA

EVIDENCE-BASED ANSWER

The clinical efficacy of 1 and 2 doses of bivalent vaccine is similar to that of 3 doses in protecting against human papillomavirus (HPV) infection (SOR: B, post hoc analysis of 2 RCTs). Two doses 6 months apart appear to elicit similar immunogenicity as 3 doses in the short term; however, the data are conflicting on how long the antibody titers remain comparable (SOR: C, heterogenous RCTs of immune response).

1. Kreimer AR, Struyf F, Del Rosario-Raymundo M, Hildesheim A, Skinner SR, Wacholder S, et al; for the HPV PATRICIA Principal Investigators/Co-Principal Investigator Collaborators; GSK Vaccines Clinical Study Support Group. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. Lancet Oncol. 2015; 16(7):775–786. [STEP 1]

2. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013; 309(17):1793–1802 [STEP 2]
3. Romanowski B, Schwarz TF, Ferguson L, Peters K, Dionne M, Behre U, et al. Sustained immunogenicity of the HPV- 16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: five-year clinical data and modelling predictions from a randomized study. Hum Vaccin Immunother. 2016; 12(1):20–29. [STEP 2]

10. Does daily caffeine intake increase the risk of anxiety?

Jerome Nymberg, MD Ying Vang, MD Nicholas Clough, MD Cheryl Masters, PhD Cabarrus FMRP Concord, NC

EVIDENCE-BASED ANSWER

Caffeine increases self-rated anxiety more than placebo, but the dose-response relationship is inconsistent (SOR: B, 2 small RCTs). This effect may be exclusive to men (SOR: C, small RCT). Patients with generalized anxiety disorder are more sensitive to the anxiogenic effects of caffeine than patients with panic disorder or no psychiatric illness (SOR: B, small RCT).

1. Brice CF, Smith AP. Effects of caffeine on mood and performance: a study of realistic consumption. Psychopharmacology (Berl). 2002; 164(2):188–192. [STEP 2]
2. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Cotreau MM, Harmatz JS, et al. Dosedependent pharmacokinetics, and psychomotor effects of caffeine in humans. J Clin Pharmacol. 1997; 37(8):693–703. [STEP 2]
3. Botella P, Parra A. Coffee increases state anxiety in males but not in females. Hum Psychopharmacol. 2003; 18(2):141–143. [STEP 2]
4. Bruce M, Scott N, Shine P, Lader M. Anxiogenic effects of caffeine in patients with anxiety disorders. Arch Gen Psychiatry. 1992; 49(11):867–869. [STEP 2]

11. Is T-SPOT.TB (tuberculosis-specific ELISPOT assay) useful for diagnosing tuberculosis in high-risk populations?

Muhammad Buttar, MD Roberto Elvir Zelaya, MD Rakshit Patnana, MD Janelle Whitt, DO OU-Tulsa School of Community Medicine Tulsa, OK

EVIDENCE-BASED ANSWER

The degree of usefulness of T-SPOT.TB for diagnosing tuberculosis in high-risk populations varies with the specific population. Concordance between T-SPOT.TB and tuberculin skin testing (TST) is 69% in children referred to a tuberculosis clinic (SOR: B, prospective cohort study). T-SPOT.TB is slightly better that TST in predicting subsequent development of active tuberculosis in patients with silicosis (SOR: B, prospective cohort study). T-SPOT.TB can lead to discordant results up to half of the time in samples drawn 2 weeks apart from healthcare workers being screened, but is less likely than TST to be positive in patients with prior BCG vaccine (SOR: B, longitudinal study). T-SPOT.TB is a good test for differentiating active tuberculosis patients from healthy controls but is less useful for differentiating among patients with other pulmonary diseases (SOR: B, case-control study).

1. Cruz AT, Geltemeyer AM, Starke JR, Flores JA, Graviss EA, Smith KC. Comparing the tuberculin skin test and T-SPOT.TB blood test in children. Pediatrics. 2011; 127(1):e31–e38. [STEP 3]
2. Leung CC, Yam WC, Yew WW, Ho PL, Tam CM, Law WS, et al. T-SPOT.TB outperforms tuberculin skin test in predicting tuberculosis disease. Am J Respir Crit Care Med. 2010; 182(6):834–840. [STEP 3]
3. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, et al; FOR THE Tuberculosis Epidemiologic Studies Consortium. Interferon-γ release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. Am J Respir Crit Care Med. 2014; 189(1):77–87. [STEP 3]
4. Zhu C, Liu Z, Li Z, Mei S, Hu Z. The performance and limitation of T-SPOT.TB for the diagnosis of TB in a high prevalence setting. J Thorac Dis. 2014; 6(6):713–719. [STEP 3]

12. What are the most effective office-based psychological interventions for patients with panic disorder?

Cynthia S. Lee, MSW, MPH Matthew B. Mackey, MD, MPH Kaiser Permanente Washington FMR Seattle, WA

EVIDENCE-BASED ANSWER

The most effective psychological interventions for panic disorder appear to be cognitive-behavioral therapy and exposure therapy with relaxation/breathing training. Sparse evidence also suggests supportive psychotherapy may be one of the more effective interventions (SOR: B, meta-analyses of RCTs with lowto very-low-quality evidence).

1. Pompoli A, Furukawa TA, Imai H, Tajika A, Efthimiou O, Salanti G. Psychological therapies for panic disorder with or without agoraphobia in adults: a network meta-analysis. Cochrane Database Syst Rev. 2016; (4):CD011004. [STEP 2]
2. Sánchez-Meca, J, Rosa-Alcázar A, Marín-Martínez F, Gómez-Conesa A. Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. Clin Psychol Rev. 2010; 30(1):37–50. [STEP 2]

13. Does omega-3 supplementation reduce cardiac mortality?

Lisa Harris, DO Karl Swinson, MD Womack Army Medical Center Fort Bragg, NC

EVIDENCE-BASED ANSWER

No. Omega-3 fatty acid supplementation does not reduce cardiac mortality in primary or secondary prevention (SOR: A, meta-analysis of RCTs and 2 RCTs).

1. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and metaanalysis. JAMA. 2012; 308(10):1024–1033. [STEP 1]
2. Risk and Prevention Study Collaborative Group. N-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013; 368(19):1800–1808. [STEP 2]

3. Writing Group for the AREDS2 Research Group. Effect of long-chain ω-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (ARED2) randomized clinical trial. JAMA Intern Med. 2014; 174(5):763–771. [STEP 2]

14. Is sleep-disordered-breathing associated with poor maternal-fetal outcomes?

Kenya Ie, MD, PhD Parul Chaudhri, DO Amy J. DiPlacido, MD Amy Haugh, MS University of Pittsburgh Medical Center St Margaret Pittsburgh, PA

EVIDENCE-BASED ANSWER

Moderate-to-severe sleep-disordered-breathing (SDB) in pregnant women is associated with various maternal and fetal morbidities: gestational diabetes mellitus, pregnancy-related hypertension, preterm delivery, intrauterine growth restriction, low birth weight, and neonatal intensive care unit (NICU) admission (SOR: B, meta-analysis of limited-quality observational studies). Limited evidence suggests a positive SDB screen with the Berlin Questionnaire is associated with hypertensive disorders of pregnancy (SOR: B, cohort study).

1. Ding XX, Wu YL, Xu SJ, Zhang SF, Jia XM, Zhu RP, et al. A systematic review and quantitative assessment of sleep-disordered breathing during pregnancy and perinatal outcomes. Sleep Breath. 2014; 18(4):703–713. [STEP 2]
2. Antony KM, Agrawal A, Arndt ME, Murphy AM, Alapat PM, Guntupalli KK, et al. Association of adverse perinatal outcomes with screening measures of obstructive sleep apnea. J Perinatol. 2014; 34(6):441–448. [STEP 3]

15. Do metabolically healthy obese individuals have the same mortality and morbidity risks as normal-weight metabolically healthy individuals?

Christine Jacobs, MD Sheran Fernando, MD Saint Louis University School of Medicine St. Louis, MO

EVIDENCE-BASED ANSWER

The answer is unclear. Cardiovascular (CV) events and mortality are increased inconsistently in metabolically healthy obese individuals compared with metabolically healthy normal-weight individuals, depending on duration of follow-up and the criteria used to define metabolic health (SOR: B, meta-analysis of cohort studies and single cohort study).

1. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. Ann Intern Med. 2013; 159(11):758–769. [STEP 2]
2. Hinnouho G, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care. 2013; 36(8):2294–2300. [STEP 3]

16. When is a CT scan necessary in children and adolescents with cervical spine injury?

Sharon Smaga, MD Fariha Rub, MD Southern Illinois University-Carbondale Carbondale, IL

EVIDENCE-BASED ANSWER

Imaging of the cervical spine should be obtained if the patient has neurologic signs or symptoms or mechanism of injury suggests cervical spine injury. Plain x-rays should be done first, with computed tomography (CT) of the cervical spine reserved for cases of diagnostic uncertainty or to confirm abnormal plain films (SOR: B, based on a systematic review of retrospective casecontrol studies and case series, and an individual retrospective case-control study).

1. Chung S, Mikrogianakis A, Wales PW, Dirks P, Shroff M, Singhal A, et al. Trauma Association of Canada Pediatric Subcommittee National Pediatric Cervical Spine Evaluation Pathway: consensus guidelines. J Trauma. 2011; 70(4):873–884. [STEP 1]
2. Chaudhry AS, Prince J, Sorrentino C, Fasanya C, McGinn J, Atanassov KD, et al. Identification of risk factors for cervical spine injury from pediatric trauma registry. Pediatr Neurosurg. 2016; 51(4):167–174. [STEP 4]

17. Is potassium citrate effective for preventing kidney stone recurrence in patients with calcium-containing stones?

Joy Welty, MD Michael D. Geurin, MD Montana FMR Billings, MT

EVIDENCE-BASED ANSWER

Potassium citrate and other potassium-containing citrate salts reduce kidney stone recurrence by 75% in patients with calcium-containing stones (SOR: A, meta-analysis and systematic review). The optimal formulation, dosing, and duration of potassium-containing citrate salt therapy is not clear.

1. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. Cochrane Database Syst Rev. 2015; (10):CD010057. [STEP 1]
2. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med. 2013; 158(7):535–543. [STEP 1]
3. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014; 192(2):316–324. [STEP 1]

18. What methods are effective to reduce operative interventions and maternal morbidity in women during the second stage of labor?

Rebecca Lauters, MD Michael Odom, MD Nellis Air Force Base FMR Las Vegas, NV

EVIDENCE-BASED ANSWER

Delayed pushing decreases the risk of operative vaginal delivery by 23% and time spent pushing by 11 minutes in nulliparous women with epidural anesthesia (SOR: A, meta-analysis of RCTs). Forceps use leads to 35% fewer failed vaginal deliveries compared with vacuum but increases maternal morbidity (third/fourth degree lacerations, vaginal trauma, flatus incontinence) (SOR: A, meta-analysis

of RCTs). Use of a dental support device may reduce the rate of operative vaginal delivery and Cesarean delivery in nulliparous women without altering the duration of second-stage labor (SOR: C, single small RCT).
1. Brancato RM, Church S, Stone PW. A meta-analysis of passive descent versus immediate pushing in nulliparous women with epidural analgesia in the second stage of labor. J Obstet Gynecol Neonatal Nurs. 2008; 37(1):4–12. [STEP 1]
2. O'Mahony F, Hofmeyr GJ, Menon V. Choice of instruments for assisted vaginal delivery. Cochrane Database Syst Rev. 2010; (11):CD005455. [STEP 1]
3. Aviram A, Ashwal E, Hiersch L, Hadar E, Wiznitzer A, Yogev Y. The effect of intrapartum dental support use among nulliparous during the second stage of labor—a randomized control study. J Matern Fetal Neonatal Med. 2016; 29(6):868–871. [STEP 2]

19. In patients with significant acute muscle strain, is heat or cold more effective for reducing symptoms?

Quincy Scott, DO Richard England, MD Southern Illinois University FMRP Carbondale, IL

EVIDENCE-BASED ANSWER

Either heat and cold therapy applied for 30 minutes combined with ibuprofen provides mild yet similar immediate relief of acute back or neck strains (SOR: C, small RCT). Heat and cold are equivalent in the treatment of acute and chronic low back pain (SOR: B, nonrandomized trial).
1. Garra G, Singer AJ, Leno R, Taira BR, Gupta N, Mathaikutty B, et al. Heat or cold packs for neck and back strain: a randomized controlled trial of efficacy. Acad Emerg Med. 2010; 17(5):484–489. [STEP 2]
2. French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. Superficial heat or cold for low back pain. Cochrane Database Syst Rev. 2006; (1):CD004750. [STEP 1]

20. What is the best treatment for seizures in patients with hyponatremia?

Erik R. Clauson, DO David A. Moss, MD Nellis FMR Las Vegas, NV

EVIDENCE-BASED ANSWER

In the setting of severe hyponatremia symptoms, including seizure, the best treatment is an infusion of 3% hypertonic saline until symptoms resolve (SOR: B, based on systematic review of consensus practice guidelines). The rate and volume recommended varies, ranging from continuous infusion to bolus doses, but correction should not exceed 10 mmol/L in the first 24 hours (SOR C, based on consensus guidelines).
1. Nagler EV, Vanmassenhove J, van der Veer SN, Nistor I, Van Biesen W, Webster AC, et al. Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. BMC Med. 2014; 12:1. [STEP 2]
2. Spasovski G, Vanholder R, Allolioet B. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med. 2014; 40(3):320–331. [STEP 1]
3. Grant P, Ayuk J, Bouloux PM, Cohen M, Cranston I, Murray RD, et al. The diagnosis and management of inpatient hyponatraemia and SIADH. Eur J Clin Invest. 2015; 45(8):888–894. [STEP 5]

21. Can ESR and CRP be used interchangeably in the management of rheumatoid arthritis?

Shrey Carpenter, MD Anthony Vettraino, MD St. Mary Mercy Hospital Livonia, MI

EVIDENCE-BASED ANSWER

Yes. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have a concordance of 69% in patients with rheumatoid arthritis (RA). The measures are nearly equal in predicting swollen joint count but both are poorly correlated with clinical disease activity (SOR: A, metaanalysis of RCTs). Evidence is conflicting about whether ESR and CRP can predict radiographic progression of RA (SOR: C, disease-oriented data from systematic review of conflicting RCTs and cohort studies).
1. Crowson C, Rahman M, Matteson E. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. J Rheumatol. 2009; 36(8):1606–1610. [STEP 1]
2. Navarro-Compan V, Gherge AM, Smolen JS, Aletaha D, Landewe R, Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford). 2015; 54(6):994–1007. [STEP 1]

22. For patients with COPD, does pneumococcal vaccination reduce the incidence of pneumococcal pneumonia?

Tania Mathew, MD Amandeep Kaur, MD Joseph Ross, MD UIC Rockford FMR Rockford, IL

EVIDENCE-BASED ANSWER

Pneumococcal vaccination in patients with chronic obstructive pulmonary disease (COPD) does not reduce pneumonia of any etiology (SOR: A, meta-analysis of 3 RCTs), but does lead to a slight reduction in incidence of pneumonia due to pneumococcus (SOR: B, RCT). Pneumonia of any etiology may be reduced in patients younger than 65 years (SOR: B, RCT).
1. Granger R, Walter J, Poole PJ, Lasserson TJ, Mangtani P, Cates CJ, et al. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006; (4):CD001390. [STEP 1]
2. Sehatzadeh S. Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based review. Ont Health Technol Assess Ser. 2012; 12(3):1–64. [STEP 1]
3. Alfageme I, Vazquez R, Reyes N, Muñoz J, Fernández A, Hernandez M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006; 61(3):189–195. [STEP 2]
4. Centers for Disease Control and Prevention. Vaccines and preventable diseases: pneumococcal vaccine resources. https://www.cdc.gov/vaccines/vpd/pneumo/hcp/references-resources.html. Last updated December 6, 2017. Accessed December 29, 2017. [STEP 5]

23. For female athletes, what sports are at high risk for concussion?

Jamille Hernandez, MD Marvin H. Sineath Jr, MD Carolyn Klatt, MLIS Memorial Health FMR Savannah, GA

EVIDENCE-BASED ANSWER

Sports with the highest risk of concussion in female high school athletes are soccer and lacrosse with about 0.35 concussions for every 1,000 athletes participating in 1 game. In college sports, ice hockey has the highest risk at nearly 1 concussion for every 1,000 athletes participating in 1 game, followed by soccer (SOR: B, descriptive epidemiologic studies).

1. Marar M, McIlvain NM, Fields SK, Comstock RD. Epidemiology of concussions among United States high school athletes in 20 sports. Am J Sports Med. 2012; 40(4):747–755. [STEP 2]
2. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. J Athl Train. 2007; 42(2):311–319. [STEP 2]
3. Gessel LM, Fields SK, Collins CL, Dick RW, Comstock RD. Concussions among United States high school and collegiate athletes. J Athl Train. 2007; 42(4):495–503. [STEP 2]

24. Before urinalysis and culture, in which patients would starting empiric antibiotics be appropriate?

Andrew Yochum, DO Khalid Sonbol, MD Southern Illinois University Family Medicine Carbondale, IL

EVIDENCE-BASED ANSWER

In nonpregnant adult women presenting with symptoms of urinary tract infection (UTI), the combination of dysuria and no vaginal discharge or irritation yields a 90% chance of a UTI. Individual signs and symptoms do not significantly change the probability of UTI (SOR: B, 2 meta-analyses of cohort, case-control, cross-sectional, and case-series studies).

1. Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Fam Pract. 2010; 11:78. [STEP 2]
2. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA. 2002; 287(20):2701–2710. [STEP 2]

25. Is psychotherapy effective in decreasing chronic low back pain?

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EVIDENCE-BASED ANSWER

Behavioral therapies such as progressive relaxation, biofeedback, operant therapy, and cognitive-behavioral therapy (CBT) slightly to moderately reduce chronic low back pain over the short term (SOR: B, meta-analysis of RCTs). Mindfulness-based stress reduction and CBT added to other medical treatments are modestly better at reducing chronic low back pain, but the effect of CBT diminishes at 1 year (SOR: B, RCTs).

1. Henschke N, Ostelo RW, van Tulder MW, Vlaeyen JW, Morley S, Assendelft WJ, et al. Behavioral treatment for chronic low-back pain. Cochrane Database Syst Rev. 2010; (7):CD002014. [STEP 1]
2. Cherkin DC, Sherman KJ, Balderson BH, Cook AJ, Anderson ML, Hawkes RJ, et al. Effects of mindfulness-based stress reduction cognitive-behavioral therapy or usual care on back pain and functional limitations among adults with chronic low back pain: a randomized clinical trial. JAMA. 2016; 315(12):1240–1249. [STEP 2]
3. Linden M, Scherbe S, Cicholas B. Randomized controlled trial on the effectiveness of cognitive behavioral group therapy in chronic back pain patients. J Back Musculoskelet Rehabil. 2014; 27(4):563–568. [STEP 2]

26. What are the benefits of folate consumption during pregnancy?

Colten Bracken, MD Sarah Daly, DO Utah Valley FMR Provo, UT

EVIDENCE-BASED ANSWER

Maternal folic acid supplementation taken from before conception through the first trimester reduces primary and recurrent neural tube defects (NTDs) by more than 65%. Folic acid supplementation during pregnancy decreases maternal megaloblastic anemia at the time of delivery by about 80%. Folic acid supplementation does not reduce rates of cleft palate, cleft lip, congenital heart defects, miscarriage, preterm delivery, or stillbirth, or affect mean birthweight (SOR: A, meta-analyses of RCTs).

1. De-Regil LM, Pena-Rosas JP, Fernandez-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2015; (12):CD007950. [STEP 1]
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27. What are the risks of using donor breast milk in preterm or low-birth-weight neonates?

Rebecca Marshburn, MD Marvin Sineath Jr, MD Memorial Health FMR Savannah, GA

EVIDENCE-BASED ANSWER

Neonates receiving donor breast milk gain about 2.6 g/kg less per day and grow about 1.4 mm less per week in length and 1.2 mm less per week in head circumference than formula-fed infants in the hospital but have about one-third the risk of necrotizing enterocolitis compared with formula-fed neonates (SOR: A, metaanalysis of RCTs). Donor breast milk-fed neonates are about 20% more likely to receive some breastfeeding on discharge from the neonatal intensive care unit (NICU) (SOR: B, meta-analysis of cohort studies and single RCT).

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Priority Updates from the Research Literature

Kate Rowland, MD, MS
Rush Copley Family Medicine Residency
Rush Medical College
Family Physicians Inquiries Network

PURLs criteria

1. Scientifically **valid**
2. **Relevant** to Family Medicine
3. Applicable in a **Medical Care Setting**
4. Immediately **implementable**
5. **Clinically meaningful**
6. **Change in practice**

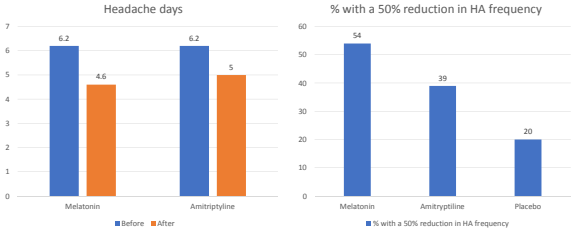
PURLs team

- University of Chicago/NorthShore
- University of Colorado
- University of North Carolina
- Madigan FMR
- Nellis FMR
- UPMC-St. Margaret FMR
- Eisenhower Army Med
- Mizzou

Melatonin for migraine prevention?

- 196 patients with migraine
- 3 attacks and at least 4 headache days/month
- Randomized to 3mg melatonin, amitriptyline 25 mg or placebo nightly
- Followed for 12 weeks
- Primary outcome: # of headache days/month

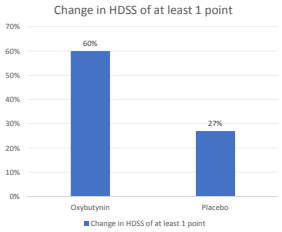
Melatonin for migraine?

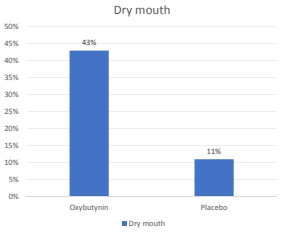


No sweat?

- 62 patients with hyperhidrosis
- Randomized to oxybutynin 2.5 mg, escalating to 7.5 mg daily, or matched placebo
- Followed for 6 weeks
- Primary outcome was score on the validated Hyperhidrosis Disease Severity Score (4 point scale, higher numbers= worse symptoms)

No sweat?





New anticoagulants and afib

- DOACs are recommended for non-valvular afib based on research data due to superior outcomes (lower stroke rates/lower bleeding rates)
- Question remains whether they are just as effective in the "real world" settings
- <50% of eligible patients in the US receive them
- Dabigatran=Pradaxa
- Rivaroxaban=Xarelto
- Apixaban=Eliquis
- [Edoxaban=Savaysa (not studied)]

New anticoagulants and afib

- Observational study
  - National database
- 61,000 patients in Denmark with new afib
  - 12,000 on dabigatran 150 mg BID
  - 7000 on rivaroxaban 20 mg daily
  - 6300 on apixaban 5 mg BID
  - 35,000 on warfarin with goal INR of 2 to 3
- Followed for 1.9 years

New anticoagulants and afib

- Stroke or embolism rate: Same or better for DOACs (2.9-3.9/100 person-years) vs warfarin (3.3/100 p-y)
- Ischemic stroke:
  - Similar between warfarin and apixaban and dabigatran. Rivaroxaban slightly fewer strokes (HR @ 1 yr: 0.83 95% CI 0.69-0.99))
- Bleeding:
  - No difference between warfarin and rivaroxaban. Less bleeding in apixaban (HR 0.63 95% CI 0.53-0.76) and dabigatran (0.61 95% CI 0.51-0.74) at 1 and 2.5 years
- Mortality was also reduced in apixaban (HR=0.65 95% CI 0.56-0.75) and dabigatran (HR=0.63 95% CI 0.48-0.82) compared with warfarin; similar in warfarin and rivaroxaban groups

PPI co-therapy on warfarin?

- 75,000 person-years
  - Medicare and Medicaid databases
- Baseline rate of hospitalization due to upper GI bleed was 127/10,000 person-years
- Examined risk reduction from PPI use
- For patients on warfarin + DAPT or NSAID+ PPI
  - HR 0.55 95% CI 0.39-0.77
- For patients on warfarin + PPI without DAPT/NSAID
  - HR 0.86 95% CI 0.70-1.06

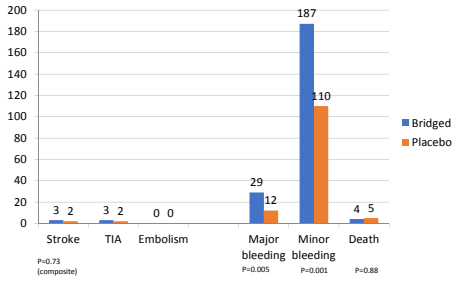
Anticoagulant bridging

- 1884 patients on warfarin for afib stroke prophylaxis undergoing surgery or another major procedure
  - 44% GI procedure
  - 17% cardiothoracic procedure
  - 10% orthopedic procedure
  - Cardiac, intracranial, spinal procedures excluded
- Stroke risk:
  - Average $CHADS_2$ score: 2.3; 38% $CHADS_2 \geq 3$
  - 9.4% had hx of CVA

Anticoagulant bridging

- All patients stopped warfarin 5 days prior to procedure and restarted 24-48 hours post op
- Randomized to
  - Dalteparin 100IU/kg daily 3 days prior to procedure until 24 hours prior, then resumed post op
  - Placebo
- Primary outcome: Arterial thromboembolism, including stroke, TIA, or embolism
- Secondary outcomes: Major bleeding
- Followed 30 days post procedure

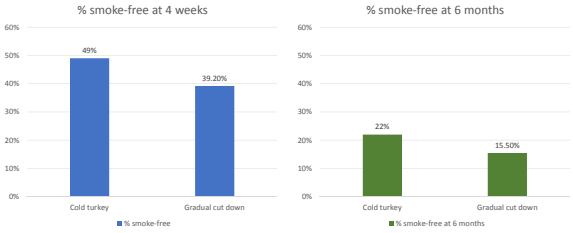
Anticoagulant bridging



Smoking cessation

- 700 people interested in quitting smoking
- Randomized to cold-turkey or gradual cessation recommendation
  - Everyone received NRT
  - Quit dates set in both groups
  - Gradual cessation told to reduce tobacco by ½, then ¼ prior to quit date
- Primary outcome was smoke-free rate at 4 weeks

Smoking cessation



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Thanks!

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Consider melatonin for migraine prevention

This affordable, over-the-counter hormone is as effective as amitriptyline, causes fewer adverse effects, and may have a surprising added benefit.

PRACTICE CHANGER

Recommend nightly melatonin 3 mg to your patients with chronic migraines, as it appears to be as effective as amitriptyline in reducing headaches and causes fewer adverse effects.

STRENGTH OF RECOMMENDATION

B: Based on a single, good quality randomized controlled trial.

Gonçalves AL, Martini Ferreira A, Ribeiro RT, et al. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry*. 2016;87:1127-1132.[1]

ILLUSTRATIVE CASE

A 32-year-old woman comes to your office for help with her recurrent migraines, which she's had since her early 20s. She is otherwise healthy and active. She is frustrated over the frequency of her migraines and the debilitation they cause. She has tried prophylactic medications in the past, but stopped taking them because of the adverse effects. What do you recommend for treatment?

Daily preventive medication can be helpful for chronic migraine sufferers whose headaches have a significant impact on their lives and who have a goal of reducing headache frequency or severity, disability, and/or avoiding acute headache medication escalation.[2] An estimated 38% of patients with migraines are appropriate candidates for prophylactic therapy, but only 3% to 13% are taking preventive medications.[3]

Evidence-based guidelines from the American Academy of Neurology and the American Headache Society state that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and many beta-blockers (metoprolol, propranolol, timolol) are effective and should be recommended for migraine prevention (level **A** recommendation; based on ≥2 class I trials).[2] Medications such as antidepressants (amitriptyline, venlafaxine) and other beta-blockers (atenolol, nadolol) are probably effective and can be considered (level **B** recommendation; based on one class I trial or 2 class II trials).[2] However, adverse effects, such as somnolence, are listed as frequent with amitriptyline and occasional to frequent with topiramate.[4]

Researchers have investigated melatonin before. But a 2010 double-blind, crossover, randomized controlled trial (RCT) of 46 patients with 2 to 7 migraine attacks per month found no significant difference in reduction of headache frequency with extended-release melatonin 2 mg taken one hour before bed compared to placebo over an 8-week period.[5]

STUDY SUMMARY

Melatonin tops amitriptyline in >50% improvement in headache frequency

This RCT conducted in Brazil compared the effectiveness of melatonin to amitriptyline and placebo for migraine prevention in

196 adults (ages 18-65 years) with chronic migraines.[1] Eligible patients had a history of at least 3 migraine attacks or 4 migraine headache days per month. Patients were randomized to take identically-appearing melatonin 3 mg, amitriptyline 25 mg, or placebo nightly. The investigators appear to have concealed allocation adequately, and used double-blinding.

The primary outcome was the number of headache days per month, comparing baseline with the 4 weeks of treatment. Secondary endpoints included reduction in migraine intensity, duration, number of analgesics used, and percentage of patients with more than 50% reduction in migraine headache days.

Compared to placebo, headache days per month were reduced in both the melatonin group (6.2 days vs 4.6 days, respectively; mean difference [MD], -1.6; 95% confidence interval [CI], -2.4 to -0.9) and the amitriptyline group (6.2 days vs 5 days, respectively; MD, -1.1; 95% CI, -1.5 to -0.7) at 12 weeks, based on intention-to-treat analysis. Mean headache intensity (0-10 pain scale) was also lower at 12 weeks in the melatonin group (4.8 vs 3.6; MD, -1.2; 95% CI, -1.6 to -0.8) and in the amitriptyline group (4.8 vs 3.5; MD, -1.3; 95% CI, -1.7 to -0.9), when compared to placebo.

Headache duration (hours/month) at 12 weeks was reduced in both groups (amitriptyline MD, -4.4 hours; 95% CI, -5.1 to -3.9; melatonin MD, -4.8 hours; 95% CI, -5.7 to -3.9), as was the number of analgesics used (amitriptyline MD, -1; 95% CI, -1.5 to -0.5; melatonin MD, -1; 95% CI, -1.4 to -0.6) when compared to placebo. There was no significant difference between the melatonin and amitriptyline groups for these outcomes.

Patients taking melatonin were more likely to have a >50% improvement in headache frequency compared to amitriptyline (54% vs 39%; number needed to treat [NNT]=7; *P*<.05); melatonin worked much better than placebo (54% vs 20%; NNT=3; *P*<.01).

Adverse events were reported more often in the amitriptyline group than in the melatonin group (46 vs 16; *P*<.03) with daytime sleepiness being the most frequent complaint (41% of patients in the amitriptyline group vs 18% of the melatonin group; number needed to harm [NNH]=5). There was no significant difference in adverse events between melatonin and placebo (16 vs 17; *P*=not significant). Melatonin resulted in weight loss (mean, -0.14 kg), whereas those taking amitriptyline gained weight (+0.97 kg; *P*<.01).

WHAT'S NEW

An effective migraine prevention alternative with minimal adverse effects

Melatonin is an accessible and affordable option for preventing migraine headaches in chronic sufferers. The 3-mg dosing reduces headache frequency—both in terms of the number of migraine headache days per month and in terms of the percentage of patients with a >50% reduction in headache events—as well as headache intensity, with minimal adverse effects.

CAVEATS

Product consistency, missing study data

This trial used 3-mg dosing, so it is not clear if other doses are also effective. In addition, because melatonin is available over-the-counter, the quality/actual doses may be less well regulated, and thus, there may be a lack of consistency between brands. Unlike clinical practice, neither the amitriptyline nor the melatonin dose was titrated according to patient response or adverse effects. As a result, we are not sure of the actual lowest effective dose, or if greater effect (with continued minimal adverse effects) could be achieved with higher doses.

Lastly, 69% to 75% of patients in the treatment groups completed the 16-week trial, but the authors of the study reported using 3 different analytic techniques to estimate missing data. The primary outcome included 178 of 196 randomized patients (90.8%). For the primary endpoint, the authors treated all missing data as non-headache days. It is unclear how these missing data would affect the outcome, although an analysis like this would tend towards a null effect.

CONTINUED

An estimated 38% of patients with migraines are appropriate candidates for prophylactic therapy, but only 3% to 13% are taking preventive medications.

CHALLENGES TO IMPLEMENTATION

Challenges are negligible

There are really no challenges to implementing this practice changer; melatonin is readily available over-the-counter and it is affordable. JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

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Oral agent offers relief from generalized hyperhidrosis

An inexpensive and well-tolerated anticholinergic reduces sweating in those with localized—and generalized—hyperhidrosis.

PRACTICE CHANGER

Use low-dose oxybutynin as a first-line treatment option for patients with primary hyperhidrosis to improve symptoms and quality of life.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single, good quality, randomized controlled trial.

Schollhammer M, Brenaut E, Menard-Andivot N, et al. Oxybutynin as a treatment for generalized hyperhidrosis: a randomized, placebo-controlled trial. *Br J Dermatol*. 2015;173:1163-1168.

ILLUSTRATIVE CASE

A 34-year-old woman presents to your office for unbearable sweating. She notes that the sweating occurs nearly daily on her hands, face, and in her axillary regions, causing social embarrassment. She has tried multiple antiperspirants to no avail. Is there anything she can take to reduce the sweating?

Hyperhidrosis is a common, self-limiting problem affecting 2% to 3% of the population in the United States.[2] Patients may complain of localized sweating of the hands, feet, face, or underarms or more systemic, generalized sweating in multiple locations. Either way, patients always note a significant impact on their quality of life.

Treatment of hyperhidrosis has traditionally focused on topical therapies to the affected areas. Research has shown that localized treatment with antiperspirants containing aluminum salt is effective by both subjective report and objective measurements at reducing sweating—particularly in the axilla, hands, and feet.[3,4] Additionally, a systematic review of observational and experimental studies found topical glycopyrrolate to be efficacious for craniofacial hyperhidrosis with minimal adverse effects.[5] The availability of low-cost prescription and over-the-counter aluminum-based antiperspirant agents makes topicals the first-line choice.

More invasive treatments are available for hyperhidrosis that is refractory to topicals. In a double-blind, randomized controlled trial, researchers injected either botulinum toxin type A (BTX-A) 50 U or placebo in patients with bilateral primary axillary hyperhidrosis.[6] Of the 207 patients who received treatment injections, 96.1% had at least a 50% reduction of axillary sweating at 4 weeks after one injection, as measured by gravimetric assessment. The BTX-A injections also produced a prolonged effect; mean duration between injections was 30.6 weeks.

Other invasive treatments include iontophoresis, surgery, and laser therapy; however, these methods are not suitable for body-wide application and are, thus, not appropriate for patients with generalized hyperhidrosis.

Oxybutynin is the first oral agent to emerge as a treatment option for hyperhidrosis. This cholinergic antagonist had historically been used to treat overactive bladder. As a cholinergic antagonist, oxybutynin not

only reduces urinary frequency, but also decreases secretions in various locations and, thus, can cause dry mouth and reduce perspiration.

In one prospective placebo-controlled trial, 50 patients with generalized hyperhidrosis were randomized to receive either oxybutynin titrated from 2.5 mg orally once daily to 5 mg orally twice daily or placebo for 6 weeks.[7] Seventeen (73.9%) patients receiving oxybutynin for palmar or axillary hyperhidrosis reported moderate to "great" resolution of their symptoms compared with 6 (27.3%) patients in the placebo group. Dry mouth was reported in 34.8% of patients receiving oxybutynin vs 9.1% of those who received placebo (P=.038); however, no patients dropped out of the study due to this adverse effect.[7]

STUDY SUMMARY

This multicenter, randomized controlled trial compared oxybutynin to placebo in 62 adults with localized or generalized hyperhidrosis from 12 outpatient dermatology practices in France. It is the first study to include patients with a localized, as well as a generalized form of the condition.

Patients were included if they were >18 years of age, enrolled in the National Health Insurance system in France, and reported a Hyperhidrosis Disease Severity Scale (HDSS) score ≥2. The HDSS is a validated, one-question tool ("How would you rate the severity of your sweating?"). Patients provide a score of 1 (no perceptible sweating and no interference with everyday life) to 4 (intolerable sweating with constant interference with everyday life).[8] Patients were excluded if they had any contraindications to the use of an anticholinergic medication.

Patients randomized to oxybutynin took 2.5 mg/d orally initially and increased gradually over 8 days until reaching an effective dose that was not more than 7.5 mg/d. They then continued at that dose for 6 weeks. The primary outcome was improvement on the HDSS by one or more points measured at the beginning of the trial and at 6 weeks. Secondary outcomes included change in quality of life, as measured by the Dermatology Life Quality Index (DLQI) and reported adverse effects. The DLQI is a dermatology-specific quality-of-life measure consisting of 10 questions. Scores range from 0 (where their disease has no impact on their quality of life) to 30 (maximum impact of their disease on their quality of life).[9]

Improved HDSS and DLQI scores. Most patients (83%) in the study had generalized hyperhidrosis. Patients were in their mid-thirties. Sixty percent of the patients in the oxybutynin group had an improvement of one point or more on the 4-point HDSS compared to 27% in the placebo group (P<.01). DLQI scores improved by 6.9 points in the oxybutynin group and 2.3 points in the placebo group (P<.01).

The most common adverse effect was dry mouth, which occurred in 13 patients (43%) in the oxybutynin group and in 3 patients (11%) in the placebo group (P<.01); it did not cause any patients to drop out of the study. The second most common adverse effect was blurred vision, which only occurred in the oxybutynin group (4 patients; 13%).

WHAT'S NEW

This is the first randomized controlled trial to demonstrate the efficacy of an oral agent for generalized primary hyperhidrosis. This trial used a relatively low dose of oxybutynin, which produced significant benefit while minimizing anticholinergic adverse effects.

CAVEATS

There are many situations for which anticholinergic medications are inappropriate, including use by geriatric patients and those with gastrointestinal disorders, urinary retention, or glaucoma.

CHALLENGES TO IMPLEMENTATION

Few if any challenges exist to the utilization of oxybutynin; inexpensive generic versions are widely available. JFP

ACKNOWLEDGEMENT
The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For

This trial used a relatively low dose of oxybutynin, which produced significant benefit while minimizing anticholinergic adverse effects.

Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

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Direct oral anticoagulants or warfarin for A fib?

A recent study evaluated the effectiveness of 3 direct oral anticoagulants and warfarin in patients with atrial fibrillation. So which agents came out on top?

PRACTICE CHANGER

Use direct oral anticoagulants instead of warfarin in patients with atrial fibrillation because they are just as effective at preventing ischemic stroke and systemic emboli as warfarin, and because apixaban and dabigatran have lower bleeding rates.

STRENGTH OF RECOMMENDATION

B: Based on a single, prospective, cohort study.

Larsen TB, Skjøth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2016;353:i3189.[1]

ILLUSTRATIVE CASE

A 66-year-old man with a history of hypertension and diabetes mellitus type 2 is hospitalized for palpitations and dizziness, and is given a diagnosis of atrial fibrillation (AF). His heart rate is successfully controlled with a beta-blocker. His CHA_2DS_2-VASc score is 3, meaning he is a candidate for anticoagulation. Which agent should you start?

Thromboembolism in patients with AF results in stroke and death and can be decreased with appropriate use of antithrombotic therapy. Evidence-based guidelines recommend patients with AF at intermediate or high risk of stroke ($CHADS_2$ score ≥2 or prior history of cardioembolic stroke or transient ischemic attack) receive antithrombotic therapy with oral anticoagulation, rather than receive no therapy or therapy with antiplatelets.[2,3]

The American College of Chest Physicians also recommends the use of the direct oral anticoagulant (DOAC) dabigatran over warfarin for those patients with nonvalvular AF with an estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2.[3]

A meta-analysis of large randomized controlled trials (RCTs) of individual DOACs (dabigatran [a direct thrombin inhibitor], rivaroxaban, apixaban, and edoxaban [factor Xa inhibitors]) revealed similar or lower rates of ischemic stroke and major bleeding (except gastrointestinal bleeds; relative risk=1.25; 95% CI, 1.01 to 1.55) when compared with warfarin (at an international normalized ratio [INR] goal of 2-3).[4] In addition, 3 separate meta-analyses that pooled results from large RCTs involving dabigatran, apixaban, and rivaroxaban also concluded that these medications result in a significant reduction in embolic stroke and reduced the risk of major bleeds and hemorrhagic stroke when compared with warfarin.[5-7]

However, we know less about the comparative effectiveness and safety of the DOACs when they are used in clinical practice, and it is not clear which, if any of these agents, are superior to others. Moreover, only about half of the patients in the United States with AF who are eligible to take DOACs are currently managed with them.[8]

STUDY SUMMARY

One DOAC is better than warfarin at one thing; 2 others are better at another

This large cohort study examined the effectiveness of 3 DOACs compared with warfarin in 61,678 patients with AF by combining data from 3 Danish national databases. The patients had newly diagnosed AF (without valvular disease or venous thromboembolism) and were prescribed standard doses of DOACs (dabigatran 150 bid [N=12,701], rivaroxaban 20 mg/d [N=7192], apixaban 5 mg bid [N=6349]) or dose-adjusted warfarin to an INR goal of 2 to 3 (N=35,436). Patients were followed for an average of 1.9 years.

Ischemic stroke, systemic emboli. In the first year of observation, there were 1702 ischemic strokes or systemic emboli. The incidence of ischemic stroke or systemic embolism was either the same or better for each of the 3 DOAC treatments than for warfarin (DOACs, 2.9-3.9 events per 100 person-years; warfarin, 3.3 events per 100 person-years; no *P* value provided). Ischemic stroke or systemic emboli events occurred less frequently in the rivaroxaban group compared with warfarin at one year (hazard ratio [HR]=0.83; 95% confidence interval [CI], 0.69-0.99) and after 2.5 years (HR=0.80; 95% CI, 0.69-0.94). The rates of ischemic stroke and systemic emboli for both apixaban and dabigatran were not significantly different than that for warfarin at one year and 2.5 years.

Bleeding events (defined as intracranial, major gastrointestinal, and traumatic intracranial) were lower in the apixaban group (HR=0.63; 95% CI, 0.53-0.76) and dabigatran group (HR=0.61; 95% CI, 0.51-0.74) than in the warfarin group at one year. Significant reductions remained after 2.5 years. There was no difference in bleeding events between rivaroxaban and warfarin.

Risk of death. Compared with warfarin, the risk of death after one year of treatment was lower in the apixaban (HR=0.65; 95% CI, 0.56-0.75) and dabigatran (HR=0.63; 95% CI, 0.48-0.82) groups, and there was no significant difference in the rivaroxaban group (HR=0.92; 95% CI, 0.82-1.03).

WHAT'S NEW

No agent "has it all," but DOACs have advantages

This comparative effectiveness and safety analysis reveals that all of the DOACs are at least as effective as warfarin in preventing ischemic stroke and systemic emboli, and that rivaroxaban may be more effective, and that apixaban and dabigatran have a lower risk of bleeding than warfarin.

CAVEATS

This non-randomized cohort trial lacked INR data

This study was a non-randomized cohort trial. And, while propensity weighting helps, the researchers were unable to completely control for underlying risk factors or unknown confounders.

INR data for patients on warfarin was not provided, so it is not clear how often patients were out of therapeutic range, which could affect the stroke and bleeding results in the warfarin group. This, however, is seen with routine use of warfarin. We feel that this study reflects the challenge of maintaining patients in warfarin's narrow therapeutic range.

CHALLENGES TO IMPLEMENTATION

It comes down to cost

Cost could be a barrier, as health insurance coverage for DOACs varies. Patients with high-deductible health insurance plans, or who find themselves in the Medicare "donut hole," may be at a particular disadvantage. JFP

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Rivaroxaban may be more effective than warfarin at preventing ischemic stroke and systemic emboli, and apixaban and dabigatran have a lower risk of bleeding.

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The benefits—and limits—of PPIs with warfarin regimens

Patients on warfarin + antiplatelet/NSAID regimens are likely to benefit from the gastroprotective effect of PPIs. For patients taking warfarin alone, it's a different story.

PRACTICE CHANGER

Prescribe a proton pump inhibitor for patients taking dual antiplatelet/antithrombotic therapy to reduce the risk of upper gastrointestinal bleeding.

STRENGTH OF RECOMMENDATION

B: Based on a cohort study

Ray WA, Chung CP, Murray KT, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. *Gastroenterology*. 2016;151:1105-1112.[1]

ILLUSTRATIVE CASE

A 60-year-old man establishes care with you. He has well-controlled osteoarthritis (as long as he takes his low-dose daily aspirin) and chronic atrial fibrillation, for which he takes warfarin. His international normalized ratio (INR) is consistently within the recommended target range of 2 to 3. He feels well and has never had gastroesophageal reflux disease (GERD) or a gastrointestinal (GI) bleed. Should you recommend a proton pump inhibitor (PPI) to decrease the likelihood of a future upper GI bleed?

Anticoagulation therapy creates a dilemma—the need to balance the benefits of preventing embolization with the risks of serious bleeding. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and other antiplatelet agents further increases the risk of the latter.[2]

Physicians have long used PPIs to treat upper GI bleeds. They prevent acid secretion and are the most efficacious drugs for healing peptic ulcers.[3,4] However, while previous case-control studies show that PPIs reduce the risk of upper GI bleeds in patients taking antiplatelet agents or NSAIDs, they do not show a statistically significant benefit for patients taking warfarin.[5,6] Further reflecting the confusion and uncertainty surrounding this issue is that while one expert consensus report recommends that patients taking dual warfarin and antiplatelet agent/NSAID therapy take a PPI to decrease the risk of upper GI bleeding,[2] other guidelines regarding anticoagulant therapy do not address this clinical question.[2,7,8]

STUDY SUMMARY

Study lends support to PPI use in a high-risk group

This retrospective cohort study sought to answer the question: "Does PPI co-therapy decrease the rate of serious upper GI bleeds in patients taking warfarin?" Researchers examined rates of hospitalization for upper GI bleeding for Medicare and Medicaid patients taking warfarin with and without PPI co-therapy (tracked via prescription fill dates). They also evaluated concomitant use of NSAIDs and antiplatelet agents.

The authors excluded patients with a recent history of a severe bleed or certain illnesses that would predispose a patient to GI bleeding (such as esophageal varices). Patients with risk factors for an upper GI bleed

(such as abdominal pain, peptic ulcer disease, anemia, etc.) were more likely to be taking PPI co-therapy. Researchers analyzed the effect of PPI co-therapy in patients with and without these additional risk factors.

Results. The study followed over 75,000 person-years of active warfarin therapy (more than 52,000 person-years in the Medicaid cohort and more than 23,000 person-years in the Medicare cohort). Hospitalizations due to upper GI bleeding occurred at a rate of 127/10,000 person-years (incidence was similar in both the Medicaid and Medicare groups).

Looking at *all* patients taking warfarin (regardless of whether or not they were also taking an NSAID or antiplatelet agent), PPI co-therapy reduced the risk of hospitalization for upper GI bleeding by 24% (adjusted hazard ratio [HR]=0.76; 95% confidence interval [CI], 0.63 to 0.91), which translates into 29 fewer hospitalizations per 10,000 person-years. The number needed to treat (NNT) was 345 person-years, meaning 345 patients taking warfarin would have to take a PPI for one year to prevent one hospitalization for an upper GI bleed. As one might expect, PPI co-therapy did not significantly reduce the risk of lower GI, other GI, or non-GI bleeding.

In patients taking both warfarin and concurrent antiplatelet agents or NSAIDs, PPI co-therapy reduced the risk of hospitalization for upper GI bleeding by about half (HR=0.55; 95% CI, 0.39-0.77). Hospitalizations decreased by 128/10,000 person-years (95% CI, -66 to -173), yielding an NNT of 78 person-years. For patients taking warfarin but *not* antiplatelet agents or NSAIDs, PPI co-therapy did not significantly decrease the risk of hospitalization for upper GI bleeding (HR=0.86; 95% CI, 0.70-1.06).

Additional risk factors for GI bleeds. Researchers also looked at patients who had additional risk factors for GI bleeds (other than the exclusion criteria). For patients taking both warfarin and an antiplatelet agent/NSAID, PPI co-therapy decreased the risk of upper GI bleeding whether or not the patients had other bleeding risk factors. Again, for patients who had additional bleeding risk factors, but were not taking an antiplatelet agent or NSAID, PPI therapy showed no statistically significant effect.

WHAT'S NEW

PPIs offer benefits, but not to patients taking warfarin alone

The statistically significant results in this large observational study suggest that PPI co-therapy is beneficial in reducing the risk of upper GI bleeding in patients taking warfarin *plus* an antiplatelet agent/NSAID, but that PPI co-therapy provides no benefit to patients taking warfarin exclusively.

CAVEATS

Study was good, but it wasn't a randomized controlled trial

This study is observational, and not a randomized control trial (RCT). Therefore, unknown confounding variables may have skewed results. For example, patients could have taken over-the-counter medications that influenced or obscured results, but were not included in the data analysis (misclassification bias).

At best, we can infer a correlation between PPIs and decreased risk of upper GI bleeds. We need RCTs to determine whether PPIs *cause* a lower risk.

Don't overlook the risk of PPIs. This study assessed the ability of PPIs to prevent bleeds, but did not address the risks of long-term PPI therapy. Adverse effects of PPIs include an increased risk of pneumonia, infection with *Clostridium difficile*, hip and spine fractures, anemia, and possibly chronic kidney disease and dementia.[9-11] In addition, cost-analysis studies of PPI therapy are limited and inconsistent.[12] Therefore, it's best to make decisions regarding PPIs after discussing other risks and benefits.

What about DOACs? Another consideration is the option to prescribe a direct oral anticoagulant (DOAC), such as dabigatran, rivaroxaban, or apixaban, instead of warfarin. DOACs are at least as effective as warfarin at preventing stroke in patients with atrial fibrillation and may even be safer.[13] Dabigatran 110 mg causes fewer "major bleeding" events than warfarin.[13] Rivaroxaban has been shown to result in fewer fatal bleeding events than warfarin due to fatal intracranial bleeds, although it is associated with more GI bleeding.[13] Compared with warfarin, apixaban is

Further research is warranted to determine if PPI therapy is beneficial to patients taking direct oral anticoagulants.

associated with fewer GI bleeds and lower bleeding rates overall.[13] Further research is warranted to determine if PPI therapy is beneficial to patients taking DOACs.

CHALLENGES TO IMPLEMENTATION

It's still a balancing act

When chronic anticoagulation is necessary, physicians and patients must attempt to prevent thrombotic events while minimizing the risk of GI bleeds. PPIs may be beneficial in preventing upper GI bleeds in patients taking dual warfarin and antiplatelet therapy, but the long-term consequences of PPI therapy should not be ignored. JFP

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Should you bypass anticoagulant "bridging" before and after surgery?

Skipping perioperative use of LMWH in low- and moderate-risk patients on warfarin for atrial fibrillation doesn't increase their risk of stroke or bleeding.

PRACTICE CHANGER

Stop using low molecular weight heparin (LMWH) for surgical procedures to "bridge" low- to moderate-risk patients with atrial fibrillation ($CHADS_2$ score ≤4) who are receiving warfarin. The risks outweigh the benefits.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single good-quality randomized control trial.

Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373:823-833.

ILLUSTRATIVE CASE

A 75-year-old man comes to your office for surgical clearance before right knee replacement surgery. He has diabetes and high blood pressure, and is taking warfarin for atrial fibrillation. He is scheduled for surgery in a week. What is the safest way to manage his warfarin in the perioperative period?

More than 2 million people are being treated with oral anticoagulation in North America to prevent stroke, or to prevent or treat venous thromboembolism.[2] Since 2010, several new oral anticoagulants have been approved, including dabigatran, apixaban, and rivaroxaban. These new medications have a shorter half-life than older anticoagulants, which enables them to be stopped 1 to 2 days before surgery.

On the other hand, warfarin—which remains a common choice for anticoagulation—has a 3- to 7-day onset and elimination.[3,4] This long clinical half-life presents a special challenge during the perioperative period. To reduce the risk of operative bleeding, the warfarin must be stopped days prior to the procedure, but physicians often worry that this will increase the risk of arterial or venous thromboembolism, including stroke.

An estimated 250,000 patients need perioperative management of their anticoagulation each year.[5] As the US population continues to age and the incidence of conditions requiring anticoagulation (particularly atrial fibrillation) increases, this number is only going to rise.[6]

Current guidelines on bridging. American College of Chest Physicians (ACCP) guidelines recommend transition to "a short-acting anticoagulant, consisting of subcutaneous low molecular weight heparin (LMWH) or intravenous unfractionated heparin, for a 10- to 12-day period during interruption of vitamin K antagonist (VKA) therapy."[5] Furthermore, for an appropriate bridging regimen, the ACCP guidelines recommend stopping VKA therapy 5 days prior to the procedure and utilizing LMWH from within 24 to 48 hours of stopping VKA therapy until up to 24 hours before surgery.[5] Postoperatively, VKA or LMWH therapy should be reinitiated within 24 hours and 24 to 72 hours,

respectively, depending on the patient's risk of bleeding during surgery.[5]

These guidelines recommend using $CHADS_2$ scoring (**TABLE**[3]) to determine arterial thromboembolism (ATE) risk in atrial fibrillation.[3,5] Patients at low risk for ATE ($CHADS_2$ score 0-2) should not be bridged, and patients at high risk ($CHADS_2$ score of 5-6) should always be bridged.[5] These guidelines are less clear about bridging recommendations for moderate-risk patients ($CHADS_2$ score 3-4).

Previous evidence on bridging. A 2012 meta-analysis of 34 studies evaluated the safety and efficacy of perioperative bridging with heparin in patients receiving VKA.[7] Researchers found no difference in ATE events in 8 studies that compared groups that received bridging vs groups that simply stopped anticoagulation (odds ratio [OR]=0.80; 95% confidence interval [CI], 0.42–1.54).[7] The group that received bridging had an increased risk of overall bleeding in 13 studies, and of major bleeding in 5 studies.[7] This meta-analysis was limited by poor study quality and variation in the indication for VKA therapy.

A 2015 subgroup analysis of a larger cohort study of patients receiving anticoagulants for atrial fibrillation found an increased risk of bleeding when their anticoagulation was interrupted for procedures (OR for major bleeding=3.84; 95% CI, 2.07-7.14; $P<.0001$).[8]

Douketis et al[1] conducted a randomized trial to clarify the need for and safety of bridging anticoagulation for ATE in patients with atrial fibrillation who were receiving warfarin.

TABLE

$CHADS_2$: Assessment of arterial thromboembolic risk in atrial fibrillation[3]

Risk factor ($CHADS_2$)	Score
Congestive heart failure	1
Hypertension	1
Age >75 years	1
Diabetes mellitus	1
Stroke/TIA	2
Maximum score	**6**

TIA, transient ischemic attack.

STUDY SUMMARY

When it comes to stroke/TIA, there's no advantage to bridging

This double blind, placebo-controlled trial compared bridging with dalteparin, a form of LMWH, to placebo among 1884 patients with atrial fibrillation on warfarin whose anticoagulation therapy needed to be interrupted for an elective procedure. Patients were included if they were receiving warfarin to prevent stroke, and had been on warfarin for at least 12 weeks, with a goal international normalized ratio (INR) of 2.0 to 3.0. Exclusion criteria included having a mechanical heart valve or having a stroke/transient ischemic attack (TIA; 12 weeks prior) or major bleeding (6 weeks prior). Cardiac, intracranial, and intraspinal surgeries were also excluded from the study.

The patients' mean $CHADS_2$ score was 2.3; 38.3% of patients had a $CHADS_2$ score ≥3, and 9.4% of patients had a history of stroke. Forty-four percent of patients underwent a gastrointestinal procedure, 17.2% underwent a cardiothoracic procedure, and 9.2% underwent an orthopedic procedure.

Patients stopped taking warfarin 5 days before their procedure, and began subcutaneous dalteparin, 100 IU/kg, or an identical placebo 3 days before the procedure. The dalteparin/placebo was stopped 24 hours before the procedure and restarted after the procedure, until the patient's INR was in the therapeutic range. Warfarin was resumed on the evening of the procedure or the following day.

The primary efficacy outcome was ATE, including stroke, TIA, or systemic embolism. The primary safety endpoint was major bleeding (defined as bleeding at a critical anatomic site, symptomatic or clinically overt bleeding, or a decrease in hemoglobin >2 g/dL). Secondary efficacy and safety outcomes included minor bleeding, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, and death. Outcomes were assessed within 37 days of the procedure.

The incidence of ATE was 0.4% (4 events)

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Guidelines are not clear about whether patients at moderate risk of arterial thromboembolism need bridging.

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in the no-bridging group vs 0.3% (3 events) in the bridging group (95% CI, -0.6 to 0.8; *P*=.01 for non-inferiority; *P*=.73 for superiority). Major bleeding occurred in 1.3% of the no-bridging group (12 events) and in 3.2% of the bridging group (29 events), indicating that no bridging was superior in terms of the major bleeding outcome (number needed to harm [NNH]=53; relative risk [RR]=0.41; 95% CI, 0.20-0.78; *P*=.005). The no-bridging group also had significantly fewer minor bleeds in comparison to the bridging group (NNH=11; 12% vs 20.9%; *P*<.001). There were no differences between groups in other secondary outcomes.

This study suggests patients who receive bridging have a higher risk of bleeding than stroke.

WHAT'S NEW

High-quality evidence suggests it's OK to stop warfarin before surgery

This is the largest good-quality study to evaluate perioperative bridging in patients with atrial fibrillation who were at low or moderate risk for ATE ($CHADS_2$ score 0-4). Previous studies suggested bridging increased bleeding and offered limited benefit for reducing the risk of ATE. However, this is the first study to include a large group of moderate-risk patients ($CHADS_2$ score 3-4). This trial provides high-quality evidence to support the practice of simply stopping warfarin in the perioperative period, rather than bridging with LMWH.

CAVEATS

Findings might not apply to patients at highest risk

Most patients in this study had a $CHADS_2$ score ≤3. About 3% had a $CHADS_2$ score ≥5 or higher. It's not clear whether these findings apply to patients with a $CHADS_2$ score of 5 or 6.

This trial categorized ATE risk using the $CHADS_2$ score, rather than the CHA_2DS_2-VASc, which includes additional risk factors and may more accurately predict stroke risk. Both patients who received bridging therapy and those who did not had a lower rate of stroke than predicted by $CHADs_2$. This may reflect a limit of the predictive value of $CHADS_2$, but should not have affected the rate of bleeding or ATE outcomes in this study.

CHALLENGES TO IMPLEMENTATION

Physicians may hesitate to disregard current guidelines

Strokes are devastating events for patients, families, and physicians, and they pose a greater risk of morbidity and mortality compared to bleeding. However, this study suggests patients who receive bridging have a higher risk of bleeding than stroke, which is in contrast to some physicians' experience and current recommendations.

A physician caring for a patient who's had a stroke may be inclined to recommend bridging despite the lack of efficacy and evidence of bleeding risk. Additionally, until guidelines reflect the most current research, physicians may be reluctant to provide care in contrast to these recommendations. JFP

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Dr. Smith is a military service member. This work was prepared as part of his official duties.

"Cold turkey" works best for smoking cessation

Counsel patients who want to quit smoking that doing so abruptly leads to higher cessation rates than does quitting gradually.

PRACTICE CHANGER

Counsel patients who want to quit smoking that abrupt smoking cessation is more effective for long-term abstinence than taking a gradual approach.

STRENGTH OF RECOMMENDATION

B: Based on one well-designed, randomized controlled trial.

Lindson-Hawley N, Banting M, West R, et al. Gradual versus abrupt smoking cessation: a randomized, controlled noninferiority trial. *Ann Intern Med.* 2016;164:585-592.[1]

ILLUSTRATIVE CASE

A 43-year-old man has a 35-pack-year smoking history and currently smokes a pack of cigarettes a day. He is eager to quit smoking after recently learning that a close friend of his has been diagnosed with lung cancer. He asks you whether he should quit "cold turkey" or gradually. What would you recommend?

Between 2013 and 2014, one in 5 American adults reported using tobacco products some days or every day, and 66% of smokers in 2013 made at least one attempt to quit.[2,3] The risks of tobacco use and the benefits of cessation are well established, and behavioral and pharmacologic interventions both alone and in combination increase smoking cessation rates.[4] The US Preventive Services Task Force recommends that health care providers address tobacco use and cessation with patients at regular office visits and offer behavioral and pharmacologic interventions.[5] Current guidelines, however, make no specific recommendations regarding gradual vs abrupt smoking cessation methods.[5]

A previous Cochrane review of 10 randomized controlled trials demonstrated no significant difference in quit rates between gradual cigarette reduction leading up to a designated quit day and abrupt cessation. The meta-analysis was limited, however, by differences in patient populations, outcome definitions, and types of interventions (both pharmacologic and behavioral).[6]

In a retrospective cohort study, French investigators reviewed an online database of 62,508 smokers who presented to nationwide cessation services. The researchers found that older participants (≥45 years of age) and heavy smokers (≥21 cigarettes/d) were more likely to quit gradually than abruptly.[7]

STUDY SUMMARY

Quitting "cold turkey" is better than gradual cessation at 6 months

Lindson-Hawley, et al, conducted a randomized, controlled, non-inferiority trial in England to assess if gradual cessation is as successful as abrupt cessation as a means of quitting smoking.[1] The primary outcome was abstinence from smoking at 4 weeks, assessed using the Russell Standard, a set of 6 standard criteria (including validation by exhaled carbon monoxide concentrations of <10 ppm) used by the National Centre for Smoking Cessation and Training to decrease variability of

reported smoking cessation rates in English studies.[8]

Study participants were recruited via letters from their primary care practice inviting them to call the researchers if they were interested in participating in a smoking cessation study. Almost 1100 people inquired about the study. In the end, 697 were randomized to either the abrupt-cessation group (n=355) or the gradual-cessation group (n=342). Baseline characteristics between the 2 groups were similar.

All participants were asked to schedule a quit date for 2 weeks after their enrollment. Patients randomized to the gradual-cessation group were provided nicotine replacement patches (21 mg/d) and their choice of short-acting nicotine replacement therapy (NRT) (gum, lozenges, nasal spray, sublingual tablets, inhalator, or mouth spray) to use in the 2 weeks leading up to the quit date, along with instructions to reduce smoking by half of the baseline amount by the end of the first week, and to a quarter of baseline by the end of the second week.

Patients randomized to the abrupt-cessation group were instructed to continue their current smoking habits until the cessation date; during those 2 weeks they were given nicotine patches (because the other group received them and some evidence suggests that precessation NRT increases quit rates), but no short-acting NRT.

Following the cessation date, treatment in both groups was identical, including behavioral support, 21 mg/d nicotine patches, and the participant's choice of short-acting NRT. Behavioral support consisted of visits with a research nurse at the patient's primary care practice weekly for 2 weeks before the quit date, the day before the quit date, weekly for 4 weeks after the quit date, and 8 weeks after the quit date.

The chosen non-inferiority margin was equal to a relative risk (RR) of 0.81 (19% reduction in effectiveness) of quitting gradually compared with abrupt cessation of smoking. Quit rates in the gradual-reduction group did not reach the threshold for non-inferiority; in fact, 4-week abstinence was significantly more likely in the abrupt-cessation group (49%) than in the gradual-cessation group (39.2%) (RR=0.80; 95% confidence interval [CI], 0.66-0.93; number needed to treat [NNT]=10). Similarly, secondary outcomes of 8-week and 6-month abstinence rates showed superiority of abrupt over gradual cessation. At 6 months after the quit date, 15.5% of the gradual-cessation group and 22% of the abrupt-cessation group remained abstinent (RR=0.71; 95% CI, 0.46-0.91; NNT=15).

Patients' preferred method of cessation plays a role

The investigators also found a difference in successful cessation based on the participants preferred method of cessation. Participants who preferred abrupt cessation were more likely to be abstinent at 4 weeks than participants who preferred gradual cessation (52.2% vs 38.3%; *P*=.007).

Patients with a baseline preference for gradual cessation were equally as likely to successfully quit when allocated to abrupt cessation against their preference as when they were allocated to gradual cessation: 4-week abstinence was seen in 34.6% of patients who preferred gradual cessation and were allocated to gradual cessation and in 42% of patients who preferred gradual cessation but were allocated to abrupt cessation (*P*=.152).

People who prefer gradual cessation are less likely to be successful at quitting—regardless of whether they try to quit abruptly or gradually.

WHAT'S NEW

Higher quality than previous studies and added element of preference

This large, well-designed, non-inferiority study showed that abrupt cessation is superior to gradual cessation. The size and design of the study, including a standardized method of assessing cessation and a standardized intervention, make this a higher quality study than those in the Cochrane meta-analysis.[6] This study also showed that participants who preferred gradual cessation were less likely to be successful—regardless of the method to which they were ultimately randomized.

CAVEATS

Generalizability limited by race and number of cigarettes smoked

Patients lost to follow-up at 4 weeks (35 in

the abrupt-cessation group and 48 in the gradual-cessation group) were assumed to have continued smoking, which may have biased the results toward abrupt cessation. That said, the large number of participants included in the study, along with the relatively small number of patients lost to follow-up, minimizes this weakness.

The participants were largely white, which may limit generalizability to non-white populations. In addition, participants smoked an average of 20 cigarettes per day and, as noted previously, an observational study of tobacco users in France found that heavy smokers (≥21 cigarettes/d) were more likely to quit gradually than abruptly, so results may not be generalizable to heavy smokers.[7]

CHALLENGES TO IMPLEMENTATION

Finding the time and staff for considerable behavioral support

One important challenge is the implementation of such a structured tobacco cessation program in primary care. Both abrupt- and gradual-cessation groups were given considerable behavioral support from research nurses. Participants in this study were seen by a nurse 7 times in the first 6 weeks of the study, and the intervention included nurse-created reduction schedules.

Even if patients in the study preferred one method of cessation to another, they were receptive to quitting either gradually or abruptly. In clinical practice, patients are often set in their desired method of cessation. In that setting, our role is then to inform them of the data and support them in whatever method they choose. **JFP**

ACKNOWLEDGEMENT

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Lipids

Gary Ferenchick MD MS

Objectives

Understand:

1. The USPSTF recommendations on statin use in adults aged 40 -75
2. The USPSTF recommendations on screening for lipid disorders in children (aged < 20)
3. That major guidelines on statin therapy differ
4. That nonfasting lipid profiles are minimally different than fasting profiles
5. Some strategies for managing statin associated muscle symptoms (SAMS)
6. Outcome data and cost concerning PCSK9 antibodies
7. The ACC AHA guidance on non-stain therapies for ASCVD

USPSTF Recommendations on statin use (ver batim)

- The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. (Grade B | Offer or provide this service.)
- Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10-year CVD event risk of less than 10%, the likelihood of benefit is smaller, because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%. (Grade C | Offer or provide this service for selected patients depending on individual circumstances.)
- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years and older without a history of heart attack or stroke. (Grade I | If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.)

In the clinical considerations, section of the document the USPSTF concluded that for primary prevention in those aged 40-75 with at least one risk factor, use of low- or moderate-dose statins was associated with *reduction* of:

- All-cause mortality | 14%
- CV mortality | 31%
- Ischemic CVA | 29%
- MI | 36%
- Composite CV outcomes | 30%

Statins used in primary prevention trials

	Low Dose (mg)	Moderate Dose (mg)
Atorvastatin		10-20
Fluvastatin	20 - 40	40 twice daily
Fluvastatin extended release		80
Lovastatin	20	40

Pitavastatin	1	2 - 4
Pravastatin	10 - 20	40 - 80
Rosuvastatin		5 - 10
Simvastatin	10	20 - 40

USPSTF | Accessed January 27 2018

1. POEM: USPSTF recommends statin use for adult s aged 40 – 75 for primary prevention of CVD

Clinical question: What are the benefits and harms of statin treatment for dyslipidemia in adults 21 years and older?
Study design: Practice guideline
Setting: Population-based
Synopsis: The USPSTF found adequate evidence of a benefit of low- to moderate-dose statins for reducing the probability of CVD events and mortality in adults aged 40 to 75 years with at least 1 CVD risk factor and a calculated 10-year CVD event risk of 10% or greater. In addition, the harms of low- to moderate-dose statins in adults aged 40 to 75 years are small. Although myalgia is a commonly reported adverse effect of statin use, controlled trial data do not support any increased risk of myalgia with the use of statins compared with placebo. The USPSTF recognizes that the best currently available risk-estimation tool in the United States uses the Pooled Cohort Equations calculator from the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Since this tool has been shown to overestimate actual risk, clinicians should use the results to discuss with individual patients whether they want to pursue lifelong statin therapy. The current recommendations do not apply to adults with a low-density lipoprotein cholesterol level greater than 190 mg/dL (4.9 mmol/L). The USPSTF does not recommend for or against the use of C-reactive protein levels as a risk factor in screening for CVD. There is also insufficient evidence that screening for dyslipidemia before age 40 is beneficial in preventing CVD. The ACC/AHA recommends statin use for primary prevention in adults aged 40 to 75 years with an estimated 10-year CVD event risk from 7.5% to 10%.
Bottom line: The United States Preventive Services Task Force (USPSTF) now recommends that adults without a history of cardiovascular disease (CVD) use a low- to moderate-dose statin for the primary prevention of CVD events when ALL THREE of the following criteria are met: The patient (1) is 40 to 75 years old; (2) has at least one CVD risk factor (ie, dyslipidemia, diabetes, hypertension, or smoking); and (3) has a calculated 10-year risk of a CVD event of 10% or greater (B recommendation). The USPSTF further concludes that statin use may be beneficial for the primary prevention of CVD events in some adults aged 40 to 70 years with at least 1 CVD risk factor and a 10-year CVD event risk of 7.5% to 10%, although the likelihood of benefit is smaller (C recommendation). Finally, current evidence is insufficient to assess whether to initiate statin therapy for prevention of CVD events in adults 76 years or older (I statement).
Bibbins-Domingo K; US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults. US Preventive Services Task Force recommendation statement. JAMA 2016;316(19):1997-2007.

2. POEM: Lipid treatment for primary prevention not effective in older adults

Clinical question: In patients older than 65 years with elevated low-density lipoprotein levels but no cardiovascular disease, is cholesterol lowering effective in decreasing mortality or morbidity?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: This report is an analysis of a trial that evaluated the primary prevention of cardiovascular disease using cholesterol lowering. It focused on patients who were at least 65 years old and had an elevated fasting low-density lipoprotein cholesterol (LDL-C) level (120 - 189 mg/dL [3.1 - 4.9 millimoles/L]). The Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) study enrolled 2867 adults 65 years or older with hypertension but without baseline atherosclerotic cardiovascular disease. The patients were randomized, using concealed allocation, to receive usual care or pravastatin 40 mg daily. Most of the patients in the usual care group were not treated with a statin. Over the 6 years of follow-up, all-cause mortality was not different between the 2 treatment groups for patients 65 to 74 years of age (hazard ratio for pravastatin vs usual care = 1.08 (95% CI, 0.85-1.37; P = .55) and was almost statistically higher for patients at least 75 years of age (hazard ratio of pravastatin vs usual care = 1.34 (0.98-1.84; P = .07). Rates of coronary heart disease events were not different between the groups in either age group. Analysis was by intention to treat. Given that this is a post-hoc analysis, the researchers did not provide a power calculation and there might be a small difference in rates that was not see in this study.
Bottom line: If a patient makes it to 65 years old without developing cardiovascular disease, lowering his or her cholesterol level at this point is not effective, and might even be harmful if treatment is started at age 75. Given the lack of benefit also shown in other studies, it might be time to stop checking—and treating—high cholesterol in these age groups.
Reference: Han BH, Sutin D, Williamson JD, et al, for the ALLHAT Collaborative Research Group. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults. The ALLHAT-LLT randomized clinical trial. JAMA Intern Med 2017; doi:10.1001/jamainternmed.2017.1442.

3. Center for Medical Education: USPSTF (I) recommendation for lipid screening in children

METHODS: The authors, writing for the USPSTF, present a clinical practice guideline that addresses screening for lipid disorders in asymptomatic children and adolescents aged 20 years or younger, representing an update to its 2007 guideline. The panel assessed the balance of benefits and harms based on two systematic reviews of the evidence in populations with heterozygous familial hypercholesterolemia (an autosomal dominant disorder of mutations in the LDL receptor gene) or multifactorial dyslipidemia (primarily due to obesity).
RESULTS: US estimates show that 8% of children aged 8-17 have elevated total cholesterol levels (200 mg/dL or higher) and 7% aged 12-19 have elevated LDL cholesterol levels (130 mg/dL or higher). Lipid elevations in general reportedly increase the risk of atherosclerosis and cardiovascular disease (CVD) events. The USPSTF found inadequate evidence that pharmacotherapy or lifestyle

changes substantially reduce lipid parameters, atherosclerosis markers or premature CVD in persons with either familial hypercholesterolemia or multifactorial dyslipidemia. Evidence was also inadequate to assess the harms of screening or long-term treatment, although overdiagnosis is possible in children with multifactorial dyslipidemia. Differences in the diagnostic yield of universal versus selective screening could not be determined. It is also unclear whether changes in lipid levels or atherosclerotic parameters directly correlate with improvements in adult CVD outcomes.
CONCLUSIONS: Evidence is insufficient to assess the benefit-risk balance of screening for lipid disorders in persons aged 20 years or younger. It is suggested that obese children older than six years should be referred for behavioral interventions. 33 references (chair@uspstf.net – no reprints)
REFERENCE: The USPSTF. SCREENING FOR LIPID DISORDERS IN CHILDREN AND ADOLESCENTS: US PREVENTIVE SERVICES TASK FORCE RECOMMENDATION STATEMENT. JAMA 316(6):625, August 9, 2016

Major Guidelines on Statin Therapy Differ

In the past 5 years, the following organizations have published major guidelines on statins for primary prevention of ASCVD:

- American College of Cardiology/American Heart Association (ACC/AHA | 2013)
- United Kingdom's National Institute for Health and Care Excellence (NICE | 2014)
- Canadian Cardiovascular Society (CCS | 2016)
- U.S. Preventive Services Task Force (USPSTF | 2016)
- European Society of Cardiology/European Atherosclerosis Society (ESC/EAS | 2016)

The five guidelines have substantial differences (in spite of being founded on the same evidence) in the:

- recommended prediction model for ASCVD
- risk threshold
- low-density lipoprotein cholesterol (LDL-C) cut point for assignment of statin use

According to Mortensen (abstract #4)

"…statin therapy now constitutes the cornerstone of all major ASCVD prevention guidelines and has become the most commonly prescribed class of medication in the United States and Europe." Given this they did a "…head-to-head comparison of the 5 major guidelines in a contemporary cohort, in which 45,750 participants were selected from the general population, were aged 40 to 75 years, and were free of ASCVD and did not use statins at baseline between 2003 and 2009".

The following table shows the overall agreement between these guidelines in stating treatment (or not) for primary prevention in adults 40 – 75 years of age. Table from Ann Intern Med. 2018 Jan 16; 168(2):85-92)

Supplement Table 4. Overall agreement in statin recommendation (to treat or not to treat) between five major guidelines on statin use for primary prevention. The percentages were calculated as the number of individuals recommended for statin by both guidelines + the number of individuals not recommended for statin by both guidelines (number shown in the cells of the table) divided by the total number of individuals aged 40-75 years in Copenhagen General Population Study (n=45750).

All

Guidelines	*CCS*	*ACC/AHA*	*NICE*	*USPSTF*
CCS				
ACC/AHA	37343/45750 (82%)			
NICE	38089/45750 (83%)	40526/45750 (89%)		
USPSTF	37057/45750 (81%)	39802/45750 (87%)	40618/45750 (89%)	
ESC/EAS	31611/45750 (69%)	30008/45750 (66%)	33666/45750 (74%)	33162/45750 (72%)

4. Pubmed: Statin guidelines recommending more persons use statins prevent more events

Background: Five major organizations recently published guidelines for using statins to prevent atherosclerotic cardiovascular disease (ASCVD): in 2013, the American College of Cardiology/American Heart Association (ACC/AHA); in 2014, the United Kingdom's National Institute for Health and Care Excellence (NICE); and in 2016, the Canadian Cardiovascular Society (CCS), the U.S. Preventive Services Task Force (USPSTF), and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS).
Objective: To compare the utility of these guidelines for primary prevention of ASCVD.
Design: Observational study of actual ASCVD events during 10 years, followed by a modeling study to estimate the effectiveness of different guidelines.
Setting: The Copenhagen General Population Study.
Participants: 45 750 Danish persons aged 40 to 75 years who did not use statins and did not have ASCVD at baseline.
Measurements: The number of participants eligible to use statins according to each guideline and the estimated number of ASCVD events that statins could have prevented.
Results: The percentage of participants eligible for statins was 44% by the CCS guideline, 42% by ACC/AHA, 40% by NICE, 31% by USPSTF, and 15% by ESC/EAS. The estimated percentage of ASCVD events that could have been prevented by using statins for 10 years was 34% for CCS, 34% for ACC/AHA, 32% for NICE, 27% for USPSTF, and 13% for ESC/EAS.
Limitation: This study was limited to primary prevention in white Europeans.
Conclusion: Guidelines recommending that more persons use statins for primary prevention of ASCVD should prevent more events than guidelines recommending use by fewer persons.
Primary Funding Source: Copenhagen University Hospital.
Reference: Mortensen MB, Nordestgaard BG.Comparison of Five Major Guidelines for Statin Use in Primary Prevention in a Contemporary General Population. Ann Intern Med. 2018 Jan 16;168(2):85-92.

Non Fasting Lipids

Mora et al have concluded that studies show "... clinically insignificant differences between fasting and nonfasting levels for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Prospective studies and meta-analyses have found that nonfasting lipids correlate with cardiovascular risk (ie, clinical events and mortality) at least as well as fasting measurements. (JAMA Intern Med. 2016 Jul 1;176(7):1005-6). Note however, the ACC still endorses fasting lipid assessments for initial assessment and follow up assessments.

5. PubMed: Non-fasting blood samples should be routinely used for lipid assessment

AIMS: To critically evaluate the clinical implications of the use of non-fasting rather than fasting lipid profiles and to provide guidance for the laboratory reporting of abnormal non-fasting or fasting lipid profiles.
METHODS AND RESULTS: Extensive observational data, in which random non-fasting lipid profiles have been compared with those determined under fasting conditions, indicate that the maximal mean changes at 1-6 h after habitual meals are not clinically significant [+0.3 mmol/L (26 mg/dL) for triglycerides; -0.2 mmol/L (8 mg/dL) for total cholesterol; -0.2 mmol/L (8 mg/dL) for LDL cholesterol; +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol; -0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol]; concentrations of HDL cholesterol,apolipoprotein A1, apolipoprotein B, and lipoprotein(a) are not affected by fasting/non-fasting status. In addition, non-fasting and fasting concentrations vary similarly over time and are comparable in the prediction of cardiovascular disease. To improve patient compliance with lipid testing, we therefore recommend the routine use of non-fasting lipid profiles, while fasting sampling may be considered when non-fasting triglycerides >5 mmol/L (440 mg/dL). For non-fasting samples, laboratory reports should flag abnormal concentrations as triglycerides ≥2 mmol/L (175 mg/dL), total cholesterol ≥5 mmol/L (190 mg/dL), LDL cholesterol ≥3 mmol/L (115 mg/dL), calculated remnant cholesterol ≥0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol ≥3.9 mmol/L (150 mg/dL), HDL cholesterol ≤1 mmol/L (40 mg/dL), apolipoprotein A1 ≤1.25 g/L (125 mg/dL), apolipoprotein B ≥1.0 g/L (100 mg/dL), and lipoprotein(a) ≥50 mg/dL (80th percentile); for fasting samples, abnormal concentrations correspond to triglycerides ≥1.7 mmol/L (150 mg/dL). Life-threatening concentrations require separate referral when triglycerides >10 mmol/L (880 mg/dL) for the risk of pancreatitis, LDL cholesterol >13 mmol/L (500 mg/dL) for homozygous familial hypercholesterolaemia, LDL cholesterol >5 mmol/L (190 mg/dL) for heterozygous familial hypercholesterolaemia, and lipoprotein(a) >150 mg/dL (99th percentile) for very high cardiovascular risk.
CONCLUSION: We recommend that non-fasting blood samples be routinely used for the assessment of plasma lipid profiles. Laboratory reports should flag abnormal values on the basis of desirable concentration cut-points. Non-fasting and fasting measurements should be complementary but not mutually exclusive.
REFERENCE: Nordestgaard BG et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016 Jul 1;37(25):1944-58.

Statin Associated Muscle Symptoms (SAMS)

In abstract # 6 (below) SAMS is defined as the "inability to tolerate two or more statins, 1 at low dose, because of unexplained skeletal muscle related symptoms (for example pain aches weakness or cramping on) that began or increased during statin treatment and resolved with statin discontinuation”

The prevalence of SAMS is noted to be between 7% and 29% in registries of observational studies. SAMS includes a broad range of clinical presentations commonly with normal or minimally elevated CK levels. Statin associated myopathy with significant CK elevations occurs in ~ 1 per 10,000 people per year on standard doses.

In the Odyssey alternative trial 14% of patients failed to complete the run in period **on placebo** due to muscle related symptoms in the absence of statin exposure

No specific diagnostic markers for SAMS, he symptoms are generally subjective and no gold standard diagnostic test exists. According to Laufs …: Typical signs and symptoms include pain, tenderness, cramps and muscle weakness during physical activity or at night; commonly starting in the calves and thighs (seldom noted in the shoulders buttocks her arms); and increasing in intensity after 3-4 weeks of treatment"

Key elements of the recommendations concerning SAMS include:

- Shared decision making
- Withdrawal of statin therapy followed by one or more rechallenges (after 2-4 week washout) | restart at the lowest dose, and only increasing the dose every 4-12 weeks OR use of intermittent (non-daily) statin (such as rosuvastatin which is long-acting)
- Use of an alternative statin (not all statins are the same) | simvastatin atorvastatin and lovastatin are lipophilic and might be at the highest risk for SAMS; alternatives including pravastatin and fluvastatin are hydrophilic and have less muscle penetration and may be associated with a lower risk of SAMS
- Check CPK at baseline, do not start lipid-lowering therapy if the baseline CK is elevated (greater than 4 times upper limit of normal) in the absence of recent physical activity
- Repeat CK only if the patient develops symptoms
- Finally with regards to vitamin D and coenzyme Q 10; the authors note that there is no routine role for the use of vitamin D or CoQ10 in patients with SAMS | however they do note "vitamin D supplementation appears to benefit a majority of statin intolerant vitamin D deficient patients" and "88-95% of statin intolerant patient's were able to take statin rechallenge without any muscle symptoms once serum vitamin D was normalized"

6. PubMed: Recommendations for SAMS

BACKGROUND AND AIMS: Statin-associated muscle symptoms (SAMS) frequently cause statin non-adherence, switching and discontinuation, contributing to adverse cardiovascular (CV) outcomes. Therefore, the management of SAMS is key in the effective treatment of patients with cardiovascular disease (CVD), through achievement of maximum-tolerated statin dosing and other practical aspects. The aim of this article is to provide practical, focused advice for healthcare professionals on the management of patients with SAMS.
METHODS: An expert working group combined current evidence, published guidelines and experiences surrounding a number of topics concerning SAMS to provide recommendations on how to best assess and manage this condition and reach the highest tolerated dose of statin for each individual patient.
RESULTS: The group collaborated to provide guidance on definitions in the SAMS field, psychological issues, re-challenging and switching treatments, as well as interpretation of current guidelines and optimal treatment of SAMS in different patient populations. An algorithm was developed to guide the management of patients with SAMS. In addition, the expert working group considered some of the more complex scenarios in a series of frequently asked questions and suggested answers.
CONCLUSIONS: The expert working group gave recommendations for healthcare professionals on the management of SAMS but highlighted the importance of tailoring the treatment approach to each individual patient. Evidence supporting the role of nutraceuticals and complementary therapies, such as vitamin D, was lacking, however the majority of the group favoured combination therapy with ezetimibe and the addition **of PCSK9 inhibitors** in high-risk patients. PMID: 28434484
REFERENCE: Laufs U et al, for the SAMS expert working group. Practical aspects in the management of statin-associated muscle symptoms (SAMS). Atheroscler Suppl. 2017 Apr;26:45-55.

With regard to vitamin D deficiency, several studies (estimated to be of low quality due to study designs) have suggested an association between vitamin D deficiency and SAMS

- Ovesjö ML et al. Low Vitamin D Levels and Genetic Polymorphism in the Vitamin D Receptor are Associated with Increased Risk of Statin-Induced Myopathy. Basic Clin Pharmacol Toxicol. 2016 Mar;118(3):214-8.
- Pereda CA et al. Is there really a relationship between serum vitamin D (25OHD) levels and the musculoskeletal pain associated with statin intake? A systematic review. Reumatol Clin. 2016 Nov - Dec;12(6):331-335.
- Palamaner Subash Shantha G et al. Association of vitamin D and incident statin induced myalgia--a retrospective cohort study. PLoS One. 2014 Feb 19;9(2):e88877.

Note that the ACC and AHA have a "Statin Intolerance App" to guides "clinicians through the process of managing and treating patients who report muscle symptoms while on statin therapy". According to the ACC "The app facilitates and adds structure to the clinician-patient discussion and includes questions to evaluate muscle-related symptoms, step-by-step guidance in the management of statin-related muscle symptoms, and a drug comparison tool for consideration of statin characteristics and potential drug–drug interactions."

Non-Statin Therapies

The inflammatory hypothesis of atherosclerosis generation is not new. According to Harrington (N Engl J Med. 2017 Sep 21;377(12):1197-1198), "Inflammatory cells and signals drive the healing response to vascular injury, allowing the initiation and growth of atherosclerotic plaque. Inflammatory reactions probably increase plaque instability, possibly resulting in plaque rupture, fissuring, or erosion and setting up the substrate for the thrombotic response that causes myocardial damage or infarction." "Canakinumab, a human monoclonal antibody against interleukin-1β (a cytokine central to the inflammatory process), is approved for use in systemic juvenile idiopathic arthritis and cryopyrin-associated periodic syndromes." The following abstract demonstrates that Canakinumab showed modest benefits in patients with established CV disease and an elevated hsCRP (lower rates of non-fatal MI, but no difference in all-cause mortality), but was also associated with harm signals (higher rates of fatal infections) and some unexplained results (lower cancer death rates). The cost is ~ $65,000 annually.

7. PubMed: Anti-inflammatory therapy with canakinumab associated with reduced CV event rates

BACKGROUND: Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.
METHODS: We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.
RESULTS: At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P=0.30); in the 150-mg group, 0.85 (95% CI, 0.74 to 0.98; P=0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P=0.031). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P=0.005). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).
CONCLUSIONS: Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)
REFERENCE: Ridker PM, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017 Sep 21;377(12):1119-1131.

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N Engl J Med. 2018 Jan 11;378(2):196-7.

8. HDL modifying drug has a small effect on CV events, no effect on mortality

Clinical question: Does the cholesteryl ester transfer protein inhibitor anacetrapib improve outcomes in patients with known vascular disease and a low LDL level who are already taking a statin?
Bottom line: In patients with known cardiovascular (CV) disease who are taking a statin, adding the cholesteryl ester transfer protein (CETP) inhibitor anacetrapib has no effect on mortality but slightly reduces the likelihood of a major vascular event (number needed to treat [NNT] = 111 over 4.1 years). If the drug costs US$300 per month (it is not yet available), it would cost approximately US$1.6 million to prevent that one event. (LOE = 1b)
Reference: The HPS3/TIMI55REVEAL Collaborative Group, Bowman L, Hopewell JC, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377(13):1217-1227.
Study design: Randomized controlled trial (double-blinded)
Funding source: Industry
Allocation: Uncertain
Setting: Outpatient (any)
Synopsis: Previous studies of CETP inhibitors have not shown any clinical benefit, and some have shown net harm. Anacetrapib is a CETP inhibitor that has been shown to be relatively safe in previous studies, although no benefit was seen in smaller trials of patients at high risk for CV disease. The current study enrolled 30,449 persons 50 years and older with known vascular disease (88% coronary heart disease, 22% cerebrovascular disease, 8% peripheral vascular disease) and gave them atorvastatin to achieve an LDL cholesterol level of less than 77 mg/dL (2 mmol/L) and a total cholesterol level of less than 155 mg/dL (4 mmol/L). They were then randomized to receive anacetrapib 100 mg once daily or matching placebo. The groups were balanced at baseline, with a mean age of 68 years, a mean LDL of 61 mg/dL while taking a statin, and a mean high-density lipoprotein (HDL) of 40 mg/dL. Follow-up was excellent over a median of 4.1 years. As expected, patients in the intervention group had a lower mean LDL level (38 vs 65 mg/dL) and a higher HDL level (85 vs 42 mg/dL). There was no efffect on all-cause mortality, CV mortality, incidence of cancer, or non-CV mortality.There was a small decrease in the primary combined outcome of CV death, myocardial infarction, and revascularization (10.8% vs 11.8%; P = .004; NNT = 100), primarily due to a decrease in the risk of myocardial infarction (4.4% vs 5.1%; P = .007; NNT = 143 over 4.1 years). The risk of any major vascular event was also slightly lower (13.6% vs 14.5%; P = .02; NNT = 111 over 4.1 years). The drug was well tolerated.

According to a new release, “Merck will not be seeking approval for anacetrapib, its cholesteryl ester transfer protein (CETP) inhibitor aimed at raising HDL cholesterol levels. The company joins several others that have abandoned development of drugs in this class owing to lack of efficacy or safety.”

According to Dr. Harlan Krumholz, "The saga of this drug class is a cautionary tale; once thought of as the path toward extinguishing heart disease because of its remarkable effect on lipids, the story ends with a whimper and lessons about the need to validate surrogate outcomes."

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Proprotein convertase subtilisin/kexin type 9 represents primarily a hepatocyte enzyme whose function includes regulating the number of low-density lipoprotein receptor (LDL-R) on hepatocytes. Briefly, when the LDL-R is complexed to an LDL particle, are both degraded in a lysosome. Inhibition of PCSK9 increases LDL-R “recycling” effectively increasing the number of LDL-R receptors on hepatocytes. The PCSK9 enzyme activity has been found to be correlated with CV disease, and **inhibition of PCSK9** is associated with **lower circulating LDL levels** (average LDL reduction of 58%).

PCSK9 inhibitors are monoclonal antibodies (with the potential for limited drug-drug interactions and ADEs). Currently there are 2 PCSK9 inhibitors (alirocumab | Praulent® and evolocumab | Repatha®) each administered subcutaneously once or twice monthly. Interesting, according to Noel and Beavers, both are also being studied in patients with HIV and in patients with DM. In addition to the cost (~$14000/year), and potential concern is a correlation of neurocognitive impairment (amnesia and delirium) and use of PCSK9 inhibitors.

In 2015 2 studies of these agents were published when *added to maximally tolerated statin therapy*. Evolocumab was associated with a decreased need for coronary revascularization (0.5% vs 1.1%, and TIA 0% vs 0.3%) but higher rates of discontinuation due to ADE (NNH 44). (N Engl J Med 2015;372(16):1500-1509). Alirocumab was associated with a decreased rate of non-fatal MI (0.9% vs 2.3%) but higher ADE (NNH = 27)

9. Cochrane: PCSK9 inhibitors | little or no effect on mortality

BACKGROUND: Despite the availability of effective drug therapies that reduce low-density lipoprotein (LDL)-cholesterol (LDL-C), cardiovascular disease (CVD) remains an important cause of mortality and morbidity. Therefore, additional LDL-C reduction may be warranted, especially for patients who are unresponsive to, or unable to take, existing LDL-C-reducing therapies. By inhibiting the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme, monoclonal antibodies (PCSK9 inhibitors) may further reduce LDL-C, potentially reducing CVD risk as well.
OBJECTIVES: Primary To quantify short-term (24 weeks), medium-term (one year), and long-term (five years) effects of PCSK9 inhibitors on lipid parameters and on the incidence of CVD. Secondary To quantify the safety of PCSK9 inhibitors, with specific focus on the incidence of type 2 diabetes, cognitive function, and cancer. Additionally, to determine if specific patient subgroups were more or less likely to benefit from the use of PCSK9 inhibitors.
SEARCH METHODS: We identified studies by systematically searching the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and Web of Science. We also searched Clinicaltrials.gov and the International Clinical Trials Registry Platform and screened the reference lists of included studies. We identified the studies included in this review through electronic literature searches conducted up to May 2016, and added three large trials published in March 2017.
SELECTION CRITERIA: All parallel-group and factorial randomised controlled trials (RCTs) with a follow-up time of at least 24 weeks were eligible.
DATA COLLECTION AND ANALYSIS: Two review authors independently reviewed and extracted data. When data were available, we calculated pooled effect estimates.
MAIN RESULTS: We included 20 studies with data on 67,237 participants (median age 61 years; range 52 to 64 years). Twelve trials randomised participants to alirocumab, three trials to bococizumab, one to RG7652, and four to evolocumab.Owing to the small number of trials using agents other than alirocumab, we did not differentiate between types of PCSK9 inhibitors used. We compared PCSK9 inhibitors with placebo (thirteen RCTs), ezetimibe (two RCTs) or ezetimibe and statins (five RCTs).Compared with placebo, PCSK9 inhibitors decreased LDL-C by 53.86% (95% confidence interval (CI) 58.64 to 49.08; eight studies; 4782 participants; GRADE: moderate) at 24 weeks; compared with ezetimibe, PCSK9 inhibitors decreased LDL-C by 30.20% (95% CI 34.18 to 26.23; two studies; 823 participants; GRADE: moderate), and compared with ezetimibe and statins, PCSK9 inhibitors decreased LDL-C by 39.20% (95% CI 56.15 to 22.26; five studies; 5376 participants; GRADE: moderate).Compared with placebo, PCSK9 inhibitors decreased the risk of CVD events, with a risk difference (RD) of 0.91% (odds ratio (OR) of 0.86, 95% CI 0.80 to 0.92; eight studies; 59,294 participants; GRADE: moderate). Compared with ezetimibe and statins, PCSK9 inhibitors appeared to have a stronger protective effect on CVD risk, although with considerable uncertainty (RD 1.06%, OR 0.45, 95% CI 0.27 to 0.75; three studies; 4770 participants; GRADE: very low). No data were available for the ezetimibe only comparison. Compared with placebo, PCSK9 probably had little or no effect on mortality (RD 0.03%, OR 1.02, 95% CI 0.91 to 1.14; 12 studies; 60,684 participants; GRADE: moderate). Compared with placebo, PCSK9 inhibitors increased the risk of any adverse events (RD 1.54%, OR 1.08, 95% CI 1.04 to 1.12; 13 studies; 54,204 participants; GRADE: low). Similar effects were observed for the comparison of ezetimibe and statins: RD 3.70%, OR 1.18, 95% CI 1.05 to 1.34; four studies; 5376 participants; GRADE: low. Clinical event data were unavailable for the ezetimibe only comparison.
AUTHORS' CONCLUSIONS: Over short-term to medium-term follow-up, PCSK9 inhibitors reduced LDL-C. Studies with medium-term follow-up time (longest median follow-up recorded was 26 months) reported that PCSK9 inhibitors (compared with placebo) decreased CVD risk but may have increased the risk of any adverse events (driven by SPIRE-1 and -2 trials). Available evidence suggests that PCSK9 inhibitor use probably leads to little or no difference in mortality. Evidence on relative efficacy and safety when PCSK9 inhibitors were compared with active treatments was of low to very low quality (GRADE); follow-up times were short and events were few. Large trials with longer follow-up are needed to evaluate PCSK9 inhibitors versus active treatments as well as placebo. Owing to the predominant inclusion of high-risk patients in these studies, applicability of results to primary prevention is limited. Finally, estimated risk differences indicate that PCSK9 inhibitors only modestly change absolute risks (often to less than 1%).
REFERENCE: Schmidt AF et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017 Apr 28;4:CD011748.

In abstract #10, 27,564 patients with atherosclerotic cardiovascular disease (i.e. MI, thrombotic CVA within 5 years, symptomatic PAD) PLUS 1 major risk factor or 2 minor risk factors and LDL levels at or above 70 mg/dL who were given evolocumab plus statin (99% were on moderate or high-intensity statins) had a significantly lower rate of the composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, and coronary revascularization, compared with patients given placebo plus a statin after 2 years' follow-up (9.8% vs. 11.3%). The mean percentage reduction of LDL vs placebo was 59% (mean baseline LDL 92 to 30 mg/dL). No significant differences were noted in ADE vs placebo (including neurocognitive effects). The log-term safety of LDL cholesterols of ~ 30 mg/dL are not known.

10. Evolocumab + a statin ↓ MACE rates more than placebo + a statin

BACKGROUND: Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.
METHODS: We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.
RESULTS: At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).
CONCLUSIONS: In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633)
REFERENCE: Sabatine MS, et al FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722.

Evolocumab previously approved for use in adults with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease whose LDL levels were still high despite other treatments has a new FDA approved indication, the prevention of cardiovascular events (e.g., myocardial infarction, stroke, coronary revascularization) in patients with existing cardiovascular disease.

The annual cost of alirocumab and evolocumab is approximately $14,000. Cost analyses suggest a price reduction of approximately 60% to ~ $5,000/yr for the agents to be considered cost-effective. Note that In Nov 2016 Pfizer announced that it was discontinuing the development progrma for another PCSK9 inhibitors (bococizumab) noting that "....is not likely to provide value to patients, physicians, or shareholders."

11. PubMed: PCSK9 inhibitors associated with ↑↑↑↑ Cost

Importance: Preliminary cost-effectiveness analyses of proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) were based on benefits estimated from reductions in low-density lipoprotein cholesterol that occurred in PCSK9i trials with variable results. The recent Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial provides better information about the effectiveness of the drug.
Objective: To use the trial results to determine the cost-effectiveness of a PCSK9i and statin treatment strategy compared with a statin alone strategy.
Design, Setting, and Participants: We derived observed rates of events, outcomes, cost of care, and health insurance from existing literature for a theoretical cohort of patients designed to resemble the FOURIER PCSK9i trial population and created a Markov model during the time horizon of a full lifetime.
Main Outcomes and Measures: We evaluated the incremental cost-effectiveness ratio from a health system perspective, and the return on investment from a private payer perspective. For both measures, we assumed an annual PCSK9i drug price of $14 300, with a lapse in US patent protection that would reduce the price by 43% in year 12. Costs were reported in 2016 US dollars.
Results: This study modeled 1000 hypothetical patients with attributes similar to those of the FOURIER trial cohort. At the current price, the incremental cost-effectiveness ratio of statin plus PCSK9i therapy was $337 729 per quality-adjusted life-year. Our probabilistic sensitivity analysis found that a statin plus PCSK9i strategy had a low probability (<1%) of being cost effective at the commonly accepted societal threshold of $100 000 per quality-adjusted life-year. Furthermore, PCSK9i produced a negative return on investment of 86% for private payers. In our threshold analysis, the price of PCSK9i would need to drop 62%, to $5459 per year, to reach $100 000 per quality-adjusted life year.
Conclusions and Relevance: At current prices, the addition of PCSK9i to statin therapy is estimated to provide an additional quality-adjusted life year for $337 729. Significant discounts are necessary to meet conventional cost-effectiveness standards.
Reference: Arrieta A et al. Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial. JAMA Cardiol. 2017 Dec 1;2(12):1369-1374.

12: Adding ezetimibe to moderate-dose statin reduces nonfatal MI only (NNT = 58 for 6 years)

Clinical question: Is ezetimibe plus simvastatin 40 mg more effective than simvastatin 40 mg alone after an episode of acute coronary syndrome?
Study design: Randomized controlled trial (double-blinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: These researchers identified adults 50 years and older who had been hospitalized for acute coronary syndrome in the previous 10 days who had a low-density lipoprotein level greater than 50 mg/dL (1.3 mmol/L) and less than 100 mg/dL (2.6 mmol/L) if already taking a statin or less than 125 mg/dL (3.2 mmol/L) if not using long-term statin therapy. The patients' mean age was 64 years, 76% were men, 84% were white, 27% had diabetes, and 70% had undergone a percutaneous coronary intervention during their episode of acute coronary syndrome. The patients were randomized to receive either simvastatin 40 mg once daily or simvastatin 40 mg once daily plus ezetimibe 10 mg once daily. Groups were balanced at the beginning of the study, with slightly more than 9000 in each group, and analysis was by intention to treat. Patients were followed up for at least 2.5 years, with a median follow-up of 6 years; the authors note that the study protocol was modified 5 times, including an increase in the sample size (presumably because they weren't finding a difference that was statistically significant with the original sample size). It took a while, but after approximately 3 to 4 years they began to see a difference between groups, ultimately a 2.0% reduction in the likelihood of a composite outcome of cardiovascular death, myocardial infarction, or stroke (32.7% vs 34.7%; P = .02; number needed to treat [NNT] = 50 for 6 years). However, the individual end points of all-cause mortality, cardiovascular death, or fatal myocardial infarction were nearly identical between groups. Most of the improvement in the composite outcome came from a reduction in nonfatal MI (13.1% vs 14.8%; P = .002; NNT = 58). There was also a small reduction in the risk of stroke (4.2% vs 4.8%; P = .05; NNT = 167 for 6 years).
Bottom line: Patients with known heart disease should have high-intensity statin therapy, so the comparison group in this study actually received less than the recommended dose of a statin. Those receiving ezetimibe plus simvastatin had a marginally better outcome: 1 fewer nonfatal myocardial infarction for every 58 patients who added ezetimibe for 6 years after an acute coronary syndrome. At best, this suggests that simvastatin plus ezetimibe may be an alternative to high-intensity statin therapy for patients who do not tolerate the latter.
Reference: Cannon CP, Blazing MA, Giugliano RP, et al, for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-2397

2017 ACC update on use of non-statin therapies for LDL-C lowering

In 2017, the ACC published a 38 page “focused update” called an Expert Consensus Decision Pathway (ECDP) on the “Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk“ mostly to accommodate the expanded use of PCSK9 Inhibition and ezetimibe in patients with clinical ASCVD already on statin therapy for secondary prevention. Only 4 pages of COI declarations are provided in this document (in small font).

The ACC is clear that this is not an evidence-based document and in the development of the ECDP, “… this process did not involve formal systematic reviews, grading of evidence, or synthesis of evidence.”

My brief synopsis of this ECDP includes:

Continued - ish endorsement the four evidence based statin-benefit groups:

1. Patients ≥ 21 years with stable clinical ASCVD;
    a) Without comorbidities
    b) With comorbidities (see below***)
    c) With baseline LDL-C > 190 mg/dL not due to secondary causes
2. Patients with LDL-C > 190 mg/dL, not due to secondary causes;
3. Patients aged 40 to 75 years with diabetes mellitus and LDL-C 70 - 189 mg/dL
4. Patients aged 40 to 75 years with no diabetes, but with LDL-C 70 to 189 mg/dL and predicted 10-year ASCVD risk >7.5%.

BUT they are now emphasizing both relative and absolute LDL “targets” – a point mentioned but not emphasized (in my opinion) in the 2013 guidelines. The 2017 document states, “these are not firm triggers” but factors that may be considered within the broader context of an individual patient’s clinical situation.”

Indicators of *efficacy* are the following targets:

- **50% LDL-C reduction** from baseline for high-intensity statin doses
- **30% to <50% LDL-C reduction** from baseline for moderate-intensity statin doses

Note that if you do not have baseline (non-treatment) LDL data, then the ACC gives tacit endorsement to using the absolute LDL level of 70 mg/dL for a high-intensity statin target or 100mg/dL for a moderate-intensity statin target. Note the strategy of "treating to target" (and these levels specifically) were not endorsed in the 2013 guideline.

If patients in the above 4 groups are not at target AND they are a) adherent, b) **on high-intensity statin**, c) engaged in lifestyle modification (including phytosterol use), then after shared decision making ….

For group 1a
- Consider ezetimibe first
- Consider PCSK9 inhibitors second (mostly if fully statin intolerant, and attempts to ↓ LDL with ezetimibe or bile acid sequestrants do not reach LDL targets)

For groups 1b, 1c and 2:
- Consider ezetimibe or PCSK9 inhibitors as initial non-statin therapies

For groups 3 and 4:

- Consider ezetimibe (or bile acid sequestrants if ezetimibe intolerant and TG's < 300mg/dL) – there is no recommendation at all for PCSK9 inhibitors in these groups

13: AHA consensus decision pathway on non-statin therapies for LDL-C

In 2016, the American College of Cardiology published the first expert consensus decision pathway (ECDP) on the role of non-statin therapies for low-density lipoprotein (LDL)-cholesterol lowering in the management of atherosclerotic cardiovascular disease (ASCVD) risk. Since the publication of that document, additional evidence and perspectives have emerged from randomized clinical trials and other sources, particularly considering the longer-term efficacy and safety of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors in secondary prevention of ASCVD. Most notably, the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial and SPIRE-1 and -2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events), assessing evolocumab and bococizumab, respectively, have published final results of cardiovascular outcomes trials in patients with clinical ASCVD and in a smaller number of high-risk primary prevention patients. In addition, further evidence on the types of patients most likely to benefit from the use of ezetimibe in addition to statin therapy after acute coronary syndrome has been published. Based on results from these important analyses, the ECDP writing committee judged that it would be desirable to provide a focused update to help guide clinicians more clearly on decision making regarding the use of ezetimibe and PCSK9 inhibitors in patients with clinical ASCVD with or without comorbidities. In the following summary table, changes from the 2016 ECDP to the 2017 ECDP Focused Update are highlighted, and a brief rationale is provided. The content of the full document has been changed accordingly, with more extensive and detailed guidance regarding decision making provided both in the text and in the updated algorithms. Revised recommendations are provided for patients with clinical ASCVD with or without comorbidities on statin therapy for secondary prevention. The ECDP writing committee judged that these new data did not warrant changes to the decision pathways and algorithms regarding the use of ezetimibe or PCSK9 inhibitors in primary prevention patients with LDL-C <190 mg/dL with or without diabetes mellitus or patients without ASCVD and LDL-C ≥190 mg/dL not due to secondary causes. Based on feedback and further deliberation, the ECDP writing committee down-graded recommendations regarding bile acid sequestrant use, recommending bile acid sequestrants only as optional secondary agents for consideration in patients intolerant to ezetimibe. For clarification, the writing committee has also included new information on diagnostic categories of heterozygous and homozygous familial hypercholesterolemia, based on clinical criteria with and without genetic testing. Other changes to the original document were kept to a minimum to provide consistent guidance to clinicians, unless there was a compelling reason or new evidence, in which case justification is provided.
Reference: Lloyd-Jones DM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Oct 3;70(14):1785-1822.

Appendix:

Phytosterols
Consider phytosterols and/or soluble dietary fibre. The FDA- approved claims for these are:

For phytosterols:
> "Foods containing at least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, *may reduce the risk of heart disease*.

For plant stanol esters:
> "Foods containing at least 1.7 g per serving of plant stanol esters, eaten twice a day with meals for a total daily intake of at least 3.4 g, as part of a diet low in saturated fat and cholesterol, *may reduce the risk of heart disease*."

For soluble dietary fibre:
> "Soluble fiber as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease"

Note also that the USDA in 2015 stated, "Dietary cholesterol is no longer a nutrient of concern"
I do not know much about a phytosterol diet, so here is a link to the Cleveland Clinic on this topic.

Comorbidities
***Comorbidities to consider in management decisions include (almost everyone with CAD!):

- DM
- Recent (< 3 months) ASCVD event
- ASCVD event while on a statin
- Poorly controlled other major ASCVD risk factors
- Elevated Lp(a)
- CKD
- CHF (symptomatic)
- Maintenance hemodialysis
- Baseline LDL > 190 mg/dLnot due to a secondary cause
- Age > 65
- Prior MI
- Prior nonhemorragic CVA
- Current smoking
- Symptomatic PAD with prior hx of MI or CVA
- Hx coronary revascularization
- Residual CAD with > 40% stenosis in > 2 large vessels
- HDL < 40 for men or < 50 for women
- Hs-CRP > 2 mg/L
- Metabolic syndrome

Ezetimibe
Mechanism of action: Reduces cholesterol absorption in small intestine.
Mean % reduction in LDL-C: Monotherapy—18%; combination therapy with statin (incremental reduction)—25%
Adverse effects: Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea. However, generally well tolerated
Cost: Generic available | goodrx.com (January 28, 2018) #30 10-mg tablets cost ~ $12

1. Is megestrol acetate safe and effective for malnourished nursing home residents?
2. How do oral NSAIDs compare to other oral analgesics right after an acute musculoskeletal injury?
3. How do hyaluronic acid and corticosteroid injections compare for knee OA relief?
4. Which interventions are effective in managing parental vaccine refusal?
5. What is the optimal frequency for dental checkups for children and adults?
6. Are oral emergency contraceptives a safe & effective form of long-term birth control?
7. What is the most effective treatment for scabies?
8. What effects—if any—does marijuana use during pregnancy have on the fetus or child?
9. Do oral decongestants have a clinically significant effect on BP in patients with hypertension?
10. Do ACE inhibitors or ARBs help prevent kidney disease in patients with diabetes and normal BP?
11. Rivaroxaban vs. Warfarin for Treatment of DVT and PE
12. Treatment for Calcaneal Apophysitis
13. Iron Deficiency in Heart Failure

1. Is megestrol acetate safe and effective for malnourished nursing home residents?

J Fam Pract. 2018 February;67(2):112-113
Author(s): Frances K. Wen, PhD James Millar, MD Linda Oberst-Walsh, MD Joan Nashelsky, MLS

EVIDENCE-BASED ANSWER:

No. Megestrol acetate (MA) is neither safe nor effective for stimulating appetite in malnourished nursing home residents. It increases the risk of deep vein thrombosis (DVT) (strength of recommendation [SOR]: C, 2 retrospective chart reviews), but isn't associated with other new or worsening events or disorders (SOR: B, single randomized controlled trial [RCT]).

Over a 25-week period, MA wasn't associated with increased mortality (SOR: B, single RCT). After 44 months, however, MA-treated patients showed decreased median survival (SOR: B, single case-control study).

Consistent, meaningful weight gain was not observed with MA treatment (SOR: B, single case-control study, single RCT, 2 retrospective chart reviews, single prospective case-series).

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2. How do oral NSAIDs compare to other oral analgesics right after an acute musculoskeletal injury?

J Fam Pract. 2018 February;67(2):110-111
Author(s): Corey Lyon, DO, Susan Piggott, MD, MPH, Shannon Langner, MD, Kristen DeSanto, MSLS, MS, RD

EVIDENCE-BASED ANSWER:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are at least as effective as other oral analgesics (opioids, acetaminophen) in relieving pain in the first few days after an acute musculoskeletal injury. Evidence also indicates that using NSAIDs results in fewer adverse events than using narcotics (strength of recommendation [SOR]: A, systematic review of randomized controlled trials [RCTs], as well as individual RCTs).

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3. How do hyaluronic acid and corticosteroid injections compare for knee OA relief?

J Fam Pract. 2018 January;67(1):E13-E14
Author(s): Corey Lyon, DO, Emily Spencer, MD, Jack Spittler, MD, Kristen Desanto, MSLS, MS, RD, AHIP

EVIDENCE-BASED ANSWER:

Inconsistent evidence shows a small amount of pain relief early (one week to 3 months) with corticosteroid (CS) injections and an equally small improvement in pain relief and function later (3 to 12 months) with hyaluronic acid (HA) injections (strength of recommendation [SOR]: B, meta-analysis of a randomized controlled trial [RCT] and inconsistent RCTs).

Guidelines state that CS injections can be considered for symptomatic knee osteoarthritis (OA), but that insufficient evidence exists to recommend HA injections (SOR: B, evidence-based guidelines).

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4. Which interventions are effective in managing parental vaccine refusal?

J Fam Pract. 2017 December;66(12):E12-E14
Author(s): Dan Brelsford, MD, Elise Knutzen, PharmD, Jon O. Neher, MD, Sarah Safranek, MLIS

EVIDENCE-BASED ANSWER:

It's unclear whether educational initiatives alone alter vaccine refusal. Although about a third of parents cite herd immunity as motivation for vaccination, its efficacy in addressing vaccine hesitancy isn't clear (strength of recommendation [SOR]: B, systematic reviews not limited to randomized controlled trials [RCTs]).

Multifaceted interventions (encompassing improved access to vaccines, immunization mandates, and patient education) may produce a ≥25% increase in vaccine uptake in groups with vaccine hesitancy and low utilization (SOR: B, extrapolated from a meta-analysis across diverse cultures).

Correcting false information about influenza vaccination improves perceptions about the vaccine, but may decrease intention to vaccinate in parents who already have strong concerns about safety (SOR: C, low-quality RCT).

Discussions about vaccines that are more paternalistic (presumptive rather than participatory) are associated with higher vaccination rates, but lower visit satisfaction (SOR: C, observational study).

Providers should thoroughly address patient concerns about safety and encourage vaccine use (SOR: C, expert opinion).

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5. What is the optimal frequency for dental checkups for children and adults?

J Fam Pract. 2017 November;66(11):699-700
Author(s): Thomas W. Hahn, MD, Connie Kraus, PharmD, Christopher Hooper-Lane, MA

EVIDENCE-BASED ANSWER:

It is unclear, but studies suggest that it should be based largely on individual risk. The American Academy of Pediatric Dentistry recommends a 6-month interval for preventive dental visits (strength of recommendation [SOR]: C, expert opinion), but a 24-month interval does not result in an increased incidence of dental caries in healthy children and young adults or increased incidence of

gingivitis in healthy adults (SOR: B, a single randomized controlled trial [RCT]). In adults with risk factors (eg, smoking or diabetes), visits at 6-month intervals are associated with a lower incidence of tooth loss (SOR: C, a retrospective cohort study). Children with risk factors (eg, caries) may benefit from a first dental visit by age 3 years (SOR: C, a retrospective cohort study).

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6. Are oral emergency contraceptives a safe & effective form of long-term birth control?

J Fam Pract. 2017 October;66(10):632-634

Author(s): Connie Kraus, PharmD , Christopher Hooper-Lane, MA

EVIDENCE-BASED ANSWER:

Yes, but not as effective as some other methods. Annual pregnancy rates in women using pericoital levonorgestrel 150 mcg to 1 mg range from 4.9% to 8.9%; menstrual irregularity is the most common adverse effect (strength of recommendation [SOR]: B, Cochrane review of lower-quality trials).

In women younger than 35 years who have sexual intercourse 6 or fewer times per month, correct and consistent use of pericoital levonorgestrel 1.5 mg results in an annual pregnancy rate of 11% (SOR: B, one large prospective, open-label trial).

Pericoital contraception is less effective than long-acting reversible contraceptives (annual pregnancy rates of 0.05%-0.8%) or perfect use of combined oral contraceptives (0.3% annual pregnancy rate), but similar to, or better than, typical use of combined oral contraception (9%) and condoms (18%).

References

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2. Festin MPR, Bahamondes L, Nguyen TMH, et al. A prospective, open-label, single arm, multicentre study to evaluate efficacy, safety and acceptability of pericoital oral contraception using levonorgestrel 1.5mg. *Hum Reprod*. 2016;31:530-540.
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7. What is the most effective treatment for scabies?

J Fam Pract. 2017 August;66(8):E11-E12

Author(s): Jonathon J. Campbell, MD, Christopher P. Paulson, MD, FAAFP, Joan Nashelsky, MLS

EVIDENCE-BASED ANSWER:

Topical permethrin is the most effective treatment for classic scabies (strength of recommendation [SOR]: A, meta-analyses with consistent results).

Topical lindane and crotamiton are inferior to permethrin but appear equivalent to each other and benzyl benzoate, sulfur, and natural synergized pyrethrins (SOR: B, limited randomized trials).

Although not as effective as topical permethrin, oral ivermectin is an effective treatment compared with placebo (SOR: B, a single small randomized trial).

Oral ivermectin may reduce the prevalence of scabies at one year in populations with endemic disease more than topical permethrin (SOR: B, a single randomized trial).

References

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8. What effects—if any—does marijuana use during pregnancy have on the fetus or child?

J Fam Pract. 2017 July;66(7):462-463,466
Author(s): Angela Zhang, DO, Robert Marshall, MD, MPH, MISM, Gary Kelsberg, MD, Sarah Safranek, MLIS

EVIDENCE-BASED ANSWER:

The effects are unclear. Marijuana use during pregnancy is associated with clinically unimportant lower birth weights (growth differences of approximately 100 g), but no differences in preterm births or congenital anomalies (strength of recommendation [SOR]: B, prospective and retrospective cohort studies with methodologic flaws).

Similarly, prenatal marijuana use isn't associated with differences in neurodevelopmental outcomes (behavior problems, intellect, visual perception, language, or sustained attention and memory tasks) at birth, in the neonatal period, or in childhood through age 3 years. However, it may be associated with minimally lower verbal/quantitative IQ scores (1%) at age 6 years and increased impulsivity and hyperactivity (1%) at 10 years. Prenatal use isn't linked to increased substance use at age 14 years (SOR: B, conflicting long-term prospective and retrospective cohort studies with methodologic flaws).

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9. Do oral decongestants have a clinically significant effect on BP in patients with hypertension?

J Fam Pract. 2017 June;66(6):E1-E2
Author(s): Joyce C. Hollander-Rodriguez, MD, Holly L. Montjoy, MD, Brynn Smedra, MD, MS, JP Prouty, MD, Andrew Hamilton, MS/MLS

EVIDENCE-BASED ANSWER:

It is unclear. Pseudoephedrine causes an average increase of 1.2 mm Hg in systolic blood pressure (BP) in patients with controlled hypertension. However, the studies are not adequately powered to provide evidence about whether this rise in systolic BP is linked to patient-oriented outcomes (strength of recommendation [SOR]: C, multiple randomized controlled trials [RCTs] supporting disease-oriented evidence). Significant variations in BP are defined differently among studies (TABLE[1-7]). In addition, we do not have data on chronic use of oral decongestants; the longest time on medication in these trials was 4 weeks.

TABLE

What effect do oral decongestants have on BP in patients with hypertension?

Study type	Intervention	Population studied	Exclusion criteria	Mean change in BP in mm Hg (95% CI, *P* value, SD)
Meta-analysis[1] (n=127)	See studies involving oral PSE outlined below.			SBP: 1.2 (0.56 to 1.84; *P*<.001)
RCT[2] (n=28)	Oral PSE (sustained release, bid)	Adults with diet- and/or medication-controlled hypertension	Active CAD or CVD, Tx with: sympathomimetics, alpha-adrenergic blockers, or MAOIs, secondary HTN, pregnancy, glaucoma, known BPH	At 48 hours: SBP: 3.1 (3.2 to 9.4) DBP: 5.5 (-1.9 to 8.9) At 72 hours: SBP: 2.7 (-1.7 to 6.7) DBP: 2.5 (-1.7 to 6.7)
RCT[3] (n=25)	Oral PSE (immediate release, qid)	Adults with medication-controlled HTN	Diabetes, CVD, PVD, CAD, Tx with alpha-blockers or combination alpha- and beta-blockers	Unknown mean change, SBP SD=9.4 (*P*>.05) DBP SD=7.7 (*P*>.05)
RCT[4] (n=20)	Oral PSE (immediate release)	Adults with diet- and/or medication-controlled HTN	Unknown	SBP: 2.9 (0.5 to 5.3) DBP: 1.1 (-0.9 to 3.1) (*P*<.03 for SBP only)
RCT[5] (n=25)	Oral PSE (immediate release tid)	Adults with medication-controlled HTN	CAD, CVD, allergy to medication, Tx with MAOIs, medical noncompliance	SBP: 0 (SD=4.1) DBP: -0.5 (SD=2.8) (*P*>.05, SBP and DBP)
RCT[6] (n=29)	Oral PSE (immediate release, varied doses)	Adults with diet-controlled HTN (studied after administration of beta-blockers)	Secondary HTN, cardiac disease, PVD, coagulopathy, chronic pulmonary disease, impaired renal or liver function, diabetes mellitus, and obesity	Insignificant SBP and DBP change after placebo, propranolol, and atenolol (all *P* values >.92)
Meta-analysis[7] (In the studies of patients with hypertension, n=78)	Oral PPA*	Adults with HTN (subset of meta-analysis)	Varied between study groups	SBP: 3.16 (-2.23 to 8.55) DBP: 2.16 (-0.98 to 5.31)

bid, 2 times daily; BP, blood pressure; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; CI, confidence interval; CVD, cerebrovascular disease; DBP, diastolic blood pressure; HTN, hypertension; MAOIs, monoamine oxidase inhibitors; PPA, phenylpropanolamine; PSE, pseudoephedrine; PVD, peripheral vascular disease; qid, 4 times daily; RCT, randomized controlled trial; SBP, systolic blood pressure; SD, standard deviation; tid, 3 times daily.

*No longer available in the United States.

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10. Do ACE inhibitors or ARBs help prevent kidney disease in patients with diabetes and normal BP?

J Fam Pract. 2017 April;66(4):257,263

Author(s): Gregory S. Trietley, PharmD, BCPS, Stephen A. Wilson, MD, MPH, Parul Chaudhri, DO, Nicole Payette, PharmD, BCPS, Ashley Higbea, PharmD, BCPS,Joan Nashelsky, MLS

EVIDENCE-BASED ANSWER:

Yes for angiotensin-converting enzyme (ACE) inhibitors, no for angiotensin receptor blockers (ARBs).

In normotensive patients with type 1 and type 2 diabetes, ACE inhibitor therapy reduces the risk of developing diabetic kidney disease, defined as new-onset microalbuminuria or macroalbuminuria, by 18% (strength of recommendation [SOR]: C, meta-analysis of randomized controlled trials [RCTs], disease-oriented evidence).
ACE inhibitor treatment improves all-cause mortality by 16% in patients with diabetes, including patients with and without hypertension. Patients on ACE inhibitor therapy are at increased risk of cough (SOR: A, meta-analysis of RCTs).
ARB therapy doesn't lower the risk of developing kidney disease in normotensive patients with type 2 diabetes (SOR: C, meta-analysis of RCTs, disease-oriented evidence); nor does it reduce all-cause mortality in patients with or without hypertension (SOR: A, meta-analysis of RCTs). ARBs aren't associated with significant adverse events (SOR: A, meta-analysis of RCTs).

References

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11. Rivaroxaban vs. Warfarin for Treatment of DVT and PE

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Am Fam Physician. 2017 Oct 15;96(8):532-533.

Clinical Question

Is rivaroxaban (Xarelto) as effective as vitamin K antagonists for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)?

Evidence-Based Answer

Rivaroxaban, along with the other factor Xa inhibitors, is as effective as or better in the short term (three months) than warfarin (Coumadin) for preventing recurrent DVT, nonfatal PE, and fatal PE, with no differences in mortality or bleeding events. (Strength of Recommendation: A, based on consistent, high-quality meta-analyses of moderate- to high-quality randomized controlled trials [RCTs] with patient-oriented outcomes.)

References

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12. Treatment for Calcaneal Apophysitis

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Am Fam Physician. 2017 Jul 15;96(2):126-127.

Clinical Question

What are effective therapies for calcaneal apophysitis (Sever disease)?

Evidence-Based Answer

Several treatments for calcaneal apophysitis may produce modest short-term improvements in pain scores. Heel inserts and prefabricated orthotics may initially improve pain scores and dysfunction, but patients have equal improvement by three months with or without therapy. (Strength of Recommendation: B, based on a comparison study and secondary outcomes of an unblinded randomized controlled trial.)

References

1. James AM, Williams CM, Haines TP. Effectiveness of footwear and foot orthoses for calcaneal apophysitis: a 12-month factorial randomised trial. *Br J Sports Med*. 2016;50(20):1268–1275.
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13. Iron Deficiency in Heart Failure

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Am Fam Physician. 2017 Apr 15;95(8):514-516.

Clinical Question

Is intravenous iron more effective than oral iron for the treatment of iron deficiency in patients with heart failure?

Evidence-Based Answer

Treatment of iron deficiency in patients with heart failure using intravenous iron improves function, fatigue, and quality of life, and decreases risk of hospitalizations compared with placebo. (Strength of Recommendation [SOR]: B, based on a randomized controlled trial [RCT].) A small RCT suggests that treatment with intravenous and oral iron is equivalent in patients with heart failure. (SOR: C, based on a small RCT with disease-oriented outcomes.) Oral iron can be used to increase hemoglobin and iron levels in patients with heart failure. (SOR: C, based on a retrospective cohort study.)

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Priority Updates from the Research Literature

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CV safety and COCs

- Observational cohort study
  - National health insurance and national hospital records
- Records from 5 million women in France
- Investigated correlation between COC formulations and risk of
  - First PE
  - Stroke
  - MI
- Adjusted for: Age, SES, HTN, DM, gynecologic history, and other insurance status

CV safety and COCs

Table 4 Adjusted relative risks of pulmonary embolism according to oestrogen dose stratified by type of progestogen

Progestogen	Oestrogen* 20 µg		Oestrogen* 30-40 µg	
	No of events	Adjusted relative risk† (95% CI)	No of events	Adjusted relative risk† (95% CI)
Levonorgestrel	98	0.74 (0.59 to 0.91)	950	1
Desogestrel	285	0.75 (0.63 to 0.88)	304	1
Gestodene	71	0.94 (0.68 to 1.29)	46	1

CV safety and COCs

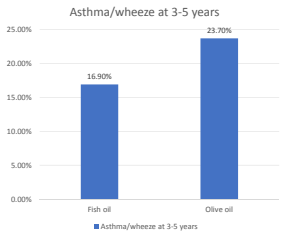
Table 5 Adjusted relative risks of pulmonary embolism according to type of progestogen stratified by oestrogen dose

Oestrogen* dose	Levonorgestrel		Desogestrel		Gestodene	
	No of events	Adjusted relative risk† (95% CI)	No of events	Adjusted relative risk† (95% CI)	No of events	Adjusted relative risk† (95% CI)
20 µg	98	1	285	2.30 (1.86 to 2.86)	71	1.96 (1.47 to 2.61)
30-40 µg	950	1	304	2.19 (1.93 to 2.48)	46	1.41 (1.05 to 1.84)

Antenatal DHA/EPA for postnatal asthma reduction

- 736 women between 22-26 WGA
- Randomized to 2.4 g/day of DHA/EPA or matched placebo
- Followed until the children born of these gestations were 5 years old
- Primary outcome was asthma or wheezing illness

Antenatal DHA/EPA for postnatal asthma reduction



P=0.035

- Effect only significant in women with the lowest DHA levels
- No change in asthma exacerbations or eczema rates
- Previous Cochrane review on this subject equivocal

Antenatal DHA/EPA for postnatal asthma reduction

- 2008 RCT 98 pregnant women with low omega-3 consumption (total of 3.4g of DHA/EPA vs olive oil placebo)
- At 2.5 years, 72 children remaining were assessed using Griffiths Mental Development Scale

Antenatal DHA/EPA for postnatal asthma reduction

- Griffiths Mental Development Scale results:
  - General domain
  - Locomotor
  - Personal-social
  - Hearing and language
  - Performance
- 114.0 vs 108 in the Eye-hand coordination group (p=0.021)

Omega-3s are also used after birth to make breast milk. With each subsequent pregnancy, mothers are further depleted. Research has confirmed that adding EPA and DHA to the diet of pregnant women has a positive effect on visual and cognitive development of the baby. Studies have also shown that higher consumption of omega-3s may reduce the risk of allergies in infants.

http://americanpregnancy.org/pregnancy-health/omega-3-fish-oil/

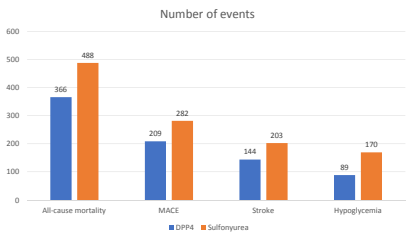
Second diabetes medication

- ADA is neutral about which med to add after metformin
  - Sulfonyureas (glimepiride, glipizide, glyburide)
  - TZDs (pioglitazone)
  - DPP-4 inhibitor (sitagliptin, saxagliptin, vildagliptin, linagliptin: Tradjenta, Januvia)
  - SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin: Invokana, Jardiance)
  - GLP-1 inhibitor (dulaglutide, liraglutide, exenatide, albiglutide: Tanzeum, Trulicity, Victoza, Byetta)
  - Basal insulin

Second diabetes medication

- Observational cohort study
- 70,000 patients on metformin in Taiwan
  - National Health Insurance database
- Compared data from patients using sulfonylureas with patients using DPP4s using propensity score matching (10,089 pairs)
  - Matched on
  - Age, sex, Charleston Comorbidity Index, hypertension, CKD, heart failure, MI, CVD
- Followed for mean 2.8 years

Second diabetes medication



Event	Hazard ratio
Mortality	0.63 95% CI 0.55-0.72
MACE	0.68 95% CI 0.55-0.83
Stroke	0.64 95% CI 0.51-0.81
Hypoglycemia	0.43 95% CI 0.33-0.56

Home BP logs for directing HTN therapy

- 286 patients with hypertension
  - Taking an average of 2.4 medications
- Diagnostic cohort study
- Took BP at home 3x/day for 7 days
- Also underwent 24 hour ambulatory BP monitoring
- Primary outcome was # of home BP readings that best predicted 24 hour ABPM results

Home BP logs for directing HTN therapy

- <3 elevated home readings:
  - Average systolic BP on ABPM: 120.4 (±9.8)
  - Average daytime systolic BP on ABPM: 132.7 (±11.1)
- ≥3 elevated home readings:
  - Average systolic BP on ABPM: 143.4 (±11.2)
  - Average daytime systolic BP on ABPM: 147.4 (±10.5)

Comparison	Sensitivity of ≥ 3/10 elevated HBP readings	Specificity of ≥ 3/10 elevated HBP readings
Amb BP >130	62.1%	80.1%
Amb BP >135 (daytime)	64.6%	77.2%

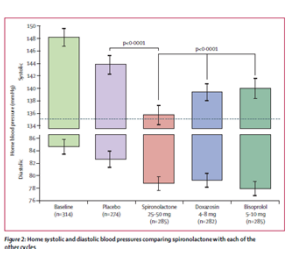
Home BP logs for directing HTN therapy

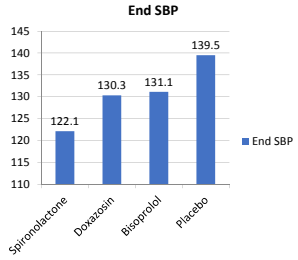
Comparison	Sensitivity of ≥ 3/10 elevated HBP readings	Specificity of ≥ 3/10 elevated HBP readings
Amb BP >130	62.1%	80.1%
Amb BP >135 (daytime)	64.6%	77.2%

Fourth med for resistant hypertension?

- 330 patients with resistant hypertension
  - Already on ACE/ARB, CCB, and thiazide
- Randomized to:
  - Spironolactone 12.5-25 mg
  - Doxazosin 4-8 mg
  - Bisoprolol 5-10 mg
  - Placebo
- Every 12 weeks, participants crossed over to a new med

What should be your 4th BP med?





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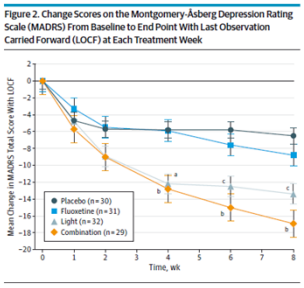
Bright light therapy for depression

- 122 adults with moderate depression
  - Off medication but no spontaneous remission
  - Goal of sleeping only between 10PM and 8AM
- Randomized to
  - 10,000 lux for 30 minutes/morning+20 mg fluoxetine
  - Light + placebo pill
  - Sham light + fluoxetine
  - Sham light + placebo pill
- Followed for 8 weeks
- Primary outcome was change on Montgomery-Asberg Depression Rating Scale
  - 10 items, 60 points, higher scores= worse depression
  - Reduction of <10 considered remission; 50% reduction considered response

Bright light therapy for depression



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Thanks!

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Which combined OC to prescribe with CV safety in mind?

With various formulations available, which combined OC should you recommend to minimize not only the risk of PE, but also the risk of stroke and MI?

PRACTICE CHANGER

When prescribing combined oral contraceptives, choose one containing levonorgestrel and low-dose estrogen (20 mcg) to minimize the risks of pulmonary embolism, ischemic stroke, and myocardial infarction.

STRENGTH OF RECOMMENDATION

B: Based on a good quality, patient-oriented cohort study.

Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ*. 2016;353:i2002.[1]

ILLUSTRATIVE CASE

A 28-year-old woman presents to your office for a routine health maintenance examination. She is currently using an oral contraceptive containing desogestrel and ethinyl estradiol for contraception and is inquiring about a refill for the coming year. What would you recommend?

When choosing a combined oral contraceptive (COC) for a patient, physicians often have "go-to" favorites—tried and true agents that are easy to prescribe on a busy clinic day. However, some of these may be placing patients at increased risk for venous thromboembolic events.

In general, when compared with nonusers, women who use COCs have a 2- to 4-fold increase in risk of venous thromboembolism (VTE) and an increased risk of myocardial infarction (MI) and stroke.[2,3] More specifically, higher doses of estrogen combined with the progesterones gestodene, desogestrel, and levonorgestrel, are associated with a higher risk of VTE.[2-6]

In 2012, the European Medicines Agency warned that COCs containing drospirenone were associated with a higher risk of VTE than other preparations, despite similar estrogen content.[7] The US Food and Drug Administration (FDA) produced a similar statement that same year, recommending that physicians carefully consider the risks and benefits before prescribing contraceptives containing drospirenone.[8]

The risks of ischemic stroke and MI have not been clearly established for varying doses of estrogen and different progesterones. This large observational study fills that informational gap by providing risk estimates for the various COC options.

STUDY SUMMARY

One combined oral contraceptive comes out ahead

The authors used an observational cohort model to determine the effects of different doses of estrogen combined with different progesterones in COCs on the risks of pulmonary embolism (PE), ischemic stroke, and MI.[1] Data were collected from the French national health insurance database and the French national hospital discharge database.[9,10] The study included just under 5 million women

15 to 49 years of age, living in France, with at least one prescription filled for COCs between July 2010 and September 2012.

The investigators calculated the absolute and relative risks of first PE, ischemic stroke, and MI in women using COC formulations containing either low-dose estrogen (20 mcg) or high-dose estrogen (30-40 mcg) combined with one of 5 progesterones (norethisterone, norgestrel, levonorgestrel, desogestrel, gestodene). The relative risk (RR) was adjusted for confounding factors, including age, complimentary universal health insurance, socioeconomic status, hypertension, diabetes, and consultation with a gynecologist in the previous year.

The absolute risk per 100,000 woman-years for all COC use was 33 for PE, 19 for ischemic stroke, and 7 for MI with a composite risk of 60. The RRs for low-dose estrogen vs high-dose estrogen were 0.75 (95% confidence interval [CI], 0.67-0.85) for PE, 0.82 (95% CI, 0.7-0.96) for ischemic stroke, and 0.56 (95% CI, 0.39-0.79) for MI. The absolute risk reduction (ARR) with low-dose estrogen vs high-dose estrogen was 14/100,000 person-years of use; the number needed to harm (NNH) was 7143.

Compared with levonorgestrel, desogestrel and gestodene were associated with higher RRs of PE but not arterial events (2.16; 95% CI, 1.93-2.41 for desogestrel and 1.63; 95% CI, 1.34-1.97 for gestodene). The ARR with levonorgestrel use as opposed to desogestrel for PE was 19/100,000 person-years of use (NNH=5263); the ARR with levonorgestrel use as opposed to gestodene was 12/100,000 person-years of use (NNH=8333). The authors concluded that for the same progesterone, using a lower dose of estrogen decreases risk of PE, ischemic stroke, and MI, and that oral contraceptives containing levonorgestrel and low-dose estrogen resulted in the lowest overall risks of PE and arterial thromboembolism.

WHAT'S NEW?

Low-dose estrogen and levonorgestrel confer lowest risk of 3 CV conditions

Prior studies have shown that COCs increase the risk of PE and may also increase the risks of ischemic stroke and MI.[3,11] Studies have also suggested that a higher dose of estrogen in COCs is associated with an increased risk of VTE.[11,12] This study shows that 20 mcg of estrogen combined with levonorgestrel is associated with the lowest risks of PE, MI, and ischemic stroke.

CAVEATS

A cohort study, no contraceptive start date, and incomplete tobacco use data

This is an observational cohort study, so it is subject to confounding factors and biases. It does, however, include a very large population, which improves validity. The study did not account for COC start date, which may be confounding because the risk of VTE is highest in the first 3 months to one year of COC use.[12] Data on tobacco use, a significant independent risk factor for arterial but not VTE, was incomplete, but in other studies has only marginally affected outcomes.[3,13]

CHALLENGES TO IMPLEMENTATION

Low-dose estrogen is associated with increased vaginal spotting

One potential challenge to implementing this practice changer may be the increased rate of vaginal spotting associated with low-dose estrogen. COCs containing 20 mcg of estrogen are associated with spotting in approximately two-thirds of menstrual cycles over the course of a year.[14] That said, women may prefer to endure the spotting in light of the improved safety profile of a lower-dose estrogen pill. JFP

ACKNOWLEDGEMENT

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Does fish oil during pregnancy help prevent asthma in kids?

The evidence on fish oil has been mixed, but this study affirms its benefits—in certain women.

PRACTICE CHANGER

Fish oil supplementation taken by women in the third trimester of pregnancy can reduce the risk of persistent wheeze, asthma, and infections of the lower respiratory tract in their children.[1]

STRENGTH OF RECOMMENDATION

B: Based on 2 double-blinded randomized controlled trials (RCTs).

Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016;375:2530-2539.[1]

ILLUSTRATIVE CASE

A 24-year-old G2P1 at 24 weeks' gestation presents to your clinic for a routine prenatal visit. Her older daughter has asthma and she is inquiring as to whether there is anything she can do to lower the risk of her second child developing asthma in the future. What do you recommend?

Asthma is the most common chronic disease in children in resource-rich countries such as the United States.[2] The Centers for Disease Control and Prevention (CDC) reported that 8.4% of children were diagnosed with asthma in 2015.[3]

Omega-3 fatty acids, found naturally in fish oil, are thought to confer anti-inflammatory properties that offer protection against asthma. Clinical trials have shown that fish oil supplementation in pregnancy results in higher levels of omega-3 fatty acids, along with anti-inflammatory changes, in offspring.[4] Previous epidemiologic studies have also found that consumption of omega-3 fatty acids decreased the risk of atopy and asthma in offspring.[5,6]

A Cochrane review published in 2015, however, concluded that omega-3 supplementation during pregnancy had no benefit on wheeze or asthma in offspring.[7] Five RCTs were included in the analysis. The largest trial by Palmer et al, which included 706 women, showed no benefit for omega-3 supplementation.[8] The second largest by Olsen et al, which included 533 women, did show a benefit (hazard ratio [HR]=0.37; 95% confidence interval [CI], 0.15-0.92; number needed to treat [NNT]=19.6).[9]

These results, however, were limited by heterogeneity in the amount of fish oil supplemented and duration of follow-up. For example, the children in the Palmer study were followed only until 3 years of age, which is around the time that asthma can be formally diagnosed, potentially leading to under-reporting.[8] In addition, the diagnosis of asthma was based on parent report of 3 episodes of wheezing, use of daily asthma medication, or use of a national registry—all of which can underestimate the incidence of asthma. The reported rate of childhood asthma with IgE-sensitization (they did not report the rate without sensitization) was 1.8% in both arms, which is much lower than the CDC's rate of 8.4%, suggesting underdiagnosis.[3,8] Due to these biases and other potential confounders, no firm conclusions can be drawn from the Cochrane review.

STUDY SUMMARY

Maternal fish oil supplementation reduces incidence of asthma in children

This single-center, double-blinded RCT of 736 pregnant women evaluated the effect of 2.4 g/d of n-3 long-chain polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or placebo (olive oil), starting at an estimated gestational age of 24 to 26 weeks, on wheeze or asthma incidence in their offspring.[1]

Eligible women were between 22 and 26 weeks' pregnant at the time of recruitment. Exclusion criteria included supplementation of 600 IU/d or more of vitamin D, or having any endocrine, cardiac, or renal disorders. The investigators randomized the women in a 1:1 ratio to either fish oil or placebo. Maternal EPA and DHA blood levels were tested at the time of randomization and one week after birth.

The primary outcome was persistent wheeze or asthma (after 3 years of age, the diagnosis of persistent wheeze was termed asthma) based on daily diary recordings of 5 episodes of troublesome lung symptoms within the last 6 months (each lasting for at least 3 consecutive days), rescue use of inhaled beta$_2$-agonists, and/or relapse after a 3-month course of inhaled glucocorticoids. Secondary outcomes included lower respiratory tract infections, asthma exacerbations, eczema, and allergic sensitization.

In total, 695 offspring were included in the study with 95.5% follow-up at 3 years and 93.1% follow-up at 5 years. The children had scheduled pediatric visits at 1 week; 1, 3, 6, 12, 18, 24, 30, and 36 months; and at 4 and 5 years, and acute visits for any pulmonary, allergic, or dermatologic symptoms that arose.

Results. The investigators found that the children of the mothers who received the fish oil had a lower risk of persistent wheeze or asthma at ages 3 to 5 years compared to those who received placebo (16.9% vs 23.7%; HR=0.69; 95% CI, 0.49-0.97; *P*=.035; NNT=14.7). But the effect of the fish oil supplementation was significant only in the children of the mothers with baseline EPA and DHA levels in the lowest third (17.5% vs 34.1%; HR=0.46; 95% CI, 0.25-0.83; *P*=.011; NNT=5.6). Similarly, in mothers who consumed the least EPA and DHA before the start of the study, fish oil supplementation had a greater benefit in terms of decreased wheeze and asthma (18.5% vs 32.4%; HR=0.55; 95% CI, 0.30-0.98; *P*=.043; NNT=7.2).

As for the secondary outcomes, only a reduction in lower respiratory tract infections was associated with the fish oil supplementation vs the control (38.8% vs 45.5%; HR=0.77; 95% CI, 0.61-0.99; *P*=.041; NNT=14.9). There was no reduction in asthma exacerbations, eczema, or risk of sensitization in the fish oil group.

WHAT'S NEW?

Study adds fuel to the fire

This study strengthens the case for fish oil supplementation during pregnancy to reduce the risk of asthma in offspring, despite the recent Cochrane review that showed no benefit.[1,7] The Palmer study used a much lower amount of omega-3s (900 mg/d fish oil vs 2400 mg/d in the current trial).[1,8] Olsen et al supplemented with a greater amount of omega-3s (2700 mg/d) and did find a benefit.[9] The NNT from the Olsen study (19.6) is consistent with that of the current investigation, suggesting that a higher dosage may be necessary to prevent the onset of asthma.

Additionally, this study followed children for a longer period than did the Palmer study, which may have led to more accurate diagnoses of asthma.[1,8] Lastly, the diagnosis of asthma in the Palmer study was based on parent survey data and use of daily asthma medicine rather than on daily diary cards, which are often more accurate.

Consider fish consumption. Both this study and the Olsen trial were performed in Denmark.[1,9] While Denmark and the United States have had a relatively similar level of fish consumption since the 1990s, women in Denmark may eat a higher proportion of oily fish than women in the United States, given the more common inclusion of mackerel and herring in their diet.[10] Thus, the effect of supplementation may be more pronounced in women in the United States.

CAVEATS

Questions remain: Ideal dose and which women to treat?

The US Food and Drug Administration cur-

This study strengthens the case for fish oil supplementation during pregnancy to reduce the risk of asthma in children.

rently recommends 8 to 12 ounces of fish per week for pregnant women, but there are no guidelines on the ideal amount of fish oil to be consumed.[11] The Palmer study,[8] using 900 mg/d fish oil, did not show a benefit, whereas there did appear to be benefit in this study (2400 mg/d)[1] and the Olsen study (2700 mg/d).[9] Further research is needed to determine the optimal dosage.

The decreased risk of persistent wheeze or asthma was seen only in the children of the women whose EPA and DHA blood levels were in the lowest third of the study population. Thus, only women whose blood levels are low to begin with will likely benefit from this intervention. Currently, EPA and DHA levels are not routinely checked, but there may be some benefit to doing so.

One proxy for blood levels is maternal intake of fish at baseline. The investigators found that there was an association between dietary intake of fish and blood levels of EPA and DHA (r=0.32; $P<.001$).[1] Therefore, additional screening questions to determine fish consumption would be useful for identifying women most likely to benefit from supplementation.

Only women whose blood levels of EPA and DHA are low to begin with will likely benefit from this intervention.

CHALLENGES TO IMPLEMENTATION

Multiple pills and additional cost

Since omega-3 fatty acids are relatively safe and the NNT in the general population is low, it may be worth supplementing all pregnant women, even without a commercially-available blood test for EPA or DHA. Nevertheless, some women may find it challenging to take up to an additional 4 pills/d for 13 or more weeks. Also, there is an associated cost with these supplements, although it is low. JFP

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Need an add-on to metformin? Consider this

Sulfonylureas have been the preferred add-on therapy to metformin for T2DM, but a study finds that DPP-4s have lower risks of death, CV events, and hypoglycemia.

PRACTICE CHANGER

Consider a dipeptidyl peptidase-4 inhibitor before a sulfonylurea for patients with type 2 diabetes mellitus who require therapy in addition to metformin.

Ou SM, Shih CJ, Chao PW, et al. Effects of clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann Intern Med.* 2015;163:663-672.[1]

STRENGTH OF RECOMMENDATION

B: Based on limited-quality, patient-oriented data from a high-quality, population-based cohort study.

ILLUSTRATIVE CASE

A 58-year-old woman with type 2 diabetes mellitus (T2DM) and heart failure returns to your office for follow-up of her T2DM. She has been on the maximum dose of metformin alone for the past 6 months, but her HbA1c is now 7.8%. She is keen to avoid injections. What do you recommend next?

There is surprisingly little consensus about what to add to metformin for patients with T2DM who require a second agent to achieve their glycemic goal. Attainment of glycemic control earlier in the course of the disease may lead to reduced overall cardiovascular risk, so the choice of a second drug is an important one.[2] While metformin is well established as initial pharmacotherapy because of its proven mortality benefit, wide availability, and low cost, no second-choice drug has amassed enough evidence of benefit to emerge as the add-on therapy of choice.

Furthermore, the professional societies and associations are of little assistance. Dual therapy recommendations from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes do not denote a specific preference, and while the American Association of Clinical Endocrinologists/American College of Endocrinology do suggest a hierarchy of choices, it is based upon expert consensus recommendation.[3,4]

Sulfonylureas can cause hypoglycemia and weight gain

Options for add-on therapy include sulfonylureas, thiazolidines, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and insulin. Providers have frequently prescribed a sulfonylurea after metformin because such agents are low in cost, have long-term safety data, and are effective at lowering HbA1c. Sulfonylureas work by directly stimulating insulin secretion by pancreatic beta cells in a glucose-*independent* manner. But as a 2010 meta-analysis revealed, they carry significant risks of hypoglycemia (relative risk [RR]=4.57; 95% confidence interval [CI], 2.11-11.45) and weight gain (2.06 kg; 95% CI, 1.15-2.96) compared to placebo.[5]

DPP-4 inhibitors, on the other hand, work by inducing insulin secretion in a glu-

cose-*dependent* manner through an incretin mechanism. Combined with metformin, they provide glucose control similar to that achieved with the combination of a sulfonylurea and metformin.[6] DPP-4 inhibitors were initially found to be associated with fewer cardiovascular events and less hypoglycemia than sulfonylureas, but were subsequently linked to an increased risk of hospitalization for heart failure.[7]

This latest large observational study provides more evidence on the effects of DPP-4s when added to metformin.[1]

STUDY SUMMARY

DPP-4s as effective as sulfonylureas with no increased risks

This population-based observational cohort study compared DPP-4 inhibitors and sulfonylureas when added to metformin for the treatment of T2DM.[1] Outcomes were all-cause mortality, major adverse cardiovascular events (MACEs; defined as hospitalization for ischemic stroke or myocardial infarction [MI]), and hospitalizations for either heart failure or hypoglycemia. Using the National Health Insurance Research Database in Taiwan, the study included data on over 70,000 patients ages 20 years and older with a diagnosis of T2DM. Individuals adherent to metformin were considered to be enrolled into the cohort on the day they began using either a DPP-4 inhibitor or a sulfonylurea, in addition to metformin.

The researchers collected additional data on the enrolled individuals regarding socioeconomic factors, urbanization, robustness of the local health care system, Charlson Comorbidity Index, adapted Diabetes Complications Severity Index, and other comorbidities and medications that could affect the outcomes of interest. Using these data, enrollees were matched by propensity score into 10,089 pairs consisting of a DPP-4 inhibitor user and a sulfonylurea user.

After a mean follow-up period of 2.8 years, the authors of the study used Cox regression analysis to evaluate the relative hazards of the outcomes. Subgroup analysis performed by age, sex, Charlson Comorbidity Index, hypertension, chronic kidney disease, hospitalization for heart failure, MI, and cerebrovascular disease yielded results similar to those of the primary analysis for each outcome. Additionally, similar results were obtained when the data were analyzed without propensity-score matching.

The researchers found that users of DPP-4 inhibitors—when compared to users of sulfonylureas—had a lower risk of all-cause mortality (366 vs 488 deaths; hazard ratio [HR]=0.63; 95% CI, 0.55-0.72; number needed to treat [NNT]=117), MACE (209 vs 282 events; HR=0.68; 95% CI, 0.55-0.83; NNT=191), ischemic stroke (144 vs 203 strokes; HR 0.64; 95% CI, 0.51-0.81; NNT=246), and hypoglycemia (89 vs 170 events; HR=0.43; 95% CI, 0.33-0.56; NNT=201). Further, there were no significant differences in either the number of MIs that occurred (69 vs 88 MIs; HR=0.75; 95% CI, 0.52-1.07) or in the number of hospitalizations for heart failure (100 vs 100 events; HR=0.78; 95% CI, 0.57-1.06) between users of DPP-4 inhibitors and those of sulfonylureas.

WHAT'S NEW

Lower risks of death, CV events, and hypoglycemia

This study found that when added to metformin, DPP-4 inhibitors were associated with lower risks for all-cause mortality, cardiovascular events, and hypoglycemia when compared to sulfonylureas. Additionally, DPP-4 inhibitors did not increase the risk of hospitalization for heart failure. A recent multicenter observational study of nearly 1.5 million patients on the effects of incretin-based treatments, including both DPP-4 inhibitors and GLP-1 agonists, similarly found no increased risk of hospitalization for heart failure, with DPP-4 inhibitors compared to other combinations of oral T2DM agents.[8]

CAVEATS

Did unmeasured confounders play a role?

Unmeasured confounders potentially bias all observational population cohort results. In this study, in particular, there may have been unmeasured, but significant, patient factors that providers used to choose diabetes medi-

Combined with metformin, DPP-4s provide glucose control similar to that achieved with the combination of a sulfonylurea and metformin.

cations. Also, the study did not evaluate diabetes control, although previous studies have shown similar glucose control between sulfonylureas and DPP-4 inhibitors when they were added to metformin.[6]

Another caveat is that the results from this study group may not be fully generalizable to other populations due to physiologic differences. People of Asian ancestry are at risk of developing T2DM at a lower body mass index than people of European ancestry, which could affect the outcomes of interest.[9]

Furthermore, the study did not evaluate outcomes based on whether patients were taking first-, second-, or third-generation sulfonylureas. Some sulfonylureas, such as glyburide, carry a higher risk of hypoglycemia, which could bias the results if a large number of patients were taking them.[10]

Lastly, the study only provides guidance when choosing between a sulfonylurea and a DPP-4 inhibitor for second-line pharmacotherapy. The GRADE trial, due to be completed in 2023, is comparing sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, and insulin as add-on medications to metformin, and may provide more data on which to base treatment decisions.[11]

Use of DPP-4s appears to have a lower risk of all-cause mortality, major adverse cardiovascular events, ischemic stroke, and hypoglycemia, compared to use of sulfonylureas.

CHALLENGES TO IMPLEMENTATION

DPP-4s have a higher price tag than sulfonylureas

Sulfonylureas and DPP-4 inhibitors are both available as generic medications, but the cost of DPP-4 inhibitors remains significantly higher.[12] Higher copays and deductibles could affect patient preference. Furthermore, for patients without health insurance, sulfonylureas are available on the discounted drug lists of many major retailers, while DPP-4 inhibitors are not. JFP

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Monitoring home BP readings just got easier

This novel method of identifying patients with uncontrolled hypertension correlates well with ambulatory BP monitoring.

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PRACTICE CHANGER

Use this easy "3 out of 10 rule" to quickly sift through home blood pressure readings and identify patients with uncontrolled hypertension who require pharmacologic management.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single, good quality, multicenter trial.

Sharman JE, Blizzard L, Kosmala W, et al. Pragmatic method using blood pressure diaries to assess blood pressure control. *Ann Fam Med.* 2016;14:63-69.

ILLUSTRATIVE CASE

A 64-year-old woman presents to your office for a follow-up visit for her hypertension. She is currently managed on lisinopril 20 mg/d and hydrochlorothiazide 25 mg/d without any problems. The patient's blood pressure (BP) in the office today is 148/84 mm Hg, but her home blood pressure (HBP) readings are much lower (see **TABLE**). Should you increase her lisinopril dose today?

Hypertension has been diagnosed on the basis of office readings of BP for almost a century, but the readings can be so inaccurate that they are not useful.[2] The US Preventive Services Task Force recommends the use of ambulatory blood pressure monitoring (ABPM) to accurately diagnose hypertension in all patients, while The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends ABPM for patients suspected of having white-coat hypertension and any patient with resistant hypertension,[3,4] but ABPM is not always acceptable to patients.[5]

HBP readings, on the other hand, correlate well with ABPM measurements and may be more accurate and more predictive of adverse outcomes than office measurements, and the process is often more tolerable to patients than ABPM.[6-8] If the average home BP reading is >135/85 mm Hg, there is an 85% probability that ambulatory BP will also be high.[8]

Guidelines recommend HBP monitoring for long-term follow-up of hypertension

The European Society of Hypertension practice guideline on HBP monitoring suggests that HBP values <130/80 mm Hg may be considered normal, while a mean HBP ≥135/85 mm Hg is considered elevated.[9] The guideline recommends HBP monitoring for 3 to 7 days prior to a patient's follow-up appointment with 2 readings taken one to 2 minutes apart in the morning and evening.[9] In a busy clinic, averaging all of these home values can be time-consuming.

So how can primary care physicians accurately and efficiently streamline the process? This study sought to answer that question.

CONTINUED

TABLE

Should you change this patient's lisinopril dose?

A 64-year-old woman is currently managed on lisinopril 20 mg/d and hydrochlorothiazide 25 mg/d. Her blood pressure (BP) in the office today is 148/84 mm Hg, but her home blood pressure (HBP) readings, as shown below, are much lower. However, the patient's HBP log notes 3 systolic readings ≥135 mm Hg, indicating uncontrolled hypertension. In light of Sharman, et al's[1] findings, the dose of lisinopril should be increased to further control this patient's BP.

Date	Time	2nd BP reading (mm Hg)
9/1/16	7:30 am	124/86
	7:35 pm	**135/88**
9/2/16	6:30 am	**145/96**
	6:35 pm	122/82
9/3/16	7:45 am	128/78
	7:50 pm	116/74
9/4/16	6:15 am	130/78
	6:30 pm	126/78
9/5/16	7:15 am	**140/88**
	7:00 pm	120/84
9/6/16	6:45 am	133/86
	6:30 pm	125/85
9/7/16	7:40 am	123/83
	7:00 pm	124/82

BP, blood pressure.

The researchers found that if at least 3 of the last 10 home BP readings were elevated, the patient was likely to have hypertension on 24-hour ambulatory monitoring.

STUDY SUMMARY

When 3 of 10 readings are elevated, it's predictive

This multicenter trial compared HBP monitoring to 24-hour ABPM in 286 patients with uncomplicated essential hypertension to determine the optimal percentage of HBP readings needed to diagnose uncontrolled BP (HBP ≥135/85 mm Hg). Patients were included if they were diagnosed with uncomplicated hypertension, not pregnant, ≥18 years of age, and taking ≤3 antihypertensive medications. Medication compliance was verified by a study nurse at a clinic visit. Patients were excluded if they had a significant abnormal left ventricular mass index (women >59 g/m^2; men >64 g/m^2), coronary artery or renal disease, secondary hypertension, serum creatinine exceeding 1.6 mg/dL, aortic valve stenosis, upper limb obstructive atherosclerosis, or BP >180/100 mm Hg.

Approximately half of the participants were women (53%), average body mass index was 29.4 kg/m^2, and the average number of hypertension medications being taken was 2.4. The patients were instructed to take 2 BP readings (one minute apart) at home 3 times daily, in the morning (between 6 am and 10 am), at noon, and in the evening (between 6 pm and 10 pm), and to record only the second reading for 7 days. Only the morning and evening readings were used for analysis in the study. The 24-hour ABP was measured every 30 minutes during the daytime hours and every 60 minutes overnight. The primary outcome was to determine the optimal number of systolic HBP readings above goal (135 mm Hg), from the last 10 recordings, that would best predict elevated 24-hour ABP. Secondary outcomes were various cardiovascular markers of target end-organ damage.

The researchers found that if at least 3 of the last 10 HBP readings were elevated (≥135 mm Hg systolic), the patient was likely to have hypertension on 24-hour ABPM (≥130 mm Hg). When patients had <3 HBP elevations out of 10 readings, their mean (±standard deviation [SD]) 24-hour ambulatory daytime systolic BP was 132.7 (±11.1) mm Hg and their mean systolic HBP value was 120.4 (±9.8) mm Hg. When patients had ≥3 HBP elevations, their mean 24-hour ambulatory daytime systolic BP was 143.4 (±11.2) mm Hg and their mean systolic HBP value was 147.4 (±10.5) mm Hg.

The positive and negative predictive values of ≥3 HBP elevations were 0.85 (95% confidence interval [CI], 0.78-0.91) and

0.56 (95% CI, 0.48-0.64), respectively, for a 24-hour systolic ABP of ≥130 mm Hg. Three elevations or more in HBP, out of the last 10 readings, was also an indicator for target organ disease assessed by aortic stiffness and increased left ventricular mass and decreased function.

The sensitivity and specificity of ≥3 elevations for mean 24-hour ABP systolic readings ≥130 mm Hg were 62% and 80%, respectively, and for 24-hour ABP daytime systolic readings ≥135 mm Hg were 65% and 77%, respectively.

WHAT'S NEW

Monitoring home BP can be simplified

The researchers found that HBP monitoring correlates well with ABPM and that their method provides clinicians with a simple way (3 of the past 10 measurements ≥135 mm Hg systolic) to use HBP readings to make clinical decisions regarding BP management.

CAVEATS

Ideal BP goals are hazy, and a lot of patient education is required

Conflicting information and opinions remain regarding the ideal intensive and standard BP goals in different populations.[10,11] Systolic BP goals in this study (≥130 mm Hg for *overall* 24-hour ABP and ≥135 mm Hg for 24-hour ABP *daytime* readings) are recommended by some experts, but are not commonly recognized goals in the United States. This study found good correlation between HBP and ABPM at these goals, and it seems likely that this correlation could be extrapolated for similar BP goals.

Other limitations are that: 1) The study focused only on systolic BP goals; 2) Patients in the study adhered to precise instructions on BP monitoring. HBP monitoring requires significant patient education on the proper use of the equipment and the monitoring schedule; and 3) While end-organ complication outcomes showed numerical decreases in function, the clinical significance of these reductions for patients is unclear.

CHALLENGES TO IMPLEMENTATION

Cost of device and improper cuff sizes could be barriers

The cost of HBP monitors ($40-$60) has decreased significantly over time, but the devices are not always covered by insurance and may be unobtainable for some people. Additionally, patients should be counseled on how to determine the appropriate cuff size to ensure the accuracy of the measurements.

The British Hypertensive Society maintains a list of validated BP devices on their Web site: http://bhsoc.org/bp-monitors/bp-monitors.[12] JFP

Patients using home blood pressure monitors should be counseled on how to determine the appropriate cuff size so that measurements are accurate.

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Resistant hypertension? Time to consider this fourth-line drug

For most adults with resistant hypertension, spironolactone is superior to doxazosin and bisoprolol as an adjunct to triple therapy.

PRACTICE CHANGER

When a triple regimen of an ACE inhibitor or ARB, calcium channel blocker, and a thiazide diuretic fails to achieve the target blood pressure, try adding spironolactone.

STRENGTH OF RECOMMENDATION

C: Based on a high-quality disease-oriented randomized controlled trial.[1]

Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386:2059–2068.

ILLUSTRATIVE CASE

Willie S, a 56-year-old with chronic essential hypertension, has been on an optimally dosed 3-drug regimen of an ACE inhibitor, a calcium channel blocker, and a thiazide diuretic for more than 3 months, but his blood pressure is still not at goal.

What is the best antihypertensive agent to add to his regimen?

Resistant hypertension—defined as inadequate blood pressure (BP) control despite a triple regimen of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and thiazide diuretic—affects an estimated 5% to 30% of those being treated for hypertension.[1,2] Guidelines from the 8th Joint National Committee (JNC-8) on the management of high BP, released in 2014, recommend beta-blockers, alpha-blockers, or aldosterone antagonists (AAs) as equivalent choices for a fourth-line agent. The recommendation is based on expert opinion.[3]

Hypertension guidelines from the UK's National Institute for Health and Care Excellence, released in 2011, recommend an AA if BP targets have not been met with the triple regimen. This recommendation, however, is based on lower-quality evidence, without comparison with beta-blockers, alpha-blockers, or other drug classes.[4]

More evidence since guideline's release

A 2015 meta-analysis of 15 studies and a total of more than 1200 participants (3 randomized controlled trials [RCTs], one nonrandomized placebo-controlled comparative trial, and 11 single-arm observational studies) demonstrated the effectiveness of the AAs spironolactone and eplerenone on resistant hypertension.[5] In the 4 comparative studies, AAs decreased office systolic blood pressure (SBP) by 24.3 mm Hg (95% confidence interval [CI], 8.65-39.87; *P*=.002) and diastolic blood pressure (DBP) by 7.8 mm Hg (95% CI, 3.79-11.79; *P*=.0001) more than placebo. In the 11 single arm studies, AAs reduced SBP by 22.74 mm Hg (95% CI, 18.21-27.27; *P* <.00001), and DBP by 10.49 mm Hg (95% CI, 8.85–12.13; *P* <.00001).

The previous year, a randomized, placebo-controlled trial examined the effect of low-dose (25 mg) spironolactone compared with placebo in 161 patients with resistant

TABLE

Home SBP after 12 weeks of treatment[1]

Treatment	Mean SBP, mm Hg (95% CI)	Change from baseline (95% CI)
Spironolactone	133.5 (132.3 to 134.8)	-14.4 (-15.6 to -13.1)
Doxazosin	138.8 (137.6 to 140.1)	-9.1 (-10.3 to -7.8)
Bisoprolol	139.5 (138.2 to 140.8)	-8.4 (-9.7 to -7.1)
Placebo	143.7 (142.5 to 145)	-4.2 (-5.4 to -2.9)

CI, confidence interval; SBP, systolic blood pressure.

hypertension.[6] At 8 weeks, 73% of those receiving spironolactone reached a goal SBP <140 mm Hg vs 41% of patients on placebo (*P*=.001). The same proportion (73%) achieved a goal DBP <90 mm Hg in the spironolactone group, compared with 63% of those in the placebo group (*P*=.223).

Ambulatory BP was likewise assessed and found to be significantly improved among those receiving spironolactone vs placebo, with a decrease in SBP of 9.8 mm Hg (95% CI, -14.2 to -5.4; *P*<.001), and a 3.2 mm Hg decline in DBP (95% CI, -5.9 to -0.5; *P*=.013).[6]

STUDY SUMMARY

First study to compare spironolactone with other drugs

The study by Williams et al—a double-blind, randomized placebo-controlled crossover trial conducted in the UK—was the first RCT to directly compare spironolactone with other medications for the treatment of resistant hypertension in adults already on triple therapy with an ACE inhibitor or ARB, a CCB, and a thiazide diuretic.[1] The trial randomized 335 individuals with a mean age of 61.4 years (age range 18 to 79), 69% of whom were male; 314 were included in the intention-to-treat analysis.[1]

Enrollment criteria for resistant hypertension specified a clinic-recorded SBP of ≥140 mm Hg (or ≥135 mm Hg in those with diabetes) and home SBP (in 18 readings over 4 days) of ≥130 mm Hg.[1] To ensure fidelity to treatment protocols, the investigators directly observed therapy, took tablet counts, measured serum ACE activity, and assessed BP measurement technique, with all participants adhering to a minimum of 3 months on a maximally dosed triple regimen.

Diabetes prevalence was 14%; tobacco use was 7.8%; and average weight was 93.5 kg (205.7 lbs).[1] Because of the expected inverse relationship between plasma renin and response to AAs, plasma renin was measured at baseline to test whether resistant hypertension was primarily due to sodium retention.[1]

Participants underwent 4, 12-week rotations

All participants began the trial with 4 weeks of placebo, followed by randomization to 12-week rotations of once daily oral treatment with 1) spironolactone 25 to 50 mg, 2) doxazosin modified release 4 to 8 mg, 3) bisoprolol 5 to 10 mg, and 4) placebo.[1] Six weeks after initiation of each study medication, participants were titrated to the higher dose. There was no washout period between cycles.

The primary outcome was mean SBP measured at home on 4 consecutive days prior to the study visits on Weeks 6 and 12. Participants were required to have at least 6 BP measurements per each 6-week period in order to establish a valid average. Primary endpoints included: the difference in home SBP between spironolactone and placebo, the difference in home SBP between spironolactone and the mean of the other 2 drugs, and the difference in home SBP between spironolactone and each of the other 2 drugs.

The results: Spironolactone lowered SBP more than placebo, doxazosin, and bisoprolol (**TABLE**),[1] and clinic measurements were consistent with home BP readings.

Overall, 58% of participants achieved goal SBP <135 mm Hg on spironolactone, compared with 42% on doxazosin, 44% on bisoprolol, and 24% on placebo.[1] The effective-

Nearly 60% of trial participants achieved their target SBP on spironolactone.

ness of spironolactone on SBP reduction was shown to exhibit an inverse relationship to plasma renin levels, a finding that was not apparent with the other 2 study drugs. However, spironolactone had a superior BP lowering effect throughout nearly the entire renin distribution of the cohort. The mean difference between spironolactone and placebo was -10.2 mm Hg; compared with the other drugs, spironolactone lowered SBP, on average, by 5.64 mm Hg more than bisoprolol and doxazosin; 5.3 mm Hg more than doxazosin alone, and 5.98 mm Hg more than bisoprolol alone.

Only 1% of trial participants had to discontinue spironolactone due to adverse events—the same proportion of withdrawals as that for bisoprolol and placebo and 3 times less than for doxazosin.[1]

Only 1% of trial participants discontinued spironolactone due to adverse events.

WHAT'S NEW

Evidence of spironolactone's superiority

This is the first RCT to compare spironolactone with 2 other commonly used fourth-line antihypertensives—bisoprolol and doxazosin—in patients with resistant hypertension. The study demonstrated clear superiority of spironolactone in achieving carefully measured ambulatory and clinic-recorded BP targets vs a beta-blocker or an alpha-blocker.

CAVEATS

Findings do not apply across the board

Spironolactone is contraindicated in patients with severe renal impairment. Although multiple drug trials have demonstrated the drug's safety and effectiveness, especially in patients with resistant hypertension, we should factor in the need for monitoring electrolytes and renal function within weeks of initiating treatment and periodically thereafter.[7,8] In this study, spironolactone increased potassium levels, on average, by 0.45 mmol/L. No gynecomastia (typically seen in about 6% of men) was found in those taking spironolactone for a 12-week cycle.[1]

This single trial enrolled mostly Caucasian men with a mean age of 61 years. Although smaller observational studies that included African American patients have shown promising results for spironolactone, the question of external validity or applicability to a diverse population has yet to be decisively answered.[9]

CHALLENGES TO IMPLEMENTATION

Potential for adverse reactions, lack of patient-oriented results

The evidence supporting this change in practice has been accumulating for the past few years. However, physicians treating patients with resistant hypertension may have concerns about hyperkalemia, gynecomastia, and effects on renal function. More patient-oriented evidence is likewise needed to assist with the revision of guidelines and wider adoption of AAs by primary care providers. **JFP**

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Light therapy for nonseasonal major depressive disorder?

While bright light therapy already has a place in the treatment of seasonal affective disorder, a recent trial spotlights its utility beyond the winter months.

PRACTICE CHANGER

Consider treatment with bright light therapy, alone or in combination with fluoxetine, for patients with nonseasonal major depressive disorder (MDD).[1]

STRENGTH OF RECOMMENDATION

B: Based on a single moderate-quality randomized control trial.

Lam RW, Levitt AJ, Levitan RD, et al. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2016;73:56-63.

ILLUSTRATIVE CASE

A 38-year-old woman recently diagnosed with MDD without a seasonal pattern comes to see you for her treatment options. Her Hamilton Depression Rating Scale (HAM-D) is 22, and she is not suicidal. Should you consider bright light therapy in addition to pharmacotherapy?

MDD is one of the most common psychiatric illnesses in the United States, affecting approximately one in 5 adults at some point in their lives.[2] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors are considered effective first-line pharmacotherapy options for MDD.[2,3] Despite their effectiveness, however, studies have shown that only about 40% of patients with MDD achieve remission with first- or second-line drugs.[2] In addition, pharmacologic agents have a higher frequency of treatment-associated adverse effects than fluorescent light therapy.[4]

A Cochrane systematic review of 20 studies (N=620) showed the effectiveness of combined light therapy and pharmacotherapy in treating nonseasonal MDD, but found no benefit to light used as a monotherapy.[5] However, the majority of the studies were of poor quality, occurred in the inpatient setting, and lasted fewer than 4 weeks.

In a 5-week, controlled, double-blind trial not included in the Cochrane review, 102 patients with nonseasonal MDD were randomized to receive either active treatment (bright light therapy) plus sertraline 50 mg daily or sham light treatment (using a dim red light) plus sertraline 50 mg daily. The investigators found a statistically significant larger reduction in depression score in the active treatment group than in the sham light group, based on the HAM-D, the Hamilton 6-Item Subscale, the Melancholia Scale, and the 7 atypical items from the Structured Interview Guide for the Seasonal Affective Disorder version of the HAM-D.[6,7]

STUDY SUMMARY

Light therapy improves depression without a seasonal component

This latest study was an 8-week randomized, double-blind, placebo- and sham-controlled clinical trial evaluating the benefit of light therapy with and without pharma-

cotherapy for nonseasonal MDD.[1] The investigators enrolled 122 adult patients (ages 19-60 years) from outpatient psychiatry clinics with a diagnosis of MDD (as diagnosed by a psychiatrist) and a HAM-D[8] score of at least 20. Subjects had to be off psychotropic medication for at least 2 weeks prior to the first visit and were subsequently monitored for one week to identify spontaneous responders and to give patients time to better regulate their sleep-wake cycle (with the goal of sleeping only between 10:00 pm and 8:00 am daily).

The investigators randomly assigned patients to one of 4 treatment groups: active light monotherapy (10,000-lux fluorescent white light for 30 min/d early in the morning) plus a placebo pill; fluoxetine 20 mg/d plus sham light therapy; placebo pills with sham light therapy; and combined active light therapy with fluoxetine 20 mg daily. Sham light therapy consisted of the use of an inactivated negative ion generator, used in the same fashion as a light box. All patients were analyzed based on modified intention to treat.

The investigators monitored patients for adherence to active and sham treatment by review of their daily logs of device treatment times. Pill counts were used to assess medication adherence. The primary outcome at 8 weeks was the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item questionnaire with a worst score of 60.[9] Secondary outcomes were treatment response (≥50% MADRS score reduction) and remission (≤10 MADRS score) at the final 8th-week visit. MADRS scoring was used because of its higher sensitivity to treatment-induced changes and its high correlation with the HAM-D scale.

At the end of 8 weeks, the mean (standard deviation [SD]) changes in MADRS scores from baseline were: light monotherapy 13.4 (7.5), fluoxetine monotherapy 8.8 (9.9), combination therapy 16.9 (9.2), and placebo 6.5 (9.6). The improvement was significant in the light monotherapy treatment group vs the placebo group (P=.006), in the combination treatment group vs the placebo group (P<.001), and in the combination group vs the fluoxetine treatment group (P=.02), but not for the fluoxetine treatment group vs the placebo group (P=.32). The effect sizes vs placebo were: fluoxetine, d=0.24 (95% confidence interval [CI], −0.27 to 0.74); light monotherapy, 0.80 (95% CI, 0.28 to 1.31); and combination therapy, 1.11 (95% CI, 0.54 to 1.64). Effect sizes of more than 0.8 are often considered large.[10]

The treatment response (≥50% MADRS improvement) rate was highest in the combination treatment group (75.9%) with response rates to light monotherapy, placebo, and fluoxetine monotherapy of 50%, 33.3%, and 29%, respectively. There was a significant response effect for the combination vs placebo treatment group (P=.005). Similarly, there was a higher remission rate in the combination treatment group (58.6%) than in the placebo, light monotherapy, or fluoxetine treatment groups (30%, 43.8%, and 19.4%, respectively) with a significant effect for the combination vs placebo treatment group (P=.02).

Combination therapy was superior to placebo in treatment response (≥50% reduction in the MADRS score) and remission (MADRS ≤10) with numbers needed to treat of 2.4 (95% CI, 1.6-5.8) and 3.5 (95% CI, 2.0-29.9), respectively.

By the end of the 8-week study period, 16 of 122 patients had dropped out; 2 reported lack of efficacy, 5 reported adverse effects, and the remainder cited administrative reasons, were lost to follow-up, or withdrew consent.

Seventy-six percent of patients treated with fluoxetine and light therapy saw at least a 50% improvement in their depression scores.

WHAT'S NEW?

New evidence on a not-so-new treatment

We now have evidence that bright light therapy, either alone or in combination with fluoxetine, is efficacious in increasing the remission rate of nonseasonal MDD.

CAVEATS

Choice of SSRI, geography, and trial duration may have affected results

A single SSRI (fluoxetine) was used in this study; other more potent SSRIs might work better. This study was conducted in southern Canada, and light therapy may not demonstrate as large a benefit in regions located farther south. The study excluded pregnant and breastfeeding women.

CONTINUED

The trial duration was relatively short, and the investigators did not attain their preplanned sample size for the study, which limited the power to detect clinically significant seasonal treatment effects and differences between the fluoxetine and placebo groups, regardless of whether they received active phototherapy.

Also, it's worth noting that there were trends for some adverse events (nausea, heartburn, weight gain, agitation, sexual dysfunction, and skin rash) to occur less frequently in the combination group than in the fluoxetine monotherapy group. Possible explanations are that the study had inadequate power, that the sham treatment did not adequately blind patients, or that light therapy can ameliorate some of the adverse effects of fluoxetine.

We now have evidence that bright light therapy, alone or in combination with fluoxetine, is efficacious in increasing the remission rate of nonseasonal major depressive disorder.

CHALLENGES TO IMPLEMENTATION

Commercial insurance doesn't usually cover light therapy

Bright light therapy is fairly safe, and some evidence exists supporting its use in the treatment of nonseasonal MDD; however, the data for its use in this area are limited.[11] Since only a few studies have tested light therapy for nonseasonal MDD, significant uncertainty remains about patient selection, as well as optimal dose, timing, and duration of light therapy in the management of nonseasonal MDD.[12] Although the risks associated with bright light therapy are minimal, the therapy can lead to mania or hypomania,[3] so clinicians need to monitor for such effects when initiating therapy.

Lastly, commercial insurance does not usually cover light therapy. The average price of the bright light devices, which can be found in medical supply stores and online outlets, ranges between $118 and $237.[4,12] However, such devices are reusable, making the amortized cost almost negligible.[13] JFP

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Liver and GI Update — Mark H. Ebell MD, MS

Objectives

1. Review diagnosis and management of appendicitis
2. Understand role (if any) for new drugs for irritable bowel.
3. Review guidelines for microscopic colitis
4. Understand new studies guiding management of acute pancreatitis.

Appendicitis

The history and physical exam isn't dead. It can help identify patients with very low and high likelihoods of appendicitis. ACEP guidelines recommend using clinical signs and symptoms to risk stratify patients with acute abdominal pain for discharge, imaging, or surgical referral.

They recommend USN over CT in kids, and for adults if CT is ordered it may be with or without contrast, although contrast does increase sensitivity somewhat over non-contrast studies.

(https://www.acep.org/Clinical---Practice-Management/Clinical-Policy--Evaluation-and-Management-of-Suspected-Appendicitis/)

Table 1. The Alvarado score and the Pediatric Appendicitis Score.[1,2]

Clinical Variable	Alvarado Score	PAS
Migration of pain	1	1
Anorexia	1	1
Nausea or vomiting	1	1
Right lower quadrant tenderness	2	2
Rebound pain	1	
Elevated temperature*	1	1
Leukocytosis (≥10,000/μL)	2	1
Shift of WBC count to the left (≥75% polymorphonucleocytes)	1	1
Cough/percussion/hopping cause pain in the RLQ		2
Total	10	10

PAS, Pediatric Appendicitis Score; *WBC*, white blood count; *RLQ*, right lower quadrant.
*Fever generally defined as greater than or equal to 37.3°C (91.2°F) for the Alvarado score and greater than or equal to 37.3°C (99.2°F) or 38.0°C (100.4°F) for PAS.

			Pretest probability						
Adults (Alvarado)	**Points**	**LR**	**20%**	**33%**	**40%**	**50%**	**60%**	**66%**	**75%**
Low risk	< 4	0.03	0.7%	1.5%	2.0%	2.9%	4.3%	**5.5%**	8.3%
Low risk	< 5	0.02	0.5%	1.0%	1.3%	2.0%	2.9%	**3.7%**	5.7%
High risk	≥ 7	3.4	47%	63%	70%	78%	84%	87%	91%
High risk	≥ 9	6.7	63%	77%	82%	87%	91%	93%	95%
Children (Alvarado)									
Low risk	< 4	0.02	0.5%	**1.0%**	1.3%	2.0%	2.9%	3.7%	5.7%
Low risk	< 5	0.04	1.0%	**1.9%**	2.6%	3.8%	5.7%	7.2%	11%
High risk	≥ 7	4.2	51%	**67%**	74%	81%	86%	89%	93%
High risk	≥ 9	8.5	68%	**81%**	85%	90%	93%	94%	96%
Children (PAS)	**Points**	**LR**	**20%**	**33%**	**40%**	**50%**	**60%**	**66%**	**75%**
Low risk	< 4	0.13	3.1%	6.0%	8.0%	11.5%	16%	**20%**	28%
High risk	≥ 8	8.1	67%	80%	84%	89%	92%	94%	96%

1. PubMed: WBC, proalcitonin and CRP not very helpful.

BACKGROUND: The aim was to evaluate the diagnostic value of procalcitonin, C-reactive protein (CRP) and white blood cell count (WBC) in uncomplicated or complicated appendicitis by means of a systematic review and meta-analysis.
METHODS: The Embase, MEDLINE and Cochrane databases were searched, along with reference lists of relevant articles, without language restriction, to September 2012. Original studies were selected that reported the performance of procalcitonin alone or in combination with CRP or WBC in diagnosing appendicitis. Test performance characteristics were summarized using hierarchical summary receiver operating characteristic (ROC) curves and bivariable random-effects models.
RESULTS: Seven qualifying studies (1011 suspected cases, 636 confirmed) from seven countries were identified. Bivariable pooled sensitivity and specificity were 33 (95 per cent confidence interval (c.i.) 21 to 47) and 89 (78 to 95) per cent respectively for procalcitonin, 57 (39 to 73) and 87 (58 to 97) per cent for CRP, and 62 (47 to 74) and 75 (55 to 89) per cent for WBC. ROC curve analysis showed that CRP had the highest accuracy (area under ROC curve 0·75, 95 per cent c.i. 0·71 to 0·78), followed by WBC (0·72, 0·68 to 0·76) and procalcitonin (0·65, 0·61 to 0·69). Procalcitonin was found to be more accurate in diagnosing complicated appendicitis, with a pooled sensitivity of 62 (33 to 84) per cent and specificity of 94 (90 to 96) per cent.
CONCLUSION: Procalcitonin has little value in diagnosing acute appendicitis, with lower diagnostic accuracy than CRP and WBC. However, procalcitonin has greater diagnostic value in identifying complicated appendicitis. Given the imperfect accuracy of these three variables, new markers for improving medical decision-making in patients with suspected appendicitis are highly desirable.
***Reference**: Yu CW1, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg. 2013 Feb;100(3):322-9. doi: 10.1002/bjs.9008. Epub 2012 Nov 30.*

	Sens	Spec	LR+	LR-
Procalcitonin	33	89	3.0	0.75
C-reactive protein	57	87	4.4	0.49
WBC	62	75	2.5	0.51

2. PubMed: POCUS fairly accurate for diagnosis of acute appendicitis

BACKGROUND: The use of ultrasonography (US) to diagnose appendicitis is well established. More recently, point-of-care ultrasonography (POCUS) has also been studied for the diagnosis of appendicitis, which may also prove a valuable diagnostic tool. The purpose of this study was through systematic review and meta-analysis to identify the test characteristics of POCUS, specifically US performed by a nonradiologist physician, in accurately diagnosing acute appendicitis in patients of any age.
METHODS: We conducted a thorough and systematic literature search of English language articles published on point-of-care, physician-performed transabdominal US used for the diagnosis of acute appendicitis from 1980 to May, 2015 using OVID MEDLINE In-Process & Other Non-indexed Citations and Scopus. Studies were selected and subsequently independently abstracted by two trained reviewers. A random-effects pooled analysis was used to construct a hierarchical summary receiver operator characteristic curve, and a meta-regression was performed. Quality of studies was assessed using the QUADAS-2 tool.
RESULTS: Our search yielded 5,792 unique studies and we included 21 of these in our final review. Prevalence of disease in this study was 29.8%, (range = 6.4%-75.4%). The sensitivity and specificity for POCUS in diagnosing appendicitis were 91% (95% confidence interval [CI] = 83%-96%) and 97% (95% CI = 91%-99%), respectively. The positive and negative predictive values were 91 and 94%, respectively. Studies performed by emergency physicians had slightly lower test characteristics (sensitivity = 80%, specificity = 92%). There was significant heterogeneity between studies (I^2 = 99%, 95% CI = 99%-100%) and the quality of the reported studies was moderate, mostly due to unclear reporting of blinding of physicians and timing of scanning and patient enrollment. Several of the studies were performed by a single operator, and the education and training of the operators were variably reported.
CONCLUSION: Point-of-care US has relatively high sensitivity and specificity for diagnosing acute appendicitis, although the data presented are limited by the quality of the original studies and large CIs. In the hands of an experienced operator, POCUS is an appropriate initial imaging modality for diagnosing appendicitis. Based on our results, it is premature to utilize POCUS as a stand-alone test or to rule out appendicitis.
Reference: Matthew Fields J, Davis J, Alsup C, et al. Accuracy of Point-of-care Ultrasonography for Diagnosing Acute Appendicitis: A Systematic Review and Meta-analysis. Acad Emerg Med. 2017 Sep;24(9):1124-1136.

Lots of new information about non-operative treatment of acute appendicitisin both adults and children. Surgeons are still not ready to embrace it, and remain concerned about long-term outcomes.

3. POEM: Many patients with uncomplicated acute appendicitis do well with antibiotic therapy

Clinical question: Is antibiotic therapy a reasonable option for the treatment of uncomplicated acute appendicitis in adults?
Study design: Randomized controlled trial (single-blinded) **Setting:** Inpatient (any location) with outpatient follow-up
Synopsis: The optimal management of acute uncomplicated appendicitis (ie, immediate surgery versus antibiotic therapy) remains controversial. These investigators identified 530 adults, aged 18 to 60 years, who presented to the emergency departments of 6 Finnish hospitals with uncomplicated acute appendicitis confirmed by computed tomographic scan. Exclusion criteria included the presence of an appendicolith, perforation, abscess, or suspicion of a tumor. Consenting patients were randomly assigned (concealed allocation) to either standard surgical appendectomy or antibiotic therapy (1 g intravenous ertapenem daily for 3 days followed by 7 days of oral levofloxacin, 500 mg once daily, and metronidazole, 500 mg 3 times daily). Outcomes were assessed via hospital records and telephone interviews for 1 year. Complete follow-up occurred for 83% of study participants. Using intention-to-treat analysis, of the 273 patients randomized to the surgical group, 272 (99.6%) underwent successful appendectomy. Of these, only 6% underwent laparoscopic appendectomy. Of the 256 patients available for 1-year follow-up in the antibiotic group, 186 (72.7%; 95% CI 66.8%-78.0%) did not require appendectomy; the rest underwent surgical intervention within 1 year of initial presentation. No patients in the antibiotic group developed an intra-abdominal abscess. The overall postintervention complication rate, including median length of sick leave, wound infection, pneumonia, diarrhea, incisional hernia, adhesion-related bowel obstructions, and persistent abdominal or incisional pain was significantly lower in the antibiotic group (2.8% vs 20.5%; number needed to treat to harm = 5.7; 4.2-8.4). Interestingly, the complication rate in the subgroup of patients in the antibiotic group who eventually underwent appendectomy was also significantly lower than the rate in the group who underwent initial appendectomy (7.0% vs 20.5%). There was no difference between the groups in all-cause mortality.
Bottom line: In this study--the largest randomized trial to date to examine this question--the approximately 75% of adults who presented with acute uncomplicated appendicitis and were treated initially with antibiotics did not require appendectomy. Those who underwent appendectomy after initial antibiotic treatment experienced fewer postsurgical complications than the group of patients who underwent appendectomy first.
Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis. The APPAC randomized clinical trial. JAMA 2015;313(23):2340-2348.

4. POEM: Meta-analysis: Antibiotics for appendicitis results in fewer surgeries but more recurrence

Clinical question: What are the trade-offs when patients with acute appendicitis are treated with antibiotics?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Inpatient (any location) with outpatient follow-up
Synopsis: These authors searched 2 databases and 2 clinical trials registries to identify randomized trials comparing antibiotics with appendectomy in patients with acute appendicitis. Two of the authors independently evaluated each study for inclusion and resolved any disagreements with a third member of the research team. The authors assessed each study's risk of bias, but the paper doesn't say whether this was done in a paired, independent manner. Ultimately the authors included 5 randomized trials with approximately 1100 patients in the main analysis and one quasi-experimental study in a sensitivity analysis. The meta-analysis included patients from 5 to 75 years of age, but 4 of the studies recruited only adults and the other 2 studies recruited only children. Computed tomography or ultrasound were not consistently used across the studies. After 1 year, the drop-out rate ranged from 7% to 22%. Virtually 100% of the 562 patients allocated to surgery underwent surgery, 75% of which were open laparotomies. Of the 550 patients allocated to receive antibiotics, approximately 8% underwent surgery within 1 month. Approximately 5% of patients treated with antibiotics experienced

major complications (compared with 8% of those undergoing surgery). Similarly, the rate of minor complications was 3% and 12%, respectively. Finally, nearly 20% of patients treated with antibiotics had a confirmed recurrence of appendicitis within the following year; another 14 patients had recurrent pain and underwent surgery only to remove normal appendices. Among the studies reporting these outcomes, surgically treated patients had nearly 12-hour shorter hospital lengths of stay, but there was no difference in the duration of sick leave. The authors reported significant heterogeneity for minor complications and hospital lengths of stay and modest heterogeneity for major complications.
Bottom line: In this meta-analysis, most patients with appendicitis who are treated with antibiotics do quite well, but 1 in 5 will have a recurrence in the following year.
Sallinen V, Akl EA, You JJ, et al. Meta-analysis of antibiotics versus appendectomy for non-perforated acute appendicitis. Br J Surg 2016;103(6):656-667.

Increasingly this is being considered as an option for children with acute appendicitis.

5. POEM: Children with appendicitis do fairly well with antibiotic treatment!

Clinical question: Do children with appendicitis treated with antibiotics do as well as those treated with surgery?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Various (meta-analysis)
Synopsis: These authors searched multiple databases and a trial registry to identify trials comparing antibiotics and surgery in children with acute uncomplicated appendicitis. Two authors independently evaluated each potential paper for inclusion and assessed each included paper's risk of bias. They included five small studies with 404 children; 168 were treated with antibiotics and 236 were treated surgically. Only one of the trials was randomized. Three studies reported one year follow up and one followed the children for 4.3 years. One planned one year of follow up but only reported a median of 4.7 months. The range of patients not available after one year ranged from 0% to 23% and was similar among those treated surgically or with antibiotics. The included studies also used different diagnostic approaches. In the children treated with antibiotics, 9.5% failed initial treatment - resolution of symptoms without needing surgery within 48 hours or recurrence of appendicitis 1 month after antibiotics while all 236 of those treated surgically had confirmed appendicitis and only one needed reoperation. In other words, about 90% of children treated with antibiotics will do well initially. Forty-five of the antibiotic-treated children (26.8%), however, underwent appendectomy within the following year, 8 of whom had normal appendices on histopathology. Children treated with antibiotics had 8 days of disability compared with 21 in those treated surgically. Four studies reported data on children with an appendicolith, three of which reported that its presence was associated with a 50% rate of antibiotic failure.
Bottom line: The existing data are limited to a few small studies. While surgery is clearly better at improving short term and long-term outcomes, it is expensive and patients need to recover. Most children treated with antibiotics will do well, but about 1 in 4 will undergo surgery within a year. This is the perfect place for shared decision-making.
Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis in Children: A Meta-analysis. JAMA Pediatr. 2017;171(5):426-434.

6. POEM: Antibiotics may equal surgery for children with appendicitis

Clinical question: Can children with appendicitis be treated with antibiotics instead of surgery?
Study design: Meta-analysis (other) **Setting:** Various (meta-analysis)
Synopsis: These researchers assembled studies that evaluated antibiotic use in the treatment of children with acute uncomplicated appendicitis (ie, without perforation or rupture or evidence of an abscess or mass). Two investigators independently searched 3 databases, including Cochrane CENTRAL, as well as reference lists, to identify all English-language studies that evaluated antibiotic treatment. Two authors independently extracted the data and evaluated its quality. All but 1 of the 10 studies (N = 766 children) were observational; 4 of the studies did not have a comparison group. Antibiotic treatment in these studies was usually intravenous for 48 hours, followed by oral treatment for an additional 3 days to 5 days. Antibiotic treatment was effective in resolving the infection without the need for appendectomy during the initial hospitalization in 396 of 413 children (97% of children; 95% CI 96% - 99%). Over prolonged follow-up (8 weeks to 4 years), appendicitis occurred in 14% (7% - 21%), but there was pronounced heterogeneity among the studies. Complications occurred similarly in children treated with surgery or with antibiotics. The studies are of low quality, for the most part, and it's time for a large randomized study (as has been done in adults: World J Surg 2016;40(10):2305-2318). Still, if these were the data used to evaluate surgery as the first-line treatment for appendicitis, we would never have instituted it.
Bottom line: Another shibboleth has toppled, or is at least teetering. Antibiotic treatment appears to be effective for children with uncomplicated appendicitis without evidence of perforation or rupture, with 97% of children discharged without surgery. Approximately 1 in 7 children will eventually have recurrence and require surgery. A couple of days of intravenous antibiotics is an option before surgery.
Georgiou R, Eaton S, Stanton MP, Pierro A, Hall NJ. Efficacy and safety of nonoperative treatment for acute appendicitis: a meta-analysis. Pediatrics 2017;139(3):e2 0163003.

Diarrheal illness

Ondansetron (Zofran) is somewhat effective for IBS-D (cost $10-$12 on www.goodrx.com):

7. POEM: Ondansetron somewhat effective for diarrhea-predominant IBS

Clinical question: Is ondansetron a safe and effective treatment for diarrhea-predominant irritable bowel syndrome?
Study design: Cross-over trial (randomized) **Setting:** Outpatient (specialty)
Synopsis: Ondansetron is a widely used anti-emetic, but it also slows colonic transit. This is the first adequately powered trial to investigate the use of the drug in patients with IBS-D. The researchers recruited 120 adults, aged 18 to 75 years, with IBS-D meeting

standard Rome III criteria from an English specialty clinic. The patients were carefully evaluated for other causes of digestive symptoms; the evaluations included colonoscopy, blood tests for celiac disease and inflammatory bowel disease, and a test for lactose intolerance. This was a crossover trial, with each participant receiving either placebo or ondansetron during two 5-week treatment periods. The trial was well-designed, with appropriate masking and allocation concealment. After the baseline assessment, participants were randomized to receive either ondansetron 4 mg tablets or placebo tablets for a 3-week dose titration period. The patients were told to begin taking 1 capsule once daily, but could increase to a maximum of 2 capsules 3 times daily. If they achieved a dosage that adequately controlled their symptoms, they were to maintain it. All patients took the final titrated dose for the last 2 weeks of the 5-week period. They then had a washout period of at least 2 weeks to get them back to their baseline stool frequency, and then they took the other medication (either placebo or ondansetron). The advantage of crossover trials is that you can get away with smaller sample sizes; the disadvantage is that it is easier for patients to determine whether they were taking active drug or placebo, and sometimes drug effects are not completely washed out. Of the 120 patients who were randomized, 98 were available for the intention-to treat-analysis. The primary outcome was the Bristol Stool Form Score [folks in Bristol must be truly honored], ranging from Type 1 (separate hard lumps, nutlike, hard to pass) to Type 7 (watery, no solid pieces, entirely liquid). During the trial, the patients taking ondansetron typically improved from Type 5 (soft blobs with clear-cut edges, passed easily), to the much more desirable Type 4 (like a sausage, but with cracks on its surface). Gut transit was measured on the last day of each treatment by plain x-ray. Compared with the period when they were taking placebo, participants taking ondansetron had approximately 1 fewer day of urgency or bloating per week ($P < .001$), and a lower frequency of defecation (11% fewer stools, 95% CI 4% - 18%), but no significant decrease in pain scores or days with pain. The median dosage was 4 mg per day in responders. Constipation was more common in patients taking ondansetron (9% vs 2%). Long-term safety data for ondansetron are not available; a similar drug, alosetron, was withdrawn from widespread use because it caused severe constipation and ischemic colitis.
Bottom line: Ondansetron (Zofran) provides a modest benefit for patients with diarrhea-predominant irritable bowel syndrome (IBS-D). The main benefit is in reducing urgency and is seen within 7 days. I look forward to a larger, longer trial of ondansetron to be assured of its safety and to assess benefits in a more typical primary care population.
Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. Gut 2014;63(10):1617-1625.

This drug for IBS with diarrhea is a bit effective but hits the wallet hard (about $1000/month):

8. POEM: Eluxadoline marginally beneficial for IBS with diarrhea, but very expensive

Clinical question: Is eluxadoline safe and effective for patients with irritable bowel syndrome?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (any)
Synopsis: Eluxadoline is a mixed mu and kappa opiod agonist (like loperamide) and delta opioid receptor antagonist that is thought to relieve IBS by reducing visceral hypersensitivity. This report is a combination of the results of 2 large randomized controlled trials of adults with diarrhea-predominant IBS based on Rome III criteria. Patients were only included if they reported significant abdominal pain, diarrhea, and IBS symptoms during a run-in period before the trial. The authors excluded patients with alcohol use disorder, gallbladder problems, or pancreas problems; those who were taking an opiate; and those who were pregnant or breastfeeding. Both studies followed up patients for 26 weeks in a double-blind manner, and then one study added 26 additional weeks of double-blind treatment for safety assessment only. Participants were randomized to receive eluxadoline 75 mg, eluxadoline 100 mg, or placebo twice daily. The mean age of participants was 46 years, approximately two-thirds were women, and the average body mass index was approximately 31 kg/m2. The groups were balanced at the beginning of the study, and analysis was by intention to treat. The primary outcome was treatment success, defined as having a 30% or greater reduction in symptom severity on at least 50% of the days. Using data pooled from both trials, at 26 weeks the response rate was 31.0% for the 100-mg dose, 26.7% for the 75-mg dose, and 19.5% for placebo. The differences between both active treatments and placebo were statistically significant, with numbers needed to treat of 9 for the 100-mg dose and 14 for the 75-mg dose. In the safety assessment, 5 patients in the eluxadoline groups had pancreatitis and 8 had sphincter of Oddi spasm, largely in the 100-mg dose group, compared with none in the placebo group. None of the patients with sphincter of Oddi spasm had a gallbladder. Cardiovascular events were also slightly more common in the intervention group (1.7% vs 1.0%), although the statistical significance was not reported.
Bottom line: Eluxadoline (Viberzi) is slightly effective for diarrhea-predominant irritable bowel syndrome (IBS), with numbers needed to treat of 9 for the 100-mg dose and 14 for the 75-mg dose. However, the drug costs approximately $1000 per month (www.goodrx.com) and has rare but serious adverse effects, such as pancreatitis and spasm of the sphincter of Oddi, especially in the (more effective) 100-mg group. This sounds like a medication to avoid until we have more data. Then, perhaps, we can use this very expensive intervention in patients who are most likely to benefit and least likely to be harmed.
Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016;374(3):242-253.

And finally, in the Department of Icky Medicine:

9. Fecal transplantation better than placebo for remission in patients with ulcerative colitis

Clinical question: Does fecal transplantation improve outcomes in patient with ulcerative colitis?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (specialty)
Synopsis: These researchers recruited adult patients with active UC diagnosed at least 3 months prior to enrollment with a Mayo severity score between 4 and 10. They allowed co-interventions (salicylates, thiopurines, methotrexate) to continue as long as the dosing was stable. Patients were allowed to continue to take prednisone but they underwent a taper so they were steroid-free by the 8-week re-evaluation. Finally, they did not allow patients to receive rectal therapies, antibiotics, probiotics, biological therapies, or calcineurin therapies during the study period. To ensure masking, the researchers added dyes, thickeners, and "perfumes" so that both the active and placebo treatments looked and smelled like feces. For the gory details on the donated feces, please read the study. After a baseline colonoscopy during which the initial infusion was administered, each patient self-administered the interventions in the form of

an enema (41 active treatment, 40 placebo) on 5 consecutive days, followed by a 2-day holiday, and so on for 8 weeks. After the initial 8-week period, the researchers offered the placebo-treated patients open-label fecal transplants. Twenty of the patients dropped out of the double-blind phase of the study. Among those assigned to placebo, 37 went into the open-label phase, but 11 of those dropped out. The main outcome was a composite of steroid-free clinical remission plus endoscopic remission or response. At the end of the initial 8 weeks, 11 (27%) of the actively treated patients achieved the endpoint compared with only 3 (8%) of the control patients (number needed to treat = 6; 95% CI 3 - 38). Approximately 80% of all patients in each group had at least one adverse event during the 8 weeks—mostly self-limited gastrointestinal symptoms. Six patients experienced serious adverse events: 5 who were receiving the active treatment (during the double-blind or the open-label phase) and 1 who was receiving the placebo. One patient with refractory UC who received active treatment withdrew from the study for deterioration and ultimately ended up with a colectomy.
Bottom line: In this small study, patients with ulcerative colitis (UC) treated with an intense program of fecal transplantation were more likely to achieve endoscopically confirmed clinical remission after 8 weeks than those treated with placebo. It is unclear what the long-term benefits and harms are for this treatment and whether less intense treatment would be as effective.
Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet 2017;389(10075):1218-1228.

In patients with chronic diarrhea, it's always important to remember that collagenous and microscopic colitis are in the differential. This Cochrane review summarizes treatment data.

10. Cochrane: Treatment of collagenous colitis

Background: Collagenous colitis is a cause of chronic diarrhea. This updated review was performed to identify therapies for collagenous colitis that have been assessed in randomized controlled trials (RCTs).
Search: We searched CENTRAL, the Cochrane IBD Group Specialized Register, MEDLINE and EMBASE from inception to 7 November 2016. We included RCTs comparing a therapy with placebo or active comparator for the treatment of active or quiescent collagenous colitis.
Data collection and analysis: Data were independently extracted by two authors. The primary outcome was clinical response or maintenance of response as defined by the included studies. Secondary outcome measures included histological response, quality of life and the occurrence of adverse events. Risk ratios (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. The Cochrane risk of bias tool was used to assess bias. The overall quality of the evidence was assessed using the GRADE criteria.
Main results: Twelve RCTs (476 participants) were included. These studies assessed bismuth subsalicylate, *Boswellia serrata* extract, mesalamine, cholestyramine, probiotics, prednisolone and budesonide therapy. Four studies were low risk of bias. One study assessing mesalamine and cholestyramine was judged to be high risk of bias due to no blinding. The other studies had an unclear risk of bias for random sequence generation (five studies) allocation concealment (six studies), blinding (one study), incomplete outcome data (one study) and selective outcome reporting (one study). Clinical response occurred in 100% (4/4) of patients who received bismuth subsalicylate (nine 262 mg $_{\text{tablets}}$ daily for 8 weeks) compared to 0% (0/5) of patients who received placebo (1 study; 9 participants; RR 10.80, 95% CI 0.75 to 155.93; GRADE = very low). Clinical response occurred in 44% (7/16) of patients who received *Boswellia serrata*extract (three 400 mg/day capsules for 8 weeks) compared to 27% (4/15) of patients who received placebo (1 study; 31 participants; RR 1.64, 95% CI 0.60 to 4.49; GRADE = low). Clinical response occurred in 80% (24/30) of budesonide patients compared to 44% (11/25) of mesalamine patients (1 study; 55 participants; RR 1.82, 95% CI 1.13 to 2.93; GRADE = low). Histological response was observed in 87% (26/30) of budesonide patients compared to 44% (11/25) of mesalamine patients (1 study, 55 participants; RR 1.97, 95% CI 1.24 to 3.13; GRADE = low). There was no difference between the two treatments with respect to adverse events (RR 0.69, 95% CI 0.43 to 1.10; GRADE = low), withdrawals due to adverse events (RR 0.09, 95% CI 0.01 to 1.65; GRADE = low) and serious adverse events (RR 0.12, 95% CI 0.01 to 2.21; GRADE = low). Clinical response occurred in 44% (11/25) of mesalamine patients (3 g/day) compared to 59% (22/37) of placebo patients (1 study; 62 participants; RR 0.74, 95% CI 0.44 to 1.24; GRADE = low). Histological response was observed in 44% (11/25) and 51% (19/37) of patients receiving mesalamine and placebo, respectively (1 study; 62 participants; RR 0.86, 95% CI 0.50 to 1.47; GRADE = low). There was no difference between the two treatments with respect to adverse events (RR 1.26, 95% CI 0.84 to 1.88; GRADE = low), withdrawals due to adverse events (RR 5.92, 95% CI 0.70 to 49.90; GRADE = low) and serious adverse events (RR 4.44, 95% CI 0.49 to 40.29; GRADE = low). Clinical response occurred in 63% (5/8) of prednisolone (50 mg/day for 2 weeks) patients compared to 0% (0/3) of placebo patients (1 study, 11 participants; RR 4.89, 95% CI 0.35 to 68.83; GRADE = very low). Clinical response occurred in 29% (6/21) of patients who received probiotics (2 capsules containing 0.5 x 1010 CFU each of *L. acidophilus LA-5* and *B. animalis subsp. lactis* strain BB-12 twice daily for 12 weeks) compared to 13% (1/8) of placebo patients (1 study, 29 participants, RR 2.29, 95% CI 0.32 to 16.13; GRADE = very low). Clinical response occurred in 73% (8/11) of patients who received mesalamine (800 mg three times daily) compared to 100% (12/12) of patients who received mesalamine + cholestyramine (4 g daily) (1 study, 23 participants; RR 0.74, 95% CI 0.50 to 1.08; GRADE = very low). Clinical response occurred in 81% (38/47) of patients who received budesonide (9 mg daily in a tapering schedule for 6 to 8 weeks) compared to 17% (8/47) of placebo patients (3 studies; 94 participants; RR 4.56, 95% CI 2.43 to 8.55; GRADE = low). Histological response was higher in budesonide participants (72%, 34/47) compared to placebo (17%, 8/47) (RR 4.15, 95% CI 2.25 to 7.66; GRADE = low). Clinical response was maintained in 68% (57/84) of budesonide patients compared to 20% (18/88) of placebo patients (3 studies, 172 participants, RR 3.30 95% CI 2.13 to 5.09; GRADE = low). Histological response was maintained in 48% (19/40) of budesonide patients compared to 15% (6/40) of placebo patients (2 studies; 80 participants; RR 3.17, 95% CI 1.44 to 6.95; GRADE = very low). No difference was found between budesonide and placebo for adverse events (5 studies; 290 participants; RR 1.18, o95% CI 0.92 to 1.51; GRADE = low), withdrawals due to adverse events (5 studies, 290 participants; RR 0.97, 95% CI 0.43 to 2.17; GRADE = very low) or serious adverse events (4 studies, 175 participants; RR 1.11, 95% CI 0.15 to 8.01; GRADE = very low).
Authors' conclusions: Low quality evidence suggests that budesonide may be effective for inducing and maintaining clinical and histological response in patients with collagenous colitis. We are uncertain about the benefits and harms of therapy with bismuth subsalicylate, *Boswellia serrata* extract, mesalamine with or without cholestramine, prednisolone and probiotics. These agents and other therapies require further study.

Kafil TS, Nguyen TM, Patton PH, MacDonald JK, Chande N, McDonald JW. Interventions for treating collagenous colitis. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD003575.

AGA Guidelines for microscopic colitis (Gastroenterology 2016; 150: 242-6) are consistent with Cochrane review:

- Budesonide (Entocort) is first line therapy. Mesalamine, prednisone, or bismuth busalicylate are alternatives if budesonide is contraindicated.
- They recommend against using “Boswellia serrata, combination of cholestyramine and mesalamine, and probiotics.

Pancreatitis

Early feeding of patients with acute pancreatitis may help those with mild to moderate severity disease, but not those with more severe pancreatitis.

11. POEM: Early feeding may benefit hospitalized patients with mild to moderate pancreatitis

Clinical question: For patients hospitalized with acute pancreatitis, does early feeding improve outcomes?
Study design: Systematic review **Setting:** Inpatient (ward only)
Synopsis: These investigators searched multiple databases including MEDLINE and EMBASE, reviewed bibliographies of relevant studies, and contacted content experts to find randomized controlled trials that compared early enteral feeding (initiated at or within 48 hours of hospitalization) versus delayed enteral feeding (initiated more than 48 hours after hospitalization) for adults hospitalized for acute pancreatitis. The primary outcomes were length of stay, mortality, and readmission. Two authors independently determined study eligibility, extracted data, and assessed for risk of bias. Ultimately, 8 randomized controlled trials and 3 conference abstracts met eligibility criteria for this review (N = 948); only 4 of the studies were assessed as having low risk of bias. Seven studies included patients with mild to moderate pancreatitis in which the early group received either oral or nasogastric feeding and the delayed group received oral feeding. The remaining 4 studies included patients with severe pancreatitis and the early group received nasojejunal feeding while the delayed group received either oral or nasojejunal feeding. For patients with mild to moderate pancreatitis, early feeding led to a reduction of length of stay in 4 studies and a reduction of GI symptoms in 3 studies. No statistically significant association was seen between early feeding and mortality or re-admission rates. For patients with severe pancreatitis, one study with an unclear risk of bias showed a reduction in length of stay with early feeding, but otherwise no significant differences were seen in mortality or GI symptoms. A meta-analysis was not performed because of heterogeneity regarding route of feeding, timing of feeding, and reported outcomes across the studies.
Bottom line: Early feeding does not lead to increased adverse events and may reduce gastrointestinal (GI) symptoms and hospital length of stay and in patients with mild to moderate pancreatitis. No clear benefit was seen in patients with severe pancreatitis.
Vaughn VM, Shuster D, Rogers MAM, et al. Early versus delayed feeding in patients with acute pancreatitis. Ann Intern Med 2017;166(12):883-892

12. POEM: Early tube feeding does not improve outcomes in acute pancreatitis

Clinical question: Does early nasoenteric feeding decrease the rate of infections or death in patients hospitalized with severe acute pancreatitis?
Study design: Randomized controlled trial (nonblinded) **Setting:** Inpatient (ward only)
Synopsis: Previous observational studies suggest that early nasoenteric feeding in patients with acute pancreatitis may reduce the rate of major infections by stimulating intestinal motility, reducing bacterial overgrowth, and increasing splanchnic blood flow. Using concealed allocation, these authors randomized patients presenting to the emergency department with severe acute pancreatitis to receive either early nasoenteric tube feeding initiated within 24 hours (n = 102) or oral feeding started at 72 hours (n = 106). If the oral diet was not tolerated, tube feeding was initiated after 96 hours. The 2 groups were similar at baseline: the mean age was 65 years and 60% of the patients had evidence of systemic inflammatory response syndrome (SIRS). Analysis was by intention to treat. One third of patients in the oral group eventually required tube feeding. For the primary composite end point of death or major infection (infected pancreatic necrosis, bacteremia, or pneumonia), there was no significant difference detected between the 2 groups. When the outcomes of major infection and death were examined separately, the 2 groups again had comparable results. Finally, patients in both groups had similar rates of admission to the intensive care unit and similar need for mechanical ventilation. Given fewer-than-expected events in the control group, it is possible that the study was too small to detect a difference in the primary outcome, if such a difference exists.
Bottom line: In patients with severe acute pancreatitis, early nasoenteric feeding initiated within 24 hours of presentation, as compared with oral feeding after 72 hours, does not improve mortality or reduce the rate of major infections.
Bakker OJ, van Brunschot S, van Santvoort HC, et al, for the Dutch Pancreatitis Study Group. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med 2014;371(21):1983-1993.

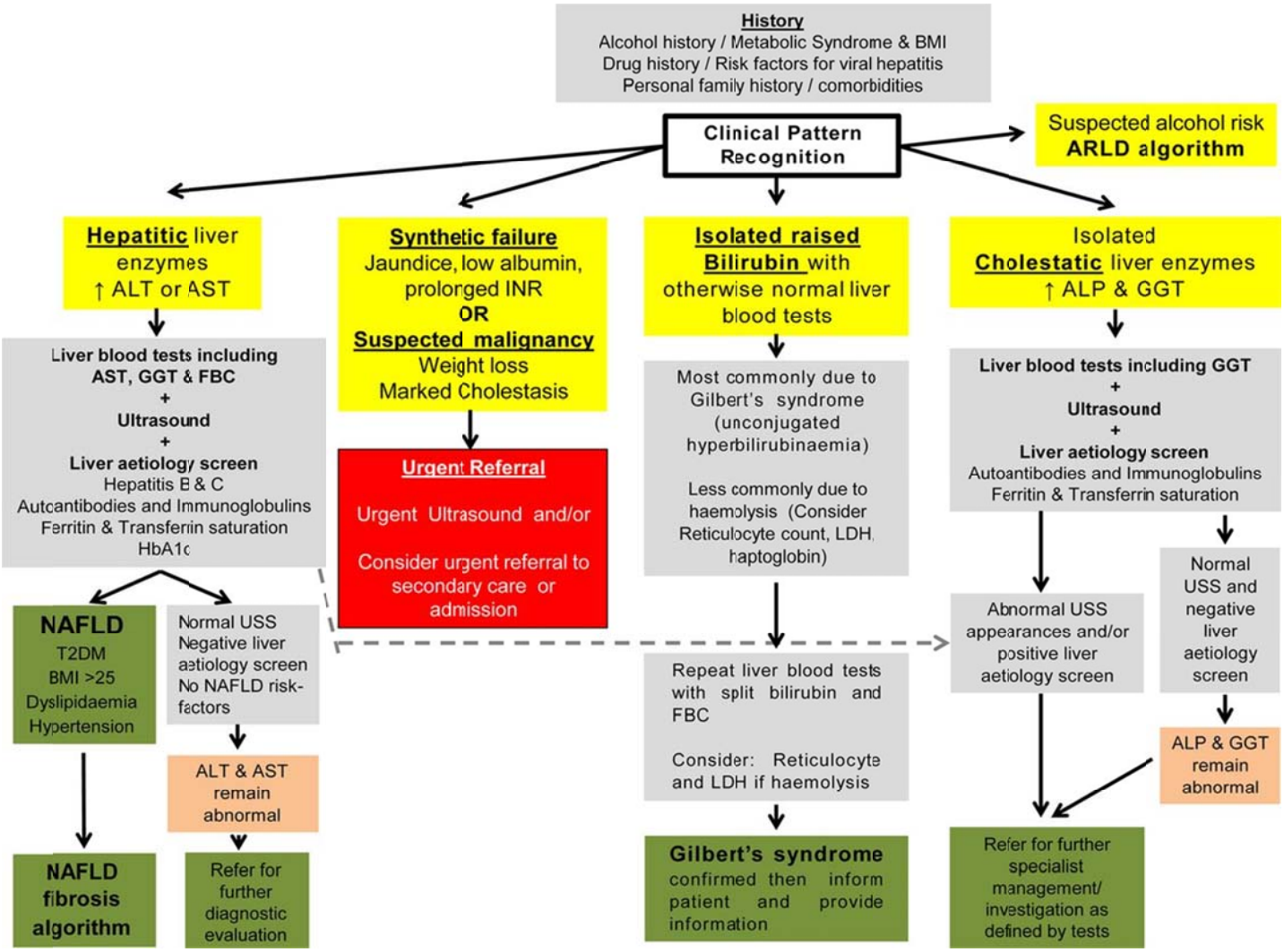
Where do they come up with these acronyms? This study found that early surgery for gallstone pancreatitis is better than late surgery (i.e. letting the pancreatitis “cool off”):

13. POEM: Patients with mild pancreatitis from gallstones do better with early surgery (PONCHO)

Clinical question: Do patients who suffer from mild pancreatitis due to gallstones have fewer complications when they undergo early surgery rather than delayed surgery?
Study design: Randomized controlled trial (nonblinded) **Setting:** Inpatient (any location) with outpatient follow-up
Synopsis: The PONCHO (Pancreatitis of biliary origin: Optimal timiNg of CHOlecystectomy—a particularly tortured acronym) study investigators recruited patients with mild gallstone-associated pancreatitis to undergo surgery on the index admission (n = 129) or to delayed surgery (n = 137). They defined mild pancreatitis based on the absence of organ failure 48 hours after admission and the absence of local complications such as necrosis or peripancreatic fluid collections on computed tomography. The study team did not randomize patients until they were stable and their hospital discharge was anticipated within 2 days. It took approximately 2.5 years and 23 centers to complete this small study. Only one patient in each group was not included in the final analysis. Prior to randomization, approximately one quarter of the patients undergoing surgery on the same day as the index admission had undergone endoscopic sphincterotomy compared with one third of the control patients. Six (5%) of the patients undergoing early surgery experienced a gallstone-related complication or died compared with 23 (17%) of those undergoing delayed surgery (number needed to treat [NNT] = 9; 95% CI 6 - 22). Additionally, 3 (2%) of the same-day surgery patients experienced recurrent pancreatitis compared with 12 (9%) of the delayed surgery group (NNT = 16; 8 - 128).
Bottom line: In this study, patients with mild gallstone-associated pancreatitis who had cholecystectomy on the index admission day had fewer complications than those who delayed the surgery.
da Costa DW, Bouwense SA, Schepers NJ, et al, for the Dutch Pancreatitis Study Group. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet 2015;386(10000):1261-1268.

Miscellaneous

Recommendations from a guideline on the management of abnormal LFTs (Gut 2018;67:6–19) from the British Society of Gastroenterology are summarized in this algorithm:



Common causes are alcohol use, and non-alcoholic fatty liver disease (NAFLD). The NAFLD Fibrosis Score is recommended for evaluating risk of liver fibrosis in patients with NAFLD. Equation below, free calculator at www.nafldscore.com.

NAFLD fibrosis score = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes=1, no=0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/L) – 0.66 × albumin (g/dL)

Take Home Points

1. Antibiotics are an option for treatment of appendicitis
2. New drugs for irritable bowel have minimal benefit, and high cost.
3. Remember microscopic colitis in the differential for patients with mild, chronic diarrhea.
4. Early feeding is may be helpful with mild to moderate, but not severe pancreatitis.
5. Guidelines can help assist in evaluation of the patient with abnormal LFT.

Exercise and Rehab Gary Ferenchick MD

Understand

1. Emerging evidence on the harmful effects of sedentary time
2. The prevalence of cardiac arrests during triathlons
3. The variable effects of wearable technology
4. The effects of exercise on fall risk in the elderly
5. The effects of physical activity interventions during pregnancy
6. The effect of exercise and rehab on several common medical conditions
7. Ethical considerations of genetic testing for athletic pre-participation cardiac screening

Sedentary Time

#1: Physical activity & sedentary time are independently associated with all-cause mortality,

BACKGROUND: Some research suggests that being sedentary increases the risk of premature mortality even in people who engage in physical activity.
METHODS: This retrospective study coordinated at the University of Mississippi examined the joint effects of objectively measured sedentary time and physical activity in 5575 adults aged 20-85 (mean 46; 52% female) included in the 2003-2006 National Health and Nutrition Examination Survey. Participants were monitored for seven days with an accelerometer to determine sedentary time (activity count of 0-99/minute, with a threshold of above or below a median of 487 minutes/day) and moderate to vigorous physical activity (activity count 2020/minute or higher, with a cut-off of a median of 14 minutes/day). The study outcome was all-cause mortality.
RESULTS: During a median follow-up of 81 months, 511 participants died. Age-adjusted mortality rates were 5.3% overall, 2.4% for participants above the median activity level versus 6.9% for those below the median activity level, and 6.3% for those above the median sedentary level versus 3.8% for those below the median sedentary level. Each increase of one minute/day of physical activity reduced mortality risk (adjusted hazard ratio [HR], 0.98; 95% CI, 0.96-0.99; p=0.04), while each one minute/day increase in sedentary time increased mortality risk (HR 1.001; 95% CI, 1.0003-1.002; p=0.008). Sedentary time raised the mortality risk only in participants who exhibited physical activity below the median level (p<0.001), and not in those who exceeded the median activity level (p=0.32).
CONCLUSIONS: Physical activity and sedentary time appear to be independently associated with all-cause mortality, but being sedentary did not negate the benefits of regular exercise. 23 references
REFERENCE: Loprinzi, P.D., et al. JOINT EFFECTS OF OBJECTIVELY-MEASURED SEDENTARY TIME AND PHYSICAL ACTIVITY ON ALL-CAUSE MORTALITY. Prev Med 90:47, September 2016

#2: Prolonged uninterrupted bouts of sedentary time associated with all-cause mortality,

Background: Excessive sedentary time is ubiquitous in Western societies. Previous studies have relied on self-reporting to evaluate the total volume of sedentary time as a prognostic risk factor for mortality and have not examined whether the manner in which sedentary time is accrued (in short or long bouts) carries prognostic relevance.
Objective: To examine the association between objectively measured sedentary behavior (its total volume and accrual in prolonged, uninterrupted bouts) and all-cause mortality.
Design: Prospective cohort study.
Setting: Contiguous United States.
Participants: 7985 black and white adults aged 45 years or older.
Measurements: Sedentary time was measured using a hip-mounted accelerometer.Prolonged, uninterrupted sedentariness was expressed as mean sedentary bout length. Hazard ratios (HRs) were calculated comparing quartiles 2 through 4 to quartile 1 for each exposure (quartile cut points: 689.7, 746.5, and 799.4 min/d for total sedentary time; 7.7, 9.6, and 12.4 min/bout for sedentary bout duration) in models that included moderate to vigorous physical activity.
Results: Over a median follow-up of 4.0 years, 340 participants died. In multivariable-adjusted models, greater total sedentary time (HR, 1.22 [95% CI, 0.74 to 2.02]; HR, 1.61 [CI, 0.99 to 2.63]; and HR, 2.63 [CI, 1.60 to 4.30]; P for trend < 0.001) and longer sedentary bout duration (HR, 1.03 [CI, 0.67 to 1.60]; HR, 1.22 [CI, 0.80 to 1.85]; and HR, 1.96 [CI, 1.31 to 2.93]; P for trend < 0.001) were both associated with a higher risk for all-cause mortality. Evaluation of their joint association showed that participants classified as high for both sedentary characteristics (high sedentary time [≥12.5 h/d] and high bout duration [≥10 min/bout]) had the greatest risk for death.
Limitation: Participants may not be representative of the general U.S. population.
Conclusion: Both the total volume of sedentary time and its accrual in prolonged, uninterrupted bouts are associated with all-cause mortality, suggesting that physical activity guidelines should target reducing and interrupting sedentary time to reduce risk for death.
REFERENCE: Diaz KM(1),et al. Patterns of Sedentary Behavior and Mortality in U.S. Middle-Aged and Older Adults: A National Cohort Study. Ann Intern Med. 2017 Oct 3;167(7):465-475.

Cardiac Arrests During Triathlons

#3: Deaths and cardiac arrests during triathlons

Background: Reports of race-related triathlon fatalities have raised questions regarding athlete safety.
Objective: To describe death and cardiac arrest among triathlon participants.
Design: Case series.
Setting: United States.
Participants: Participants in U.S. triathlon races from 1985 to 2016.
Measurements: Data on deaths and cardiac arrests were assembled from such sources as the U.S. National Registry of Sudden Death in Athletes (which uses news media, Internet searches, LexisNexis archival databases, and news clipping services) and USA Triathlon (USAT) records. Incidence of death or cardiac arrest in USAT-sanctioned races from 2006 to 2016 was calculated.
Results: A total of 135 sudden deaths, resuscitated cardiac arrests, and trauma-related deaths were compiled; mean (±SE) age of victims was 46.7 ± 12.4 years, and 85% were male. Most sudden deaths and cardiac arrests occurred in the swim segment (n = 90); the others occurred during bicycling (n = 7), running (n = 15), and postrace recovery (n = 8). Fifteen trauma-related deaths occurred during the bike segment. Incidence of death or cardiac arrest among USAT participants (n = 4 776 443) was 1.74 per 100 000 (2.40 in men and 0.74 in women per 100 000; P < 0.001). In men, risk increased substantially with age and was much greater for those aged 60 years and older (18.6 per 100 000 participants). Death or cardiac arrest risk was similar for short, intermediate, and long races (1.61 vs. 1.41 vs. 1.92 per 100 000 participants). At autopsy, 27 of 61 decedents (44%) had clinically relevant cardiovascular abnormalities, most frequently atherosclerotic coronary disease or cardiomyopathy.
Limitations: Case identification may be incomplete and may underestimate events, particularly in the early study period. In addition, prerace medical history is unknown in most cases.
Conclusion: Deaths and cardiac arrests during the triathlon are not rare; most have occurred in middle-aged and older men. Most sudden deaths in triathletes happened during the swim segment, and clinically silent cardiovascular disease was present in an unexpected proportion of decedents.
Primary Funding Source: Minneapolis Heart Institute Foundation.
Reference: Harris KM et al. Death and Cardiac Arrest in U.S. Triathlon Participants, 1985 to 2016: A Case Series. Ann Intern Med. 2017 Oct 17;167(8):529-535. PMID: 28975231 [Indexed for MEDLINE]

Male, first-time participants had the highest mortality risk, and most arrests occurred during the swimming portion of events.

#4: Cardiac arrests during triathlons

BACKGROUND: The incidence of sudden cardiac arrest during participation in sports activities remains unknown. Preparticipation screening programs aimed at preventing sudden cardiac arrest during sports activities are thought to be able to identify at-risk athletes; however, the efficacy of these programs remains controversial. We sought to identify all sudden cardiac arrests that occurred during participation in sports activities within a specific region of Canada and to determine their causes.
METHODS: In this retrospective study, we used the Rescu Epistry cardiac arrest database (which contains records of every cardiac arrest attended by paramedics in the network region) to identify all out-of-hospital cardiac arrests that occurred from 2009 through 2014 in persons 12 to 45 years of age during participation in a sport. Cases were adjudicated as sudden cardiac arrest (i.e., having a cardiac cause) or as an event resulting from a noncardiac cause, on the basis of records from multiple sources, including ambulance call reports, autopsy reports, in-hospital data, and records of direct interviews with patients or family members.
RESULTS: Over the course of 18.5 million person-years of observation, 74 sudden cardiac arrests occurred during participation in a sport; of these, 16 occurred during competitive sports and 58 occurred during noncompetitive sports. The incidence of sudden cardiac arrest during competitive sports was 0.76 cases per 100,000 athlete-years, with 43.8% of the athletes surviving until they were discharged from the hospital. Among the competitive athletes, two deaths were attributed to hypertrophic cardiomyopathy and none to arrhythmogenic right ventricular cardiomyopathy. Three cases of sudden cardiac arrest that occurred during participation in competitive sports were determined to have been potentially identifiable if the athletes had undergone preparticipation screening.
CONCLUSIONS: In our study involving persons who had out-of-hospital cardiac arrest, the incidence of sudden cardiac arrest during participation in competitive sports was 0.76 cases per 100,000 athlete-years. The occurrence of
sudden cardiac arrest due to structural heart disease was uncommon during participation in competitive sports. (Funded by the National Heart, Lung, and Blood Institute and others.)
Reference: Landry CH et al. Sudden Cardiac Arrest during Participation in Competitive Sports. N Engl J Med. 2017 Nov 16;377(20):1943-1953.

Wearable Technology

#5: Adults show a small increase (10%) in steps when given pedometers

Clinical question: Is the use of a pedometer an effective way to increase activity in adults?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: These investigators recruited 1023 individuals from primary care practices who were at least 45 years of age (30% were aged 65 to 75 years). Although the enrollment criteria specified that they did not perform moderate to vigorous physical activity for at least 30 minutes, 5 days a week, the participants were fairly active people: At baseline, the average participant recorded 7479 steps

and spent 94 minutes a week in moderate to vigorous activity. Approximately 63% were women, 80% were white, fewer than 10% were smokers, 65% were overweight or obese, and most described themselves as being in good health. The participants were randomized (concealed allocation unknown) to continue to receive usual care, to receive a pedometer by mail, or to receive a pedometer by mail and have nurse-led consultations 3 times over the first 9 weeks of the study. The 2 pedometer groups also received a physical activity diary and a 12-week walking program. After 1 year, both intervention groups recorded an additional 642 to 677 steps as compared with the control group (P < .001) and an additional 33 to 35 minutes spent in moderate to vigorous physical activity. Weight loss, depression scores, and anxiety scores were similar across all 3 groups, including adverse effects.
Bottom line: In a group of adults who were already fairly active, giving them a pedometer increased their steps per day by an average 650 steps. As with a previous study in younger people (Jakicic JM, et al. JAMA 2016;316:1161-71), the use of the pedometer did not promote weight loss.
Harris T, Kerry SM, Limb ES. Effect of a primary care walking intervention with and without nurse support on physical activity levels in 45- to 75-year-olds: the pedometer and consultation evaluation (PACE-UP) cluster randomised clinical trial. PLoS Med 2017;14(1):e1002210.

#6: Wearable technology combined with lifestyle intervention = LESS weight loss

Clinical question: Compared with standard behavioral weight-loss programs, does a technology-enhanced weight-loss intervention, including a wearable device, result in greater long-term weight loss in adults?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (any)
Synopsis: Many commercial technologies, including wearable devices, are available to provide feedback on physical activity and diet. However, there are limited data on the long-term effectiveness of these technologies. These investigators identified adults, aged 18 to 35 years, with a body mass index (BMI) of 25.0 to 39.9. Eligible participants (N = 470) randomly received assignment (concealed) to either a standard behavioral weight-loss intervention group or the technology-enhanced weight-loss group. Both groups received behavioral weight loss education on diet and exercise for 6 months, and at 6 months both groups also received weekly telephone counseling sessions, weekly text message prompts, and access to study materials on a website. After 6 months, participants in the standard group initiated self-monitoring of diet and physical activity, while those in the technology-enhanced group began using a wearable device along with a web-based interface (FITCore; Body Media) to monitor physical activity and diet. Individuals who assessed outcomes remained masked to treatment group assignment. Complete follow-up occurred for 74.5% of participants at 24 months. Intention-to-treat analysis showed that participants in the enhanced-intervention group lost significantly less weight at 24 months that those in the standard-intervention group (mean loss = 3.5 kg; 95% CI 2.6 - 4.5 vs mean loss = 5.9 kg; 5.0 - 6.8; mean difference = 2.4 kg; 1.0 - 3.7). The percent weight loss was also significantly less in the enhanced-intervention group than in the standard-intervention group (3.6% vs 6.4% at 24 months). No significant group differences occurred for fat mass, lean mass, percent body fat, bone mineral density, or cardiorespiratory fitness.
Bottom line: This study found that a weight-loss program for adults, aged 18 to 35 years, that included technology-enhanced weight-loss interventions (a wearable device and a web-based interface) resulted in LESS weight loss than standard weight-loss education focusing on dietary changes and increased physical activity. Here's how I think it went down: Should I eat that yummy piece of chocolate cake? Those in the standard group said "Nope" (because they figured they shouldn't). Those in the technology-enhanced group, however, said, "Let me look at my device. I've walked a lot today, so I'm eating the cake!"
Jakicic JM, Davis KK, Rogers RJ, et al. Effect of wearable technology combined with a lifestyle intervention on long-term weight loss. The IDEA randomized clinical trial. JAMA 2016;316(11):1161-1171.

Exercise / Rehab for medical conditions

#7: In stable CHD, more exercise associated with lower mortality

BACKGROUND: Recommendations for physical activity in patients with stable coronary heart disease (CHD) are based on modest evidence.
OBJECTIVES: The authors analyzed the association between self-reported exercise and mortality in patients with stable CHD.
METHODS: A total of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) study completed questions at baseline on hours spent each week taking mild, moderate, and vigorous exercise. Associations between the volume of habitual exercise in metabolic equivalents of task hours/week and adverse outcomes during a median follow-up of 3.7 years were evaluated.
RESULTS: A graded decrease in mortality occurred with increased habitual exercise that was steeper at lower compared with higher exercise levels. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for covariates, HR: 0.90; 95% CI: 0.87 to 0.93). These associations were similar for cardiovascular mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96), but myocardial infarction and stroke were not associated with exercise volume after adjusting for covariates. The association between decrease in mortality and greater physical activity was stronger in the subgroup of patients at higher risk estimated by the ABC-CHD (Age, Biomarkers, Clinical-Coronary Heart Disease) risk score (p for interaction = 0.0007).
CONCLUSIONS: In patients with stable CHD, more physical activity was associated with lower mortality. The largest benefits occurred between sedentary patient groups and between those with the highest mortality risk.
REFERENCE: Stewart RAH et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. J Am Coll Cardiol. 2017 Oct 3;70(14):1689-1700.

#8: Exercise reduces the risk of injurious falls in older adults

Clinical question: Are there specific interventions that are effective in reducing the risk of injurious falls in older adults?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, the Cochrane Register, Ageline, and reference lists of relevant trials and reviews for randomized controlled trials that examined fall-prevention interventions for adults 65 years or older. Study authors were also contacted for unpublished studies or additional data. Two investigators independently reviewed all potential studies for inclusion criteria and methodologic quality using standard risk-of-bias scoring tools. Conflicts were resolved by consensus agreement with a third reviewer. The primary outcome of interest was the number of injurious falls and fall-related hospitalizations. A total of 283 randomized trials and 20 companion reports (N = 159,910 participants) met inclusion criteria. The overall risk of bias among the studies was moderate, with an unclear risk of bias for allocation concealment, contamination, and selective outcome reporting. A funnel plot analysis found no evidence of publication bias. Four interventions were significantly associated with a reduced risk of injurious falls compared with usual care: exercise alone; combined exercise and vision assessment and treatment; combined exercise, vision assessment and treatment, and environmental assessment and modification; and combined clinic-level quality improvement strategies, multifactorial assessment and treatment, calcium supplementation and vitamin D supplementation. Combined exercise and vision assessment and treatment was the most effective intervention. In a subgroup analysis, the best intervention for reducing the risk of hip fracture was combined osteoporosis treatment, calcium supplementation, and vitamin D supplementation.
Bottom line: Exercise alone; exercise combined with vision assessment/treatment; exercise combined with vision assessment/treatment and environmental assessment/modification; and clinic-level quality improvement strategies combined with multifactorial assessment/treatment and calcium and vitamin D supplementation are all effective interventions for reducing the risk of injurious falls in older adults.
Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults. A systematic review and meta-analysis. JAMA 2017; 318(17):1687-1699.

#9: Tai chi decreases the risk of falls in at-risk adults and elderly

Clinical question: Does tai chi decrease the risk of falls in at-risk adults and the elderly?
Study design: Meta-analysis (randomized controlled trials)
Setting: Outpatient (any)
Synopsis: These authors systematically searched several databases and the reference lists of retrieved articles to identify randomized trials of tai chi that reported fall rates. The authors tried to statistically assess for publication bias, but they do not describe a formal search for unpublished negative studies that could reduce the pooled benefit. Ultimately they included 10 studies with 2645 participants. The study participants were generally older and had previous falls, though some studies included "pre-frail" elders or those at an increased risk of falls. Five studies reported that tai chi decreased the short-term risk of falls (relative risk [RR] = 0.57; 95% CI 0.46 - 0.70) and 6 studies reported a decrease in the long-term risk of falls (RR = 0.87; 0.77 - 0.99). Only one study, rated at high risk of bias, assessed falls that caused actual injury. Sadly, the authors don't report enough data to estimate the numbers needed to treat nor the rate of harms associated with tai chi. The authors report no significant heterogeneity in the data.
Bottom line: In this systematic review, tai chi was associated with a decreased risk of falls. However, only one low-quality study assessed injurious falls.
Lomas-Vega R, Obrero-Gaitan E, Molina-Ortega FJ, Del-Pino-Casado R. Tai chi for risk of falls. A meta-analysis. J Am Geriatr Soc 2017;65(9):2037-2043.

#10: Exercise = knee surgery for degenerative meniscal tear

Clinical question: Is arthroscopic surgery better than exercise therapy to treat symptoms associated with degenerative meniscal tears in middle-aged patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: The researchers (orthopedists practicing in Norway) enrolled 140 patients (between the ages of 35 and 60 years) who were referred for care for unilateral knee pain with medial degenerative meniscal tear confirmed by magnetic resonance imaging. Most (96%) had no or minimal radiographic changes associated with osteoarthritis. Pain had to be present for at least 2 months without a history of major knee trauma. The patients were randomized, using concealed allocation, to receive either exercise therapy 2 or 3 times weekly for 3 months or arthroscopic meniscectomy. There were no sham treatments; patients assigned to exercise did not get arthroscopy without meniscal repair and patients undergoing surgery did not have additional sham or actual exercise. Patients reported on pain, function, knee-related quality of life, and other symptoms using the knee injury and osteoarthritis outcome score. Using intention-to-treat analysis at 2 years, there was no difference between the 2 groups. Approximately 1 in 5 (19%) patients who received exercise therapy eventually underwent arthroscopic surgery without any additional benefit.
Bottom line: Despite a significant initial bump in benefit due to the placebo effect, arthroscopic meniscectomy in patients without a history of acute trauma and without a history of knee locking does not reduce pain and improve function after 2 years as compared with 3 months of exercise therapy. This study did not evaluate surgery with exercise versus exercise alone, but other studies have done so and found no additional benefit.
Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ 2016 July 20;354:i3740.

#11: Exercise = knee surgery for degenerative meniscal tear

Early PT for acute low back pain is cost-effective, but gain in quality of life is likely too small to notice
Clinical Question: Is physical therapy cost-effective in the initial management of patients with acute low back pain?
Bottom Line: At $30,000 per quality-adjusted life year (QALY) gained, early physical therapy (PT) for acute low back pain in primary care is cost-effective by the usual criteria of $50,000 to $100,000 per QALY. However, the magnitude of improvement in quality of life is small and is probably not clinically meaningful. PT is an option to consider if it is not too difficult to find nor too expensive for your patients. (LOE = 3b)
Reference: Fritz JM, Kim M, Magel JS, Asche CV. Cost-effectiveness of primary care management with or without early physical therapy for acute low back pain: economic evaluation of a randomized clinical trial. Spine 2017;42(5):285-290.
Study Design: Cost-effectiveness analysis
Funding: Government
Setting: Outpatient (any)
Allocation: Unknown
Synopsis: A previous randomized trial compared early PT with delayed referral in primary care patients with acute low back pain. They found better short-term outcomes with early PT, and although the results were statistically significant, the effect sizes did not meet the prespecified criteria for a minimally clinically important difference. There were also no differences at 1 year. Of note, the PT consisted of only 4 sessions over 4 weeks, and the smoking rates were lower than in the general population. In this study, the authors used those results to determine if early PT was cost-effective when considering broader outcomes, such as lost productivity and impact on quality of life. They performed a basic cost-effectiveness analysis, although it is limited by only performing a sensitivity analysis for those patients with complete diary data. The model appears to be fairly simplistic, and was not performed using standard modeling software, such as TreeAge. They found that although early PT results in higher total costs in their adjusted analysis ($1442 vs $862 over 1 year), it was also associated with a small increase in QALYs (0.02) and quality of life scores. They calculated an incremental cost-effectiveness ratio of $29,000 per additional QALY, and found a similar $32,058 per QALY using a bootstrapping analysis.

#12: Physical therapy doesn't add anything to standard treatment of ankle pain

Clinical question: In patients with mild to moderate ankle sprain, does physical therapy (physiotherapy) hasten or improve recovery?
Study design: Randomized controlled trial (nonblinded)
Setting: Emergency department
Synopsis: These authors studied the effect of longitudinal, supervised, stepwise physical therapy in addition to usual acute management of mild to moderate ankle sprain (grade 1 or 2) in 503 patients, 16 years or older, who presented to an emergency department in Canada. It's interesting that 84% of patients received an x-ray although approximately 30% of patients had mild (grade 1) sprain and any patients who required immobilization were excluded. One week after evaluation and basic management with RICES (rest, ice, compression, elevation, splinting), patients were randomized, using concealed allocation, to continue with usual care or to add stepwise physical therapy of up to seven 30-minute visits combined with home exercise. The main outcome was a score of "excellent" (at least 450) at 3 months on a 500-point patient questionnaire of symptoms, stiffness, pain, function, recreational activity, and quality of life. At 3 months approximately 40% of patients scored at least 450, with no difference between groups (42% vs 40%). After 6 months, the percentage of patients experiencing excellent recovery was slightly higher in the usual care group than in the intervention group, but the difference was not statistically significant between groups (65% vs 56%; P = .09). In addition to patient reports of symptoms and function, the researchers also conducted clinical and biomechanical evaluation, again not finding any difference between the groups. The study had the power of at least 80% to find an increase in excellent recovery from 60% to 75%, if one existed.
Bottom line: Physical therapy (up to 7 sessions) does not hasten resolution of symptoms or improve function in adults with ankle sprain: Approximately 60% of patients who receive usual care or physical therapy do not achieve "excellent" resolution. Send patients home with the usual RICES protocol: rest, ice, compression, elevation, and splinting.
Reference: *Brison RJ, Day AG, Pelland L, et al. Effect of early supervised physiotherapy on recovery from acute ankle sprain: randomised controlled trial. BMJ 2016;355:i5650.*

Genetic Testing

#13: The role of genetic testing in athletic pre-participation cardiac screening

These authors from Belgium and the UK present a commentary on the ethics of genetic testing before sports participation. They introduce a hypothetical asymptomatic professional soccer player in his or her 20s (i.e., not a minor) who has an abnormal cardiac screen or a family history of sudden cardiac death. Genetic testing is problematic because genotype may not adequately predict disease phenotype (i.e., onset or severity), and some people will be genotype-positive but phenotype-negative. False-positive and false-negative rates of testing can, therefore, be high. Level of risk varies with the specific mutation and the type of sport involved. Family history (and physician liability) will lead to a low threshold for testing given that the first disease manifestation could be a fatal cardiac arrest. American and European guidelines differ on criteria for disqualification from sports participation, with the US requiring a threshold level of phenotypic expression and Europe requiring only a genetic mutation. Disqualification of an athlete from play is equivalent to loss of employment, and genetic testing is against the law for prospective employees in other venues, yet athletes may feel compelled to undergo further diagnostic testing. Diagnosis of a genetic condition has ramifications for psychological well-being, life and disability insurance, and livelihood. The ethics demand patient autonomy before cardiac screening and genetic testing, involvement of a genetics counselor, clear informed consent (including the right not to know the results), and confidentiality. Genetic testing should be performed by an independent team not associated with the cardiac screening so that the results are not used in sports eligibility decisions.

REFERENCE: Magavern, E.F., et al, ETHICAL CONSIDERATIONS FOR GENETIC TESTING IN THE CONTEXT OF MANDATED CARDIAC SCREENING BEFORE ATHLETIC PARTICIPATION Genet Med 19(5):493, May 2017

Bottom Lines

- Physical activity and sedentary time appear to be independently associated with all-cause mortality
- Deaths and cardiac arrests during the triathlon are ~ 1/100,000 participants
- Wearable technology has variable effects on outcomes
- Exercise is associated with better outcomes in patients with ischemic heart disease, fall risk in the elderly, degenerative meniscal tears and ankle sprain
- Ethical considerations exist for athletic pre-participation cardiac screening

Appendix

Exercise in Pregnancy

#14: Regular, moderately intense exercise during pregnancy is beneficial

Clinical question: Does a supervised exercise program during pregnancy reduce the risks of pregnancy complications?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: In this randomized controlled trial healthy pregnant women (N = 840) either participated in a supervised exercise program or received standard care. Women were included if they had an uncomplicated singleton pregnancy, no prior preterm birth, and no contraindications to exercise. The exercise intervention included three 50- to 55-minute sessions weekly from 9 to 11 weeks' gestation to 38 to 39 weeks' gestation (approximately 85 total sessions) conducted by a fitness professional at the hospital where the women received care. Each session included aerobic, resistance, and stretching exercises and consisted of a warm-up and cool-down of 10 minutes each and vigorous exercise for 25 to 30 minutes. Women in the control group were encouraged to exercise and would have been excluded if they reported regular exercise for more than 20 minutes daily (which no one did). Loss to follow-up was similar between groups. Preterm birth was similar between groups and those women were excluded from analysis. Compliance was high, which may not be true of other populations. Women in the exercise group were less likely to develop hypertension (2.1% vs 5.7%; P = .009; number needed to treat [NNT] = 27, 95% CI 15-113) or to develop gestational diabetes (2.4% vs 5.5%; P = .03; NNT = 32, 16-290). Although mean weight gain was similar between groups, women in the exercise group were less likely to gain excessive weight (26% vs 34%; P = .03; NNT = 13, 7-80). Mean infant birth weight was not significantly different between groups, but the incidence of macrosomia (> 4000 g) was lower in the intervention group (1.8% vs 4.7%; P = .03; NNT = 35, 18-320). There were no differences in other secondary outcomes including gestational age at delivery, low birth weight, type of delivery, Apgar scores, or umbilical artery pH of the newborn at birth.
Bottom line: Healthy Spanish women who participated in a supervised exercise program from late first trimester until term were less likely to develop hypertension or gestational diabetes, to gain excess weight, or to give birth to a macrosomic infant. Similar interventions should be tested in other populations to determine whether these results are generalizable.
Reference: *Barakat R, Pelaez M, Cordero Y, et al. Exercise during pregnancy protects against hypertension and macrosomia: randomized clinical trial. Am J Obstet Gynecol 2016;214(5):649.e1-8.*

#15: Physical activity interventions in pregnancy decrease weight gain & risk of GDM

Clinical question: Do interventions to increase physical activity during pregnancy reduce the risks of excessive weight gain and gestational diabetes?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: For this meta-analysis of programs of physical activity during pregnancy the authors selected 13 unmasked randomized controlled trials (N = 2873 women). Studies were included if the participants were healthy women with singleton pregnancies whose physical activity level was fewer than 20 minutes 3 times weekly, the control group did not receive an exercise program, and the considered outcomes included GDM and maternal weight gain. The exercise interventions varied markedly in number, duration, and content. In all but 1 study the programs were supervised; the program was home-based in the remaining study. The methodology for the meta-analysis was thoroughly described and well-executed. Of the included studies 11 had adherence rates of greater than 85%. Drop-outs were also low overall, with 12 studies reporting rates of less than 20%. Only 2 studies were conducted in the United States. Only 4 studies provided intention-to-treat analysis. The calculated relative risk (RR) for GDM among the intervention groups was 0.69 (95% CI 0.52-0.91; P = .009). The weighted mean difference for weight gain was -1.14 kg (95% CI -1.5 to -0.78 kg; P < .001). In planned subgroup analyses the authors found that there was a lower risk of GDM when the program was implemented throughout the pregnancy than when it began in second trimester (RR 0.64, 95% CI 0.36-0.98; P = .038), without a corresponding effect on weight gain. There was also a lower risk of GDM with combined exercise programs that included aerobic exercise and resistance or strength training (RR 0.69, 95% CI 0.48-0.99; P = .043).
Bottom line: Structured programs of moderate physical exercise decreased the risk of gestational diabetes mellitus (GDM) and decreased maternal weight gain among otherwise healthy sedentary women. Programs that were continuous throughout the pregnancy had more benefit that those started in the second trimester. Programs that combined aerobic exercise and resistance or strength

training were also more beneficial.
Sanabria-Martinez G, Garcia-Hermoso A, Poyatos-Leon R, Alvarez-Bueno C, Sanchez-Lopez M, Martinez-Vizcaino V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis. BJOG 2015;122(9):1167-1174.

#16: Cycling during pregnancy reduced the rate of GDM in overweight and obese women

Clinical question: Does a regular cycling exercise program in pregnancy reduce the risk of gestational diabetes mellitus in overweight and obese women?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: These investigators enrolled 300 overweight and obese women at 10 weeks' gestational age. The investigators used Chinese criteria to define overweight (BMI > 24 and < 28) and obesity (BMI at least 28). Eligible women were at least 18 years old, nonsmokers, with a singleton pregnancy. Women were excluded if they had cervical insufficiency or shortened cervix according to ultrasound (< 25 mm at < 24 weeks), were taking medication for any pre-existing chronic disease, or were currently being treated with metformin or corticosteroids. Allocation was concealed, but the study was otherwise unmasked. Women allocated to the exercise group attended supervised stationary cycling classes for 30 minutes at least 3 times per week, starting within 3 days of randomization and continuing until at least 36 weeks' gestation. All women, including the control patients, received general advice regarding the benefits of physical activity during pregnancy. Women in the exercise group were highly compliant, with 90% attending at least 80% of classes. Physical activity was estimated using the International Physical Activity Questionnaire at 25 weeks' gestation. The results in the cycling versus control groups were 1741 +/- 798 and 1327 +/- 1300 metabolic equivalent minutes per week, respectively. Among the 88% of participants who underwent screening for GDM, women in the cycling group had an incidence of 22% vs 41% among control patients (odds ratio 0.412; 95% CI 0.24 - 0.71; P < .001; number needed to treat = 5; 3 - 13). Gestational weight gain was significantly less among women in the cycling group (8.38 kg +/- 3.65 vs 10.47 +/- 3.33; P < .001). There were no differences in other maternal outcomes including hypertensive disorders, cesarean delivery, and gestational age at birth. There were no differences in incidence of macrosomia, large-for-gestational-age infants, or Apgar scores. Birthweight was lower in the cycling group by a mean of 100 g. There were also 3 small-for-gestational-age infants in the cycling group with none in the control group, but the sample size was too small for statistical analysis.
Bottom line: In this randomized controlled trial a supervised stationary cycling program started early in pregnancy reduced the incidence of gestational diabetes mellitus (GDM). Birthweight was also significantly lower in the cycling group by a mean of approximately 100 g, and the cycling group included 3 cases of infants who were small-for-gestational age. A larger study would be required to determine whether the level of physical activity used in this intervention increases the risk of growth restriction. The study was conducted in a compliant Chinese population using Chinese body mass index (BMI) criteria, which is lower than the US criteria.
Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese women. Am J Obstet Gynecol 2017;216(4):340-351.

Essentials Update on Women's Health

Emily Hall, MD
Written by William Wadland, MD

The following presentation is intended to be an update and not a comprehensive review. It is based on a selective search of the current Essentials data base, Cochrane reviews, and Pub Med. The update focuses on common conditions: osteoporosis, menopause, dysmenorrhea, sexual dysfunction, fibroids, vaginal atrophy, and contraception. Cancer screening and care is not included.

Objectives: after this presentation, participants should be able to:

1. Describe treatment recommendations for osteoporosis and menopausal symptoms
2. Describe interventions for common conditions: dysmenorrhea, sexual dysfunction, fibroids, and vaginal atrophy
3. Describe current studies on contraception

Osteoporosis

1. ACP clinical guidelines for osteoporosis treatment

Clinical question: Based on recent research, what changes to osteoporosis management are recommended by the American College of Physicians?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This 2017 ACP guideline on the treatment of osteoporosis to prevent fractures in men and women is an update from the prior guideline in 2008, with endorsement from the American Academy of Family Physicians. The guideline is based on a systematic review of the literature and the focus of the recommendations is on improving patient-oriented outcomes (fractures, especially of the hip). The evidence is graded and the recommendations are labeled as either strong or weak. Neither the chair nor the majority of the development committee had conflicts of interest, and the committee included a methodologist. New or modified recommendations: • Treat women with osteoporosis with a bisphosphonate (alendronate, risendronate, or zolendronic acid) or a monoclonal antibody (denosumab). (strong recommendation, high-quality evidence) • Treat for only 5 years -- benefit beyond this duration has not been demonstrated. (weak recommendation, low-quality evidence) • Do not monitor bone mineral density while treating. (weak recommendation; low-quality evidence) • Treat men with osteoporosis with a bisphosphonate to decrease the risk of vertebral fracture. (weak recommendation, low-quality evidence) • The effect of calcium with vitamin D supplementation to prevent fracture is uncertain. • Citing greater risk than benefit, the group recommends against use of estrogens or raloxifene (Evista). (strong recommendation, moderate-quality evidence) • The group suggests discussing possible treatment with women 65 years or older who are osteopenic and at high risk for fracture.
Bottom line: The American College of Physicians (ACP) recommends treating women with osteoporosis with alendronate (Fosamax), risendronate (Actonel), zoledronic acid (Zometa), or denosumab (Prolia, Xgeva) for up to 5 years only, which makes sense since we don't have longer studies yet and because the bisphosphonates are sequestered in bone and slowly re-released. The guideline also suggests not monitoring bone density after the start of treatment. Menopausal estrogen therapy and selective estrogen receptor modulators (raloxifene) are no longer recommended. For men with osteoporosis, the ACP recommends bisphosphonate treatment, though this is a weak recommendation limited by low-quality evidence.
Qaseem A, Forciea MA, McLean RM, Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166(11):818-839.

2. Vitamin D supplementation: good for bones and fall prevention, but little else

Clinical question: Is supplementation with vitamin D effective?
Study design: Systematic review
Setting: Uncertain
Synopsis: These authors searched the Cochrane Database of Systematic Reviews and PubMed to identify randomized controlled trials and systematic reviews/meta-analyses of studies that evaluated vitamin D for 10 common uses. Two researchers performed the searches and reviewed the research. The studies were compiled without formal explanation of how the authors included or excluded studies and they did not perform a quality analysis, analyze for publication bias, or try to combine the results via meta-analysis. In other words, this is a "trust us" type of review, which is okay in this case since the evidence that supports many common uses is sparse and not suitable for formal analysis. Vitamin D supplementation in older people (without regard to their vitamin D levels or risk of osteoporosis) may slightly reduce falls and the number of people who experience a fall. It also reduces hip fractures and other fractures by 10% to 15% in patients with osteoporosis, when given with calcium, though extremely high doses increase the risk. Vitamin D supplementation does not, however, affect the following: (1) respiratory tract infections in Western populations; (2) mental well-being scores in the general population without clear depression, even when vitamin D levels are low (data in patients with depression are conflicting and of poor quality); (3) rheumatoid arthritis, neither as prevention nor treatment; (4) multiple sclerosis symptoms; (5) overall mortality; or (6) the likelihood of any cancer.

Bottom line: Vitamin D supplementation may reduce falls in older people and, given with calcium, will reduce the risk of hip fracture in women. It does not reduce respiratory tract infection risk, improve mental well-being, affect rheumatoid arthritis or multiple sclerosis, or prevent cancer. Vitamin D levels do not need to be checked in most patients.
Allan GM, Cranston L, Lindblad A, et al. Vitamin D: A narrative review examining the evidence for ten beliefs. J Gen Intern Med 31(7):780-791.

3. Treating low vitamin D levels is ineffective in postmenopausal women

Clinical question: Does vitamin D supplementation in women with low levels of the vitamin affect bone mineral density, muscle mass, strength, or falls risk?
Study design: Randomized Controlled Trials
Setting: Outpatient (any)
Synopsis: These investigators, through community advertising, enrolled a total of 230 postmenopausal women, 90% of whom were white, with an average age of 61 years and baseline vitamin D levels of 14 ng/mL through 27 ng/mL (39 - 67 nmol/L). A "low" 25-hydroxyvitamin D level is typically less than 30 ng/mL (75 nmol/L). The women had low-normal hip T scores of bone mineral density (average -1 SD). Using typical tests of balance and lower extremity strength, the women were at low risk of falls. The women were randomized, using concealed allocation, to receive either placebo, daily vitamin D3 800 IU (20 mcg), or twice- monthly vitamin D3 50,000 IU (125 mcg). The twice-monthly, high-dose group had their vitamin D levels monitored and the dose was increased if levels did not increase to at least 30 ng/mL (75 nmol/L). After 1 year, neither vitamin D treatment regimen changed bone mineral density, muscle mass, functional status, or physical activity. The number of women reporting at least one fall—almost of half of the women—was not different among the groups. The study was only 1 year in length, which should be long enough to see changes in vitamin D levels and muscle mass though perhaps not long enough to see changes in fall rates (if there is a difference). The US Preventive Services Task Force concludes there is insufficient evidence to recommend for or against screening for vitamin deficiency; the National Institute of Health and Care Excellences recommends vitamin D supplementation in members of high-risk groups.
Bottom line: "But her vitamin D level is low! I have to treat it." No, you don't, if your patient is a typical community-dwelling postmenopausal women younger than 75 years. The usual dose of vitamin D, 800 IU (20 mcg) daily, will not increase levels even after a year of therapy and has little effect on calcium absorption or bone mineral density. A high dosage -- 50,000 IU (125 mcg) twice monthly -- will raise levels but is similarly ineffective in improving minimally low bone mineral density, muscle strength, functional status, physical activity, or risk of falls. Not checking vitamin D levels will make it easier not to (ineffectively) treat low levels.
Hansen KE, Johnson RE, Chambers KR, et al. Treatment of vitamin D insufficiency in postmenopausal women: A randomized clinical trial. JAMA Intern Med. 2015;175(10):1612-1621.

4. Long-term use of bisphosphonates increases the risk of fractures in older women

Clinical question: Does long-term use of bisphosphonates increase the risk of fractures in older women?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: The Women's Health Initiative had 2 components, a randomized trial that busted a bunch of myths about hormone replacement therapy and an observational study with nearly 100,000 women that serves as the basis for this study. These authors pulled a subset of women who had taken an oral bisphosphonate for at least 2 years, had follow-up data, and who had a FRAX score placing their 5-year fracture risk at 1.5% or higher. Additionally the authors excluded women who took medications that affect bone metabolism (eg, calcitonin, parathyroid hormone, aromatase, inhibitors, and so forth). Ultimately, they included 5120 women. They then compared the rate of clinical fractures in women who had taken oral bisphosphonates for only 2 years with those who had taken them for 3 to 5 years, 6 to 9 years, and 10 to 13 years. It would have been helpful if they had included a group of women with no bisphosphonate exposure. The women were, on average, 80 years old. The women had an average of 4 years of follow-up data and reported 127 hip fractures, 159 wrist or forearm fractures, 235 clinical vertebral fractures, and a total of 1313 clinical fractures (presumably hip plus wrist plus forearm plus clinical vertebral plus all other fractures). After taking into account other factors that might influence the rate of fractures, 10 to 13 years of bisphosphonate use was associated with a higher risk of any clinical fracture (but not at any single specific site) than 2 years of use (hazard ratio = 1.29; 95% CI 1.07 - 1.57). There was no significant association between intermediate-term use of bisphosphonates and fracture risk. When the authors only looked at women with a fracture after age 54, the relationship between long-term bisphosphonate use and subsequent fracture remained.
Bottom line: In this cohort study, older women at a high risk of fractures who used oral bisphosphonates for 10 to 13 years had a higher risk of fractures than women who used bisphosphonates for only 2 years.
Drieling RL, LaCroix AZ, Beresford SAA, et al. Long-term oral bisphosphonate therapy and fractures in older women: The Women's Health Initiative. J Am Geriatr Soc 2017;65(9):1924-1931.
Menopause:

5. Transdermal estrogen and progestogen most effective to reduce menopausal vasomotor symptoms

Clinical question: What treatments are most effective for the relief of vasomotor symptoms among naturally menopausal women?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: This meta-analysis of 47 randomized controlled trials (RCTs) was conducted on behalf of the United Kingdom National Institute of Health and Care Excellence for the purpose of clinical guideline development. The authors used a technique called network meta-analysis, which is suitable for decision-making when multiple treatments are being considered for one indication and the treatments have not been directly compared in the same trials. In this case, the question considered was the effectiveness of pharmacologic and nonpharmacologic treatment for VMS among naturally menopausal women (defined as amenorrhea for at least 12 consecutive months). Trials of nonpharmacological treatments had to be of at least 4 weeks duration and those to assess

pharmacologic treatment had to be of at least 12 weeks. The authors considered 26 weeks to be the maximum follow-up time. There were 32 RCTs of 12 treatment classes that assessed the frequency of VMS at the end of treatment, the principal end point considered. Combination treatment with transdermal estrogen and progestogen (E+P) had the highest probability (69%) of being the most effective treatment. The combination of oral E+P had a point estimate suggesting it was similarly effective to transdermal E+P, but with a wide confidence interval. There was strong evidence that transdermal E+P was more effective for relief of VMS than raloxifene, SSRIs, SNRIs, isoflavones, and Chinese herbal medicine. Isoflavones and black cohosh were found to be better than placebo at reducing VMS. There were 21 RCTs that assessed treatment discontinuation. Non-oral E+P had significantly lower odds of discontinuation due to short-term adverse effects than placebo, while SSRIs and SNRIs had higher odds of discontinuation than placebo. The authors intended to assess the effect of treatments on vaginal bleeding, but data from the 5 included trials that assessed that outcome were insufficient to draw conclusions. Long-term adverse effects, such as cardiovascular events and breast cancer, were not assessed.
Bottom line: Transdermal estrogen plus progestogen or oral estrogen plus progestogen are the treatments most likely to effectively reduce the frequency of vasomotor symptoms (VMS) among menopausal women. Isoflavones and black cohosh were found to be better than placebo. Other treatments, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), were not likely to be beneficial and were more likely to be discontinued than placebo.
Sarri G, Pedder H, Dias S, Guo Y, Lumsden MA. Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute for Health and Care Excellence guideline on menopause. BJOG 2017;124(10):1514-1523.

6. Plant-based therapies with soy isoflavones may be effective for menopausal symptoms

Clinical question: Are plant-based therapies, including phytoestrogens, useful in the management of menopausal symptoms?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: Because of the concerns with using hormone replacement therapy many women use complementary therapies to treat menopausal symptoms. These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, and the Cochrane CENTRAL registry for randomized trials that assessed the effects of plant-based therapy compared with placebo or no treatment in perimenopausal, menopausal, and postmenopausal women. Outcomes of interest included hot flashes, night sweats, and vaginal dryness. Two independent reviewers assessed individual studies for inclusion criteria and methodologic quality using standard risk-of-bias scoring tools. Disagreements were resolved by consensus discussion with a third independent reviewer. Overall, most of the studies showed a moderate to high risk of bias. A total of 62 studies (N = 6653) met the inclusion criteria, including 36 studies of phytoestrogens, 16 of black cohosh, and 10 of various medicinal herbs. Duration of interventions ranged from 4 weeks to 2 years. Overall, phytoestrogen use was associated with a significant reduction in the number of daily hot flashes (-1.31; 95% CI -2.01 to -0.61) and vaginal dryness (mean difference of change from baseline on a 4-point scale: -0.31; -0.52 to -0.10, with higher numbers indicating worse symptoms). There were no significant changes reported in night sweats with phytoestrogen use. In particular, soy isoflavone use alone or as a supplement replicated the findings of the combined analyses of phytoestrogens, whereas red clover did not significantly reduce hot flashes or vaginal dryness. Black cohosh use was also not significantly associated with changes in the number of daily hot flashes, vaginal dryness, or number of night sweats. Results were mixed regarding the use of evening primrose, flaxseed, St. John's wort, wheat germ, and Chinese medicinal herbs. A statistical analysis did show a significant amount of heterogeneity in the results between the different studies. Minimal, if any, evidence of publication bias existed for phytoestrogens.
Bottom line: This meta-analysis found some evidence that phytoestrogens, especially dietary and supplemental soy isoflavones, are significantly associated with improvement in daily hot flashes and vaginal dryness in women with menopausal symptoms. No evidence of a benefit was found for red clover or black cohosh. The overall quality of the evidence was poor, with a moderate to high risk of bias and significant hetereogeneity among the included studies.
Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms. A systematic review and meta-analysis. JAMA 2016;315(23):2554-263.

7. Duration of vasomotor symptoms can be quite long during menopause

Clinical question: How long can women expect the vasomotor symptoms associated with menopause to last?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: These investigators enrolled 1449 women identified at 7 sites across the United States. The women were between the ages of 42 and 52 years, reported a menstrual cycle in the 3 months before screening, and were not taking oral contraceptives or hormone therapy. The women were followed up for 13 years. The median duration of vasomotor symptoms was 7.4 years for all women. Women who were premenopausal or early perimenopausal when they first reported frequent vasomotor symptoms (occurring on at least 6 days over 2 weeks) had a median duration of more than 11.8 years, including a median 9.4 years following their final menstrual period. Some women continued to have symptoms at the end of the 13 years of study. Women who were postmenopausal at the onset of vasomotor symptoms experience these symptoms for a median 3.4 years. African-American women reported the longest total duration (median 10.1 years) and Japanese and Chinese women had the shortest total durations (median 4.8 - 5.4 years). For the 881 women for whom a final menstrual period could be determined, the median duration was 4.5 years following this final menstrual period. Perceived stress and depressive symptoms were associated with an increase in vasomotor symptom duration (hazard ratio 0.75 and 0.66, respectively).
Bottom line: Vasomotor symptoms last a median 7.4 years in women progressing through menopause. Women who begin to have frequent symptoms early (during premenopause or perimenopause) will experience symptoms for a median of 11.8 years, including 9.4 years after their final menstrual period. African-American women will experience vasomotor symptoms longer (median 10.1 years), but symptoms disappear more quickly in Japanese and Chinese women (median ~5 years).
Avis NE, Crawford SL, Greendale G, et al, for the Study of Women's Health Across the Nation (SWAN). Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175(4):531-539.

8. Long-term hormone therapy for perimenopausal and postmenopausal women

Background: Hormone therapy (HT) is widely provided for control of menopausal symptoms and has been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005.
Objectives: To assess effects of long-term HT (at least 1 year's duration) on mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition in perimenopausal and postmenopausal women during and after cessation of treatment.
Search methods: We searched the following databases to September 2016: Cochrane Gynaecology and Fertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO. We searched the registers of ongoing trials and reference lists provided in previous studies and systematic reviews.
Selection criteria: We included randomised double-blinded studies of HT versus placebo, taken for at least 1 year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via the oral, transdermal, subcutaneous or intranasal route.
Data collection and analysis: Two review authors independently selected studies, assessed risk of bias and extracted data. We calculated risk ratios (RRs) for dichotomous data and mean differences (MDs) for continuous data, along with 95% confidence intervals (CIs). We assessed the quality of the evidence by using GRADE methods.
Main results: We included 22 studies involving 43,637 women. We derived nearly 70% of the data from two well-conducted studies (HERS 1998; WHI 1998). Most participants were postmenopausal American women with at least some degree of comorbidity, and mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (i.e. generally fit, without overt disease), combined continuous HT increased the risk of a coronary event (after 1 year's use: from 2 per 1000 to between 3 and 7 per 1000), venous thromboembolism (after 1 year's use: from 2 per 1000 to between 4 and 11 per 1000), stroke (after 3 years' use: from 6 per 1000 to between 6 and 12 per 1000), breast cancer (after 5.6 years' use: from 19 per 1000 to between 20 and 30 per 1000), gallbladder disease (after 5.6 years' use: from 27 per 1000 to between 38 and 60 per 1000) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: from 5 per 1000 to between 6 and 13 per 1000). Oestrogen-only HT increased the risk of venous thromboembolism (after 1 to 2 years' use: from 2 per 1000 to 2 to 10 per 1000; after 7 years' use: from 16 per 1000 to 16 to 28 per 1000), stroke (after 7 years' use: from 24 per 1000 to between 25 and 40 per 1000) and gallbladder disease (after 7 years' use: from 27 per 1000 to between 38 and 60 per 1000) but reduced the risk of breast cancer (after 7 years' use: from 25 per 1000 to between 15 and 25 per 1000) and clinical fracture (after 7 years' use: from 141 per 1000 to between 92 and 113 per 1000) and did not increase the risk of coronary events at any follow-up time.Women over 65 years of age who were relatively healthy and taking continuous combined HT showed an increase in the incidence of dementia (after 4 years' use: from 9 per 1000 to 11 to 30 per 1000). Among women with cardiovascular disease, use of combined continuous HT significantly increased the risk of venous thromboembolism (at 1 year's use: from 3 per 1000 to between 3 and 29 per 1000). Women taking HT had a significantly decreased incidence of fracture with long-term use. Risk of fracture was the only outcome for which strong evidence showed clinical benefit derived from HT (after 5.6 years' use of combined HT: from 111 per 1000 to between 79 and 96 per 1000; after 7.1 years' use of oestrogen-only HT: from 141 per 1000 to between 92 and 113 per 1000). Researchers found no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analysed subgroups of 2839 relatively healthy women 50 to 59 years of age who were taking combined continuous HT and 1637 who were taking oestrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thromboembolism in women taking combined continuous HT: Their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded, as this study was not designed to have the power to detect differences between groups of women within 10 years of menopause. For most studies, risk of bias was low in most domains. The overall quality of evidence for the main comparisons was moderate. The main limitation in the quality of evidence was that only about 30% of women were 50 to 59 years old at baseline, which is the age at which women are most likely to consider HT for vasomotor symptoms.
Authors' conclusions: Women with intolerable menopausal symptoms may wish to weigh the benefits of symptom relief against the small absolute risk of harm arising from short-term use of low-dose HT, provided they do not have specific contraindications. HT may be unsuitable for some women, including those at increased risk of cardiovascular disease, increased risk of thromboembolic disease (such as those with obesity or a history of venous thrombosis) or increased risk of some types of cancer (such as breast cancer, in women with a uterus). The risk of endometrial cancer among women with a uterus taking oestrogen-only HT is well documented. HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for prevention of deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk for whom non-oestrogen therapies are unsuitable. Data are insufficient for assessment of the risk of long-term HT use in perimenopausal women and in postmenopausal women younger than 50 years of age.
Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub5.

9. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials

Objective: To examine total and cause-specific cumulative mortality, including during the intervention and extended post-intervention follow-up, of the 2 Women's Health Initiative hormone therapy trials.
Design, Setting, and Participants: Observational follow-up of US multiethnic postmenopausal women aged 50 to 79 years enrolled in 2 randomized clinical trials between 1993 and 1998 and followed up through December 31, 2014.
Interventions: Conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8506) vs placebo (n = 8102) for 5.6 years (median) or CEE alone (n = 5310) vs placebo (n = 5429) for 7.2 years (median).
Main Outcomes and Measures: All-cause mortality (primary outcome) and cause-specific mortality (cardiovascular disease mortality, cancer mortality, and other major causes of mortality) in the 2 trials pooled and in each trial individually, with prespecified analyses by 10-year age group based on age at time of randomization.
Results: Among 27 347 women who were randomized (baseline mean [SD] age, 63.4 [7.2] years; 80.6% white), mortality follow-up was available for more than 98%. During the cumulative 18-year follow-up, 7489 deaths occurred (1088 deaths during the intervention phase and 6401 deaths during postintervention follow-up). All-cause mortality was 27.1% in the hormone therapy group vs 27.6% in the placebo group (hazard ratio [HR], 0.99 [95% CI, 0.94-1.03]) in the overall pooled cohort; with CEE plus MPA, the HR was 1.02 (95% CI, 0.96-1.08); and with CEE alone, the HR was 0.94 (95% CI, 0.88-1.01). In the pooled cohort for cardiovascular mortality, the HR was 1.00 (95% CI, 0.92-1.08 [8.9 % with hormone therapy vs 9.0% with placebo]); for total cancer mortality, the HR was 1.03 (95% CI, 0.95-1.12 [8.2 % with hormone therapy vs 8.0% with placebo]); and for other causes, the HR was 0.95 (95% CI, 0.88-1.02 [10.0% with hormone therapy vs 10.7% with placebo]), and results did not differ significantly between trials. When examined by 10-year age groups comparing younger women (aged 50-59 years) to older women (aged 70-79 years) in the pooled cohort, the ratio of nominal HRs for all-cause mortality was 0.61 (95% CI, 0.43-0.87) during the intervention phase and the ratio was 0.87 (95% CI, 0.76-1.00) during cumulative 18-year follow-up, without significant heterogeneity between trials.
Conclusions and Relevance: *Among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.*
Manson, J.E., Aragaki, A.K., Rossouw, J.E., Anderson, G.L., Prentice, R.L. (2017). Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women's health initiative randomized trials. JAMA, 318 (10). 927-938.

Dysmenorrhea

10. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea

Background: Dysmenorrhoea is a common gynaecological problem consisting of painful cramps accompanying menstruation, which in the absence of any underlying abnormality is known as primary dysmenorrhoea. Research has shown that women with dysmenorrhoea have high levels of prostaglandins, hormones known to cause cramping abdominal pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs that act by blocking prostaglandin production. They inhibit the action of cyclooxygenase (COX), an enzyme responsible for the formation of prostaglandins. The COX enzyme exists in two forms, COX-1 and COX-2. Traditional NSAIDs are considered 'non-selective' because they inhibit both COX-1 and COX-2 enzymes. More selective NSAIDs that solely target COX-2 enzymes (COX-2-specific inhibitors) were launched in 1999 with the aim of reducing side effects commonly reported in association with NSAIDs, such as indigestion, headaches and drowsiness.
Objectives: To determine the effectiveness and safety of NSAIDs in the treatment of primary dysmenorrhoea.
Search methods: We searched the following databases in January 2015: Cochrane Menstrual Disorders and Subfertility Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, November 2014 issue), MEDLINE, EMBASE and Web of Science. We also searched clinical trials registers (ClinicalTrials.gov and ICTRP). We checked the abstracts of major scientific meetings and the reference lists of relevant articles.
Selection criteria: All randomised controlled trial (RCT) comparisons of NSAIDs versus placebo, other NSAIDs or paracetamol, when used to treat primary dysmenorrhoea.
Data collection and analysis: Two review authors independently selected the studies, assessed their risk of bias and extracted data, calculating odds ratios (ORs) for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs). We used inverse variance methods to combine data. We assessed the overall quality of the evidence using GRADE methods.
Main results: We included 80 randomised controlled trials (5820 women). They compared 20 different NSAIDs (18 non-selective and two COX-2-specific) versus placebo, paracetamol or each other.
NSAIDs versus placebo: Among women with primary dysmenorrhoea, NSAIDs were more effective for pain relief than placebo (OR 4.37, 95% CI 3.76 to 5.09; 35 RCTs, I2 = 53%, low quality evidence). This suggests that if 18% of women taking placebo achieve moderate or excellent pain relief, between 45% and 53% taking NSAIDs will do so. However, NSAIDs were associated with more adverse effects (overall adverse effects: OR 1.29, 95% CI 1.11 to 1.51, 25 RCTs, I2 = 0%, low quality evidence; gastrointestinal adverse effects: OR 1.58, 95% CI 1.12 to 2.23, 14 RCTs, I2 = 30%; neurological adverse effects: OR 2.74, 95% CI 1.66 to 4.53, seven RCTs, I2 = 0%, low quality evidence). The evidence suggests that if 10% of women taking placebo experience side effects, between 11% and 14% of women taking NSAIDs will do so. NSAIDs versus other NSAIDs: When NSAIDs were compared with each other there was little evidence of the superiority of any individual NSAID for either pain relief or safety. However, the available evidence had little power to detect such differences, as most individual comparisons were based on very few small trials. Non-selective NSAIDs versus COX-2-specific selectors: Only two of the included studies utilised COX-2-specific inhibitors (etoricoxib and celecoxib). There was no evidence that COX-2-specific inhibitors were more effective or tolerable for the treatment of dysmenorrhoea than traditional NSAIDs; however data were very scanty. NSAIDs versus paracetamol: NSAIDs appeared to be more effective for pain relief than paracetamol (OR 1.89, 95% CI 1.05 to 3.43, three RCTs, I2 = 0%, low quality evidence). There was no evidence of a difference with regard to

adverse effects, though data were very scanty. Most of the studies were commercially funded (59%); a further 31% failed to state their source of funding.
Authors' conclusions: NSAIDs appear to be a very effective treatment for dysmenorrhoea, though women using them need to be aware of the substantial risk of adverse effects. There is insufficient evidence to determine which (if any) individual NSAID is the safest and most effective for the treatment of dysmenorrhoea. We rated the quality of the evidence as low for most comparisons, mainly due to poor reporting of study methods.
Marjoriebanks, J., Ayeleke, R.O., Farquhar, C., Proctor, M. (2015). Nonsteroidal anti-inflammatory drugs for dysmenorrhea. Cochrane Database of Systematic Reviews, 2015(7). Art. No.: CD001751. DOI: 10.1002/14651858.CD001751.pub3.

11. Effect of transcutaneous electrical nerve stimulation therapy for the treatment of primary dysmenorrhea

Background: This study aimed to investigate the effect and safety of transcutaneous electrical nerve stimulation (TENS) therapy for relieving pain in women with primary dysmenorrhea (PD).
Methods: In this study, 134 participants with PD were randomly divided into the intervention group and the sham group, with 67 participants in each group. Participants in the intervention group received TENS, whereas those in the sham group received sham TENS. The primary outcome was measured by the Numeric Rating Scale (NRS). The secondary outcomes were measured by the duration of relief from dysmenorrheal pain, number of ibuprofen tablets taken, and the World Health Organization quality of life (WHOQOL)-BREF score, as well as the adverse events.
Results: A total of 122 participants completed the study. Compared to sham TENS, TENS showed a greater effect in pain relief with regard to the NRS ($P<.01$), duration of relief from dysmenorrheal pain ($P<.01$), and number of ibuprofen tablets taken ($P<.01$). However, no significant differences in the quality of life, measured by the WHOQOL-BREF score, were found between 2 groups. The adverse event profiles were also similar between 2 groups.
Conclusion: TENS was efficacious and safe in relieving pain in participants with PD.
Bai, H.Y., Bai, H.Y., Yang, Z.Q. (2017). Effect of transcutaneous electrical nerve stimulation therapy for the treatment of primary dysmenorrheal. Medicine (Baltimore), 96(36).

12. Dietary supplements for dysmenorrhea

Background: Dysmenorrhoea refers to painful menstrual cramps and is a common gynaecological complaint. Conventional treatments include non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCPs), which both reduce myometrial activity (contractions of the uterus). A suggested alternative approach is dietary supplements. We used the term 'dietary supplement' to include herbs or other botanical, vitamins, minerals, enzymes, and amino acids. We excluded traditional Chinese medicines.
Objectives: To determine the efficacy and safety of dietary supplements for treating dysmenorrhoea.
Search methods: We searched sources including the Cochrane Gynaecology and Fertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, PsycINFO (all from inception to 23 March 2015), trial registries, and the reference lists of relevant articles.
Selection criteria: We included randomised controlled trials (RCTs) of dietary supplements for moderate or severe primary or secondary dysmenorrhoea. We excluded studies of women with an intrauterine device. Eligible comparators were other dietary supplements, placebo, no treatment, or conventional analgesia.
Data collection and analysis: Two review authors independently performed study selection, performed data extraction and assessed the risk of bias in the included trials. The primary outcomes were pain intensity and adverse effects. We used a fixed-effect model to calculate odds ratios (ORs) for dichotomous data, and mean differences (MDs) or standardised mean differences (SMDs) for continuous data, with 95% confidence intervals (CIs). We presented data that were unsuitable for analysis either descriptively or in additional tables. We assessed the quality of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.
Main results: We included 27 RCTs (3101 women). Most included studies were conducted amongst cohorts of students with primary dysmenorrhoea in their late teens or early twenties. Twenty-two studies were conducted in Iran and the rest were performed in other middle-income countries. Only one study addressed secondary dysmenorrhoea. Interventions included 12 different herbal medicines (German chamomile (*Matricaria chamomilla, M recutita, Chamomilla recutita)*, cinnamon (*Cinnamomum zeylanicum, C. verum)*, Damask rose (*Rosa damascena),* dill (*Anethum graveolens*), fennel (*Foeniculum vulgare*), fenugreek (*Trigonella foenum-graecum*), ginger (*Zingiber* officinale), guava (Psidium guajava), rhubarb (Rheum emodi), uzara (Xysmalobium undulatum), valerian (Valeriana officinalis), and zataria (Zataria multiflora)) and five non-herbal supplements (fish oil, melatonin, vitamins B1 and E, and zinc sulphate) in a variety of formulations and doses. Comparators included other supplements, placebo, no treatment, and NSAIDs. We judged all the evidence to be of low or very low quality. The main limitations were imprecision due to very small sample sizes, failure to report study methods, and inconsistency. For most comparisons there was only one included study, and very few studies reported adverse effects.
Effectiveness of supplements for primary dysmenorrhea: We have presented pain scores (all on a visual analogue scale (VAS) 0 to 10 point scale) or rates of pain relief, or both, at the first post-treatment follow-up.
Supplements versus placebo or no treatment: There was no evidence of effectiveness for vitamin E (MD 0.00 points, 95% CI −0.34 to 0.34; two RCTs, 135 women).There was no consistent evidence of effectiveness for dill (MD -1.15 points, 95% CI −2.22 to −0.08, one RCT, 46 women), guava (MD 0.59, 95% CI −0.13 to 1.31; one RCT, 151 women); one RCT, 73 women), or fennel (MD −0.34 points, 95% CI −0.74 to 0.06; one RCT, 43 women).There was very limited evidence of effectiveness for fenugreek (MD −1.71 points, 95% CI −2.35 to −1.07; one RCT, 101 women), fish oil (MD 1.11 points, 95% CI 0.45 to 1.77; one RCT, 120 women), fish oil plus vitamin B1 (MD −1.21 points, 95% CI −1.79 to −0.63; one RCT, 120 women), ginger (MD −1.55 points, 95% CI −2.43 to −0.68; three RCTs, 266 women; OR 5.44, 95% CI 1.80 to 16.46; one RCT, 69 women), valerian (MD −0.76 points, 95% CI −1.44 to −0.08; one RCT, 100 women), vitamin B1 alone (MD −2.70 points, 95% CI −3.32 to −2.08; one RCT, 120 women), zataria (OR 6.66, 95% CI 2.66 to 16.72;

one RCT, 99 women), and zinc sulphate (MD −0.95 points, 95% CI −1.54 to −0.36; one RCT, 99 women).Data on chamomile and cinnamon versus placebo were unsuitable for analysis.
Supplements versus NSAIDS: There was no evidence of any difference between NSAIDs and dill (MD 0.13 points, 95% CI −1.01 to 1.27; one RCT, 47 women), fennel (MD −0.70 points, 95% CI −1.81 to 0.41; one RCT, 59 women), guava (MD 1.19, 95% CI 0.42 to 1.96; one RCT, 155 women), rhubarb (MD −0.20 points, 95% CI −0.44 to 0.04; one RCT, 45 women), or valerian (MD points 0.62 , 95% CI 0.03 to 1.21; one RCT, 99 women),
There was no consistent evidence of a difference between Damask rose and NSAIDs (MD −0.15 points, 95% CI −0.55 to 0.25; one RCT, 92 women). There was very limited evidence that chamomile was more effective than NSAIDs (MD −1.42 points, 95% CI −1.69 to −1.15; one RCT, 160 women).
Supplements versus other supplements: There was no evidence of a difference in effectiveness between ginger and zinc sulphate (MD 0.02 points, 95% CI −0.58 to 0.62; one RCT, 101 women). Vitamin B1 may be more effective than fish oil (MD −1.59 points, 95% CI −2.25 to −0.93; one RCT, 120 women).
Effectiveness of supplements for secondary dysmenorrhea: There was no strong evidence of benefit for melatonin compared to placebo for dysmenorrhoea secondary to endometriosis (data were unsuitable for analysis).
Safety of supplements: Only four of the 27 included studies reported adverse effects in both treatment groups. There was no evidence of a difference between the groups but data were too scanty to reach any conclusions about safety.
Authors' conclusions: There is no high quality evidence to support the effectiveness of any dietary supplement for dysmenorrhoea, and evidence of safety is lacking. However for several supplements there was some low quality evidence of effectiveness and more research is justified.

Sexual Dysfunction

13. Flibanserin ineffective for hypoactive sexual desire disorder in women

Clinical question: Is flibanserin a safe and effective treatment of hypoactive sexual desire disorder in premenopausal women?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: To assemble studies for inclusion, these authors searched 3 trial registries and 13 electronic databases, including the Cochrane Library, along with reference lists of retrieved articles to identify randomized studies. They included studies published in any language. Two researchers independently identified the studies for inclusion; data were extracted by one reviewer and checked by another. They included 5 published and 3 unpublished studies that enrolled a total of 5914 premenopausal and postmenopausal women. The overall study quality was low: many women dropped out, some authors shifted endpoints mid-study, and some authors used the "last observation carried forward." Benefit was statistically significant but clinically minimal for most outcomes. On average across the studies, treatment, as compared with placebo, resulted in one additional satisfying sexual event every 2 months. Diary scores for sexual desire increased from 1.7 to 2.30 points on a scale of 0 to 84 (4 studies) and scores on the female sexual function index increased an average of 0.2 to 0.4 on a scale of 1.2 to 6.0. There was either minimal or no change in the women's mean global impression of improvement. Patients who received treatment were twice as likely to drop out because of adverse effects, including dizziness, which was 4 times more likely in that group.
Bottom line: Flibanserin (Addyi) produces a minimal effect on sexual desire and minimally increases the number of satisfying sexual events in women (less than 1/2 an event per month increase). Many women will be unable to tolerate the side effects.
Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: A systematic review and meta-analysis. JAMA Intern Med 2016;176(4):453-462.

Fibroids

14. Imaging for Polyps and Leiomyomas in Women With Abnormal Uterine Bleeding: A Systematic Review

Objective: To evaluate the accuracy of saline infusion sonohysterography in comparison with transvaginal ultrasonography for diagnosing polyps and submucosal leiomyomas in women with abnormal uterine bleeding.
Data sources: We searched the databases MEDLINE, EMBASE, CENTRAL, and ClinicalTrials.gov as well as citations and reference lists to the end of November 2015.
Methods of Study Selection: Two authors screened 5,347 citations for eligibility. We included randomized controlled trials or prospective cohort studies published in English, assessing the accuracy of saline infusion sonohysterography and transvaginal ultrasonography for diagnosing polyps and submucosal leiomyomas in women with abnormal uterine bleeding. We considered studies using histopathologic specimens obtained at either hysteroscopy or hysterectomy as criterion standard.
Tabulation, Integration, and Results: Twenty-five studies were eligible. Two authors extracted data and assessed the quality of included studies. Bivariate random-effects models were used to compare the different tests and evaluate sources of heterogeneity. Saline infusion sonohysterography was superior to transvaginal ultrasonography with pooled sensitivity and specificity of 0.92 and 0.89 compared with 0.64 and 0.90, respectively (P<.001). Transvaginal ultrasound sensitivity for diagnosing polyps was particularly low (0.51). Saline infusion sonohysterography was also compared with hysteroscopy in seven studies and had similar sensitivity but inferior specificity (0.93 and 0.83 compared with 0.95 and 0.90, respectively, P=.007). All three procedures were well-tolerated by women. Saline infusion sonohysterography was successfully completed in 95% of women. Technical variations such as the use of balloon catheters were not found to affect diagnostic accuracy.
Conclusion: Transvaginal ultrasonography lacks sensitivity to be used alone to exclude the presence of polyps and leiomyomas in women with abnormal uterine bleeding. Although less specific than hysteroscopy, saline infusion sonohysterography offers a similar

detection rate and permits concomitant visualization of the ovaries and myometrium. Cost, convenience, and tolerability of different imaging techniques require further evaluation.
Maheux-Lacroix, S., Li, F., Laberge, P,Y., Abbott, J. (2016) Imaging for polyps and leiomyomas in women with abnormal uterine bleeding: a systemic review. Obstet Gynecol 128(6). 1425-1436.

15. Uterine artery embolization for symptomatic uterine fibroids

Objectives: To review the benefits and risks of uterine artery embolization (UAE) versus other medical or surgical interventions for symptomatic uterine fibroids.
Search methods: We searched sources including the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and trial registries. The search was last conducted in April 2014. We contacted authors of eligible randomised controlled trials to request unpublished data.
Selection criteria: Randomised controlled trials (RCTs) of UAE versus any medical or surgical therapy for symptomatic uterine fibroids. The primary outcomes of the review were patient satisfaction and live birth rate (among women seeking live birth).
Data collection and analysis: Two of the authors (AS and JKG) independently selected studies, assessed quality and extracted data. Evidence quality was assessed using GRADE methods.
Main results: Seven RCTs with 793 women were included in this review. Three trials compared UAE with abdominal hysterectomy, two trials compared UAE with myomectomy, and two trials compared UAE with either type of surgery (53 hysterectomies and 62 myomectomies).With regard to patient satisfaction rates, our findings were consistent with satisfaction rates being up to 41% lower or up to 48% higher with UAE compared to surgery within 24 months of having the procedure (odds ratio (OR) 0.94; 95% confidence interval (CI) 0.59 to 1.48, 6 trials, 640 women, I2 = 5%, moderate quality evidence). Findings were also inconclusive at five years of follow-up (OR 0.90; 95% CI 0.45 to 1.80, 2 trials, 295 women, I2 = 0%, moderate quality evidence). There was some indication that UAE may be associated with less favourable fertility outcomes than myomectomy, but it was very low quality evidence from a subgroup of a single study and should be regarded with extreme caution (live birth: OR 0.26; 95% CI 0.08 to 0.84; pregnancy: OR 0.29; 95% CI 0.10 to 0.85, 1 study, 66 women).Similarly, for several safety outcomes our findings showed evidence of a substantially higher risk of adverse events in either arm or of no difference between the groups. This applied to intra-procedural complications (OR 0.91; 95% CI 0.42 to 1.97, 4 trials, 452 women, I2 = 40%, low quality evidence), major complications within one year (OR 0.65; 95% CI 0.33 to 1.26, 5 trials, 611 women, I2 = 4%, moderate quality evidence) and major complications within five years (OR 0.56; CI 0.27 to 1.18, 2 trials, 268 women). However, the rate of minor complications within one year was higher in the UAE group (OR 1.99; CI 1.41 to 2.81, 6 trials, 735 women, I2 = 0%, moderate quality evidence) and two trials found a higher minor complication rate in the UAE group at up to five years (OR 2.93; CI 1.73 to 4.93, 2 trials, 268 women).UAE was associated with a higher rate of further surgical interventions (re-interventions within 2 years: OR 3.72; 95% CI 2.28 to 6.04, 6 trials, 732 women, I2 = 45%, moderate quality evidence; within 5 years: OR 5.79; 95% CI 2.65 to 12.65, 2 trials, 289 women, I2 = 65%). If we assumed that 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE.The evidence suggested that women in the UAE group were less likely to require a blood transfusion than women receiving surgery (OR 0.07; 95% CI 0.01 to 0.52, 2 trials, 277 women, I2 = 0%). UAE was also associated with a shorter procedural time (two studies), shorter length of hospital stay (seven studies) and faster resumption of usual activities (six studies) in all studies that measured these outcomes; however, most of these data could not be pooled due to heterogeneity between the studies.The quality of the evidence varied, and was very low for live birth, moderate for satisfaction ratings, and moderate for most safety outcomes. The main limitations in the evidence were serious imprecision due to wide confidence intervals, failure to clearly report methods, and lack of blinding for subjective outcomes.
Authors' conclusions: When we compared patient satisfaction rates at up to two years following UAE versus surgery (myomectomy or hysterectomy) our findings are that there is no evidence of a difference between the interventions. Findings at five year follow-up were similarly inconclusive. There was very low quality evidence to suggest that myomectomy may be associated with better fertility outcomes than UAE, but this information was only available from a selected subgroup in one small trial.We found no clear evidence of a difference between UAE and surgery in the risk of major complications, but UAE was associated with a higher rate of minor complications and an increased likelihood of requiring surgical intervention within two to five years of the initial procedure. If we assume that 7% of women will require further surgery within two years of hysterectomy or myomectomy, between 15% and 32% will require further surgery within two years of UAE. This increase in the surgical re-intervention rate may balance out any initial cost advantage of UAE. Thus although UAE is a safe, minimally invasive alternative to surgery, patient selection and counselling are paramount due to the much higher risk of requiring further surgical intervention.
Gupta, J.K., Sinha, A., Lumsden, M.A., Hickey, M. (2014). Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database of Systemic Reviews, 2014(12). CD005073. DOI: 10.1002/14651858.CD005073.pub4.

Vaginal atrophy

16. Local oestrogen for vaginal atrophy in postmenopausal women

Background: Vaginal atrophy is a frequent complaint of postmenopausal women; symptoms include vaginal dryness, itching, discomfort and painful intercourse. Systemic treatment for these symptoms in the form of oral hormone replacement therapy is not always necessary. An alternative choice is oestrogenic preparations administered vaginally (in the form of creams, pessaries, tablets and the oestradiol-releasing ring). This is an update of a Chochrane systematic review; the original version was first published in October 2006.
Objectives: The objective of this review was to compare the efficacy and safety of intra-vaginal oestrogenic preparations in relieving the symptoms of vaginal atrophy in postmenopausal women.
Search methods: We searched the following databases and trials registers to April 2016: Cochrane Gynaecology and Fertility Group Register of trials, The Cochrane Central Register of Controlled Trials (CENTRAL; 2016 issue 4), MEDLINE, Embase, PsycINFO, DARE, the Web of Knowledge, OpenGrey, LILACS, PubMed and reference lists of articles. We also contacted experts and researchers

in the field.
Selection criteria: The inclusion criteria were randomised comparisons of oestrogenic preparations administered intravaginally in postmenopausal women for at least 12 weeks for the treatment of symptoms resulting from vaginal atrophy or vaginitis.
Data collection and analysis: Two review authors independently assessed trial eligibility and risk of bias and extracted the data. The primary review outcomes were improvement in symptoms (participant-assessed), and the adverse event endometrial thickness. Secondary outcomes were improvement in symptoms (clinician-assessed), other adverse events (breast disorders e.g. breast pain, enlargement or engorgement, total adverse events, excluding breast disorders) and adherence to treatment. We combined data to calculate pooled risk ratios (RRs) (dichotomous outcomes) and mean differences (MDs) (continuous outcomes) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I2 statistic. We assessed the overall quality of the evidence for the main comparisons using GRADE methods.
Main results: We included 30 RCTs (6235 women) comparing different intra-vaginal oestrogenic preparations with each other and with placebo. The evidence was low to moderate quality; limitations were poor reporting of study methods and serious imprecision (effect estimates with wide confidence intervals)
1. Oestrogen ring versus other regimens. Other regimens included oestrogen cream, oestrogen tablets and placebo. There was no evidence of a difference in improvement in symptoms (participant assessment) either between oestrogen ring and oestrogen cream (odds ratio (OR) 1.33, 95% CI 0.80 to 2.19, two RCTs, n = 341, I2 = 0%, low-quality evidence) or between oestrogen ring and oestrogen tablets (OR 0.78, 95% CI 0.53 to 1.15, three RCTs, n = 567, I2 = 0%, low-quality evidence). However, a higher proportion of women reported improvement in symptoms following treatment with oestrogen ring compared with placebo (OR 12.67, 95% CI 3.23 to 49.66, one RCT, n = 67). With respect to endometrial thickness, a higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring (OR 0.36, 95% CI 0.14 to 0.94, two RCTs, n = 273; I2 = 0%, low-quality evidence). This may have been due to the higher doses of cream used. 2. Oestrogen tablets versus other regimens. Other regimens in this comparison included oestrogen cream, and placebo. There was no evidence of a difference in the proportions of women who reported improvement in symptoms between oestrogen tablets and oestrogen cream (OR 1.06, 95% CI 0.55 to 2.01, two RCTs, n = 208, I2 = 0% low-quality evidence). A higher proportion of women who were treated with oestrogen tablets reported improvement in symptoms compared to those who received placebo using a fixed-effect model (OR 12.47, 95% CI 9.81 to 15.84, two RCTs, n = 1638, I2 = 83%, low-quality evidence); however, using a random-effect model did not demonstrate any evidence of a difference in the proportions of women who reported improvement between the two treatment groups (OR 5.80, 95% CI 0.88 to 38.29). There was no evidence of a difference in the proportions of women with increase in endometrial thickness between oestrogen tablets and oestrogen cream (OR 0.31, 95% CI 0.06 to 1.60, two RCTs, n = 151, I2 = 0%, low-quality evidence).
3. Oestrogen cream versus other regimens. Other regimens identified in this comparison included isoflavone gel and placebo. There was no evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and isoflavone gel (OR 2.08, 95% CI 0.08 to 53.76, one RCT, n = 50, low-quality evidence). However, there was evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and placebo with more women who received oestrogen cream reporting improvement in symptoms compared to those who were treated with placebo (OR 4.10, 95% CI 1.88 to 8.93, two RCTs, n = 198, I2 = 50%, low-quality evidence). None of the included studies in this comparison reported data on endometrial thickness.
Authors' conclusions: There was no evidence of a difference in efficacy between the various intravaginal oestrogenic preparations when compared with each other. However, there was low-quality evidence that intra-vaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. There was low-quality evidence that oestrogen cream may be associated with an increase in endometrial thickness compared to oestrogen ring; this may have been due to the higher doses of cream used. However there was no evidence of a difference in the overall body of evidence in adverse events between the various oestrogenic preparations compared with each other or with placebo.
Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD001500. DOI: 10.1002/14651858.CD001500.pub3.

Contraception:

17. Free contraception associated with reduced long-term pregnancy and birth rates in teens (CHOICE study)

Clinical question: Does education about contraceptive alternatives and the provision of free contraception, including long-acting reversible methods, reduce pregnancy and birth rates in teens?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: This was a cohort study that enrolled 1404 adolescents between the ages of 14 and 19 years between 2007 and 2011 in metropolitan St. Louis, Missouri. The patents were all sexually active and were either not currently using contraception or were interested in switching to a new, reversible method. Demographically, 63% were black, 30% white, and 8% another race. Almost half had low socioeconomic status, only 43% had private health insurance, and almost half had experienced a previous unintended pregnancy. They were educated about their contraceptive options in order from most effective to least effective, with an emphasis on long-acting reversible contraceptives (LARCs), such as intrauterine devices and implants. The benefits and harms of each method were described as part of the educational session, and the participant was able to choose her preferred method. In the absence of contraindications such as pregnancy, the LARC device was inserted on the same day. If a delay was needed, an alternative contraceptive was provided until it could be inserted. The chosen contraceptive method was IUD for 37% of patients, etonogestrel implant for 34%, oral contraceptive for 12%, depot medroxyprogesterone acetate injection for 9%, and another method for 7%. Thus, more than 70% chose a LARC method. Participants were followed up for up to 3 years via telephone calls every 6 months. The follow-up rate was 82% at 2 years and 75% at 3 years, which is decent for a cohort study of this kind. It is possible that self-selection bias could dampen the findings, if young women who were lost to follow-up were more likely to become pregnant or give birth than their adherent counterparts. Pregnancy, birth, and abortion rates were significantly lower for members of the study cohort (34.0, 19.4, and

9.7 per 1000 teens, respectively) than for a general US population sample of sexually experienced teens (158.5, 94.0, and 41.5 per 1000 teens) and lower than a general US population sample of all teens (57.4, 34.4, and 14.7 per 1000 teens). Results were similar when stratified for possible confounders such as race and age group. Most of the 56 participants who became pregnant were using either no method (25) or oral contraceptives (13). Failure rates for IUD and implant were approximately 5 per 1000 person-years (or ~ 0.5% per year). These results are probably affected to some extent by selection bias, as participants were responding to an advertisement offering free contraception or were referred for contraception. Pregnancy was self-reported, so there may have also been an ascertainment bias with regard to the primary outcome. Because the nationwide teen birth rate declined during the study period, comparing 2013 results to 2008 baseline data may somewhat overestimate the effect.
Bottom line: This prospective cohort study found that the provision of free, largely long-acting, contraception to sexually active teens was associated with lower rates of pregnancy, birth, and abortion.
Secura GM, Madden T, McNicholas C, et al. Provision of no-cost, long-acting contraception and teenage pregnancy. N Engl J Med 2014;371(14):1316-1323.

18. Long-acting contraceptive methods effective longer than approved duration

Clinical question: Do the etonogestrel implant and the levonorgestrel intrauterine device remain effective beyond the approved duration of use?
Study design: Cohort (prospective)
Setting: Outpatient (any)
Synopsis: In this observational study 500 women volunteered to continue to use beyond the stated expiration date a long-acting reversible contraceptive (LARC) method that was already in place. The majority of women enrolled were participants in a prior study designed to promote the use of LARC methods by eliminating barriers including cost, access, and knowledge deficits. There were an additional 58 participants recruited through local advertisements. The LARC methods used were etonogestrel implant (Nexplanon R) and levonorgestrel IUD (Mirena R). Participants were categorized into 3 categories of body mass index: less than 25.0, 25.0 to 29.9, and 30.0 or higher. Of the 237 implant users 123 had used it for at least 1 year beyond the 3-year approved duration and 34 used it for an additional 2 years (median extended duration = 12.5 months; range 5-40). Serum etonogestrel levels indicate that the implant contains adequate hormone levels for ovulation suppression at the end of both 3 years and 4 years of use. Of the 263 IUD users 108 had used it for at least 1 year beyond the approved 5-year duration (median extended duration = 12 months; range 5-36). There were no pregnancies among implant users. There was one pregnancy in an IUD user with conception estimated to be in the month prior to IUD expiration date and a physical examination that demonstrated partial expulsion of the device.
Bottom line: Both the etonogestrel implant and the levonorgestrel intrauterine device (IUD) remain highly effective for at least 1 year beyond the FDA-approved durations. This study adds to the evidence from a recent systematic review concluding that IUDs, including 52-mg levonorgestrel IUDs, could be safely used for up to 7 years.
McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of etonogestrel implant and levonorgestrel intrauterine device beyond the US Food and Drug Administration–approved duration. Obstet Gynecol 2015;125(3):599-604.

19. Third-generation oral contraceptives associated with greater risk of PE, stroke, and MI

Clinical question: Which oral contraceptive combinations have the highest risk of cardiovascular effects?
Study design: Cohort (retrospective)
Setting: Population-based
Synopsis: This study, conducted in France, used the national health insurance database to identify all women who filled at least one prescription for an oral contraceptive between July 2010 and September 2012. The authors compared these data with the hospital discharge database to identify whether any of these women experienced an admission for pulmonary embolism, cancer, ischemic stroke, or myocardial infarction over the same period. They identified almost 5 million women with a total of 5,443,916 woman-years of oral contraceptive use. The risk of cardiovascular effects was very low: roughly 6 events per 10,000 woman-years, which is similar to other reports. However, the authors found some differences among products: After adjustment for progestogen and risk factors, stroke, pulmonary embolus, and myocardial infarction risk were all statistically lower with lower-dose estrogen (20 mcg vs 30-40 mcg). They also found, after adjustment, that progestogen mattered: desogestrel (in Desogen, Mircette) and gestodene (Gynera, Femoden, and many others) were associated with higher risk of pulmonary embolus than levonorgestrel. Norethisterone (in Loestrin, Microgestin, and others) was associated with lower pulmonary embolus risk. The combination of estrogen 20 mcg and levonorgestrel is associated with the lowest risk. These risks are still small (numbers needed to treat to harm are in the thousands). This study doesn't tell us about products that contain other estrogens or progestogens since these are the only combinations covered by French national health insurance. Also, the database doesn't allow for analysis by smoking status.
Bottom line: Although there is risk with any current oral contraceptive combination, those that contain lower doses of estrogen, and levonorgestrel instead of desogestrel or gestodene, are associated with the least risk of ischemic stroke, myocardial infarction, or pulmonary embolus. These safer products are older, so are often less expensive. This is not the first study to show this difference, but I think its enrollment of 5 million women makes it the largest.
Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ 2016;353:i2002.

20. Progestin-only contraceptives: effects on weight

Background: Progestin-only contraceptives (POCs) are appropriate for many women who cannot or should not take estrogen. POCs include injectables, intrauterine contraception, implants, and oral contraceptives. Many POCs are long-acting, cost-effective methods of preventing pregnancy. However, concern about weight gain can deter the initiation of contraceptives and cause early discontinuation among users.
Objectives: The primary objective was to evaluate the association between progestin-only contraceptive use and changes in body

weight.
Search methods. Until 4 August 2016, we searched MEDLINE, CENTRAL, POPLINE, LILACS, ClinicalTrials.gov, and ICTRP. For the initial review, we contacted investigators to identify other trials.
Selection criteria: We considered comparative studies that examined a POC versus another contraceptive method or no contraceptive. The primary outcome was mean change in body weight or mean change in body composition. We also considered the dichotomous outcome of loss or gain of a specified amount of weight.
Data collection and analysis: Two authors extracted the data. Non-randomized studies (NRS) need to control for confounding factors. We used adjusted measures for the primary effects in NRS or the results of matched analysis from paired samples. If the report did not provide adjusted measures for the primary analysis, we used unadjusted outcomes. For RCTs and NRS without adjusted measures, we computed the mean difference (MD) with 95% confidence interval (CI) for continuous variables. For dichotomous outcomes, we calculated the Mantel-Haenszel odds ratio (OR) with 95% CI.
Main results: We found 22 eligible studies that included a total of 11,450 women. With 6 NRS added to this update, the review includes 17 NRS and 5 RCTs. By contraceptive method, the review has 16 studies of depot medroxyprogesterone acetate (DMPA), 4 of levonorgestrel-releasing intrauterine contraception (LNG-IUC), 5 for implants, and 2 for progestin-only pills. Comparison groups did not differ significantly for weight change or other body composition measure in 15 studies. Five studies with moderate or low quality evidence showed differences between study arms. Two studies of a six-rod implant also indicated some differences, but the evidence was low quality. Three studies showed differences for DMPA users compared with women not using a hormonal method. In a retrospective study, weight gain (kg) was greater for DMPA versus copper (Cu) IUC in years one (MD 2.28, 95% CI 1.79 to 2.77), two (MD 2.71, 95% CI 2.12 to 3.30), and three (MD 3.17, 95% CI 2.51 to 3.83). A prospective study showed adolescents using DMPA had a greater increase in body fat (%) compared with a group not using a hormonal method (MD 11.00, 95% CI 2.64 to 19.36). The DMPA group also had a greater decrease in lean body mass (%) (MD -4.00, 95% CI -6.93 to -1.07). A more recent retrospective study reported greater mean increases with use of DMPA versus Cu IUC for weight (kg) at years 1 (1.3 vs 0.2), 4 (3.5 vs 1.9), and 10 (6.6 vs 4.9). Two studies reported a greater mean increase in body fat mass (%) for POC users versus women not using a hormonal method. The method was LNG-IUC in two studies (reported means 2.5 versus -1.3; P = 0.029); (MD 1.60, 95% CI 0.45 to 2.75). One also studied a desogestrel-containing pill (MD 3.30, 95% CI 2.08 to 4.52). Both studies showed a greater decrease in lean body mass among POC users.
Authors' conclusions: We considered the overall quality of evidence to be low; more than half of the studies had low quality evidence. The main reasons for downgrading were lack of randomizations (NRS) and high loss to follow-up or early discontinuation.These 22 studies showed limited evidence of change in weight or body composition with use of POCs. Mean weight gain at 6 or 12 months was less than 2 kg (4.4 lb) for most studies. Those with multiyear data showed mean weight change was approximately twice as much at two to four years than at one year, but generally the study groups did not differ significantly. Appropriate counseling about typical weight gain may help reduce discontinuation of contraceptives due to perceptions of weight gain.
Lopez , L.M., Ramesh S, Chen M, Edelman A, Otterness C, Trussell J, Helmerhorst FM. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD008815. DOI: 10.1002/14651858.CD008815.pub4.

21. Interventions for emergency contraception

Background: Emergency contraception (EC) is using a drug or copper intrauterine device (Cu-IUD) to prevent pregnancy shortly after unprotected intercourse. Several interventions are available for EC. Information on the comparative effectiveness, safety and convenience of these methods is crucial for reproductive healthcare providers and the women they serve. This is an update of a review previously published in 2009 and 2012.
Objectives: To determine which EC method following unprotected intercourse is the most effective, safe and convenient to prevent pregnancy.
Search methods: In February 2017 we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, Popline and PubMed, The Chinese biomedical databases and UNDP/UNFPA/WHO/World Bank Special Programme on Human Reproduction (HRP) emergency contraception database. We also searched ICTRP and ClinicalTrials.gov as well as contacting content experts and pharmaceutical companies, and searching reference lists of appropriate papers.
Selection criteria: Randomised controlled trials including women attending services for EC following a single act of unprotected intercourse were eligible.
Data collection and analysis: We used standard methodological procedures recommended by Cochrane. The primary review outcome was observed number of pregnancies. Side effects and changes of menses were secondary outcomes.
Main results: We included 115 trials with 60,479 women in this review. The quality of the evidence for the primary outcome ranged from moderate to high, and for other outcomes ranged from very low to high. The main limitations were risk of bias (associated with poor reporting of methods), imprecision and inconsistency.Comparative effectiveness of different emergency contraceptive pills (ECP) Levonorgestrel was associated with fewer pregnancies than Yuzpe (estradiol-levonorgestrel combination) (RR 0.57, 95% CI 0.39 to 0.84, 6 RCTs, n = 4750, I2 = 23%, high-quality evidence). This suggests that if the chance of pregnancy using Yuzpe is assumed to be 29 women per 1000, the chance of pregnancy using levonorgestrel would be between 11 and 24 women per 1000.
Mifepristone (all doses) was associated with fewer pregnancies than Yuzpe (RR 0.14, 95% CI 0.05 to 0.41, 3 RCTs, n = 2144, I2 = 0%, high-quality evidence). This suggests that if the chance of pregnancy following Yuzpe is assumed to be 25 women per 1000 women, the chance following mifepristone would be between 1 and 10 women per 1000. Both low-dose mifepristone (less than 25 mg) and mid-dose mifepristone (25 mg to 50 mg) were probably associated with fewer pregnancies than levonorgestrel (RR 0.72, 95% CI 0.52 to 0.99, 14 RCTs, n = 8752, I2 = 0%, high-quality evidence; RR 0.61, 95% CI 0.45 to 0.83, 27 RCTs, n = 6052, I2 = 0%, moderate-quality evidence; respectively). This suggests that if the chance of pregnancy following levonorgestrel is assumed to be 20 women per 1000, the chance of pregnancy following low-dose mifepristone would be between 10 and 20 women per 1000; and that if the chance of pregnancy following levonorgestrel is assumed to be 35 women per 1000, the chance of pregnancy following mid-dose mifepristone would be between 16 and 29 women per 1000.Ulipristal acetate (UPA) was associated with fewer pregnancies than levonorgestrel (RR 0.59; 95% CI 0.35 to 0.99, 2 RCTs, n = 3448, I2 = 0%, high-quality evidence). Comparative effectiveness of different ECP doses. It was unclear whether there was any difference in pregnancy rate between single-dose levonorgestrel (1.5 mg) and the standard two-dose regimen (0.75 mg 12 hours apart) (RR 0.84, 95% CI 0.53 to 1.33, 3 RCTs, n = 6653, I2 = 0%, moderate-quality evidence). Mid-dose

mifepristone was associated with fewer pregnancies than low-dose mifepristone (RR 0.73; 95% CI 0.55 to 0.97, 25 RCTs, n = 11,914, I2 = 0%, high-quality evidence). Comparative effectiveness of Cu-IUD versus mifepristone. There was no conclusive evidence of a difference in the risk of pregnancy between the Cu-IUD and mifepristone (RR 0.33, 95% CI 0.04 to 2.74, 2 RCTs, n = 395, low-quality evidence). Adverse effects. Nausea and vomiting were the main adverse effects associated with emergency contraception. There is probably a lower risk of nausea (RR 0.63, 95% CI 0.53 to 0.76, 3 RCTs, n = 2186 , I2 = 59%, moderate-quality evidence) or vomiting (RR 0.12, 95% CI 0.07 to 0.20, 3 RCTs, n = 2186, I2 = 0%, high-quality evidence) associated with mifepristone than with Yuzpe. levonorgestrel is probably associated with a lower risk of nausea (RR 0.40, 95% CI 0.36 to 0.44, 6 RCTs, n = 4750, I2 = 82%, moderate-quality evidence), or vomiting (RR 0.29, 95% CI 0.24 to 0.35, 5 RCTs, n = 3640, I2 = 78%, moderate-quality evidence) than Yuzpe. Levonorgestrel users were less likely to have any side effects than Yuzpe users (RR 0.80, 95% CI 0.75 to 0.86; 1 RCT, n = 1955, high-quality evidence). UPA users were more likely than levonorgestrel users to have resumption of menstruation after the expected date (RR 1.65, 95% CI 1.42 to 1.92, 2 RCTs, n = 3593, I2 = 0%, high-quality evidence). Menstrual delay was more common with mifepristone than with any other intervention and appeared to be dose-related. Cu-IUD may be associated with higher risks of abdominal pain than mifepristone (18 events in 95 women using Cu-IUD versus no events in 190 women using mifepristone, low-quality evidence).
Authors' conclusions: Levonorgestrel and mid-dose mifepristone (25 mg to 50 mg) were more effective than Yuzpe regimen. Both mid-dose (25 mg to 50 mg) and low-dose mifepristone(less than 25 mg) were probably more effective than levonorgestrel (1.5 mg). Mifepristone low dose (less than 25 mg) was less effective than mid-dose mifepristone. UPA was more effective than levonorgestrel. Levonorgestrel users had fewer side effects than Yuzpe users, and appeared to be more likely to have a menstrual return before the expected date. UPA users were probably more likely to have a menstrual return after the expected date. Menstrual delay was probably the main adverse effect of mifepristone and seemed to be dose-related. Cu-IUD may be associated with higher risks of abdominal pain than ECPs.
Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD001324. DOI: 10.1002/14651858.CD001324.pub5.

Summary of Key Points

Osteoporosis:

1. Treat women with bisphosphonates or monoclonal antibody for only five years, long term increases fractures
2. Calcium with vitamin D to prevent fractures is uncertain
3. Treating low vitamin D levels is ineffective in post- menopausal women

Menopause:

1. Vasomotor symptoms can be quite long
2. Transdermal estrogen and progesterone are most effective in reducing vasomotor symptoms
3. Plant based therapies with soy isoflavones may be effective for menopausal symptoms
4. Long-term (> 1 year) use of HT increases absolute risk for CVD (heart attacks), venous thrombosis, strokes, breast cancer, and death from lung cancer. Balance risks and benefits per patient
5. USPSTF recommends against (D) the use of hormones (estrogen and progestin) for primary prevention of chronic conditions

Dysmenorrhea:

1. NSAIDs and TENs can be helpful
2. Acupuncture and dietary supplements showing inconsistent results or no evidence

Sexual Dysfunction:

1. Fibanserin (Addyi) –probably more harm than benefit for hypoactive sexual desire disorder (HSDD)
2. Costs-nearly $1000 per month

Fibroids:

1. Transvaginal ultrasound lacks sensitivity to be used alone to exclude polyps or leiomyomas with abnormal uterine bleeding
2. Uterine artery embolization is a treatment option

Contraception:

1. Free contraception is associated with more use and less pregnancy in teens
2. Third generation OCTs with more risk of PE, stroke, and MI than older combinations with low estrogen or levonorgestrel
3. Progestin only has little impact on weight
4. Emergency contraception with levonorgestrel and mifepristone is more effective than Yuzpe regimen (estradiol with levonorgestrel)

Atrial Fibrillation | Anticoagulation — Gary Ferenchick MD

Objectives| Understand:

1. The AAFP updated guideline on the "Pharmacologic Management of Newly Detected Atrial Fibrillation"
2. That subclinical atrial fibrillation (AF) is common
3. AF represents a risk factor for silent cerebral infarcts and anticoagulation for AF is associated with lower dementia
4. Ibutilide (Corvert®) converts AF 50% of the time in an ED setting
5. Periprocedural heparin bridging in patients receiving oral anticoagulation is not effective
6. The "real world" use of Direct Acting Oral Anticoagulants (DOACs) and important drug-drug interactions
7. Management of major bleeding in patients on DOACS
8. Periprocedural management of patients on DOACS

#1: The AAFP published a guideline on guideline on the "Pharmacologic Management of Newly Detected Atrial Fibrillation"

Recommendation 1

- The AAFP strongly recommends rate control in preference to rhythm control for the majority of patients who have atrial fibrillation (strong recommendation, moderate-quality evidence). Preferred options for rate-control therapy include nondihydropyridine calcium channel blockers and beta-blockers. Rhythm control may be considered for certain patients based on patient symptoms, exercise tolerance, and patient preferences (weak recommendation, low-quality evidence).

Recommendation 2

- The AAFP recommends lenient rate control (<110 beats per minute resting) over strict rate control (<80 beats per minute resting) for patients who have atrial fibrillation (weak recommendation, low-quality evidence).

Recommendation 3

- The AAFP recommends that clinicians discuss the risk of stroke and bleeding with all patients considering anticoagulation (good practice point). Clinicians should consider using the continuous CHADS2 or continuous CHA2DS2-VASc for prediction of risk of stroke (weak recommendation, low-quality evidence) and HAS-BLED for prediction of risk for bleeding (weak recommendation, low-quality evidence) in patients who have atrial fibrillation.

Recommendation 4

- The AAFP strongly recommends that patients who have atrial fibrillation receive chronic anticoagulation unless they are at low risk of stroke (CHADS2 <2) or have specific contraindications (strong recommendation, high-quality evidence). Choice of anticoagulation therapy should be based on patient preferences and patient history. Options for anticoagulation therapy may include warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban.

Recommendation 5

- The AAFP strongly recommends against dual treatment with anticoagulant and antiplatelet therapy in most patients who have atrial fibrillation (strong recommendation, moderate-quality evidence).

Reference: Hauk L. Newly Detected Atrial Fibrillation: AAFP Updates Guideline on Pharmacologic Management. Am Fam Physician. 2017 Sep 1;96(5):332-333.

AF is the most common cardiac arrhythmia affecting about 2.7 million in the US and ~ 10% of adults over the age of 85. About 1% of the adult population in the US has undiagnosed AF. About 20% of patients with AF are first diagnosed when presenting with a CVA. ~ 30% of patients with AF who have experienced a CVA die within one year and another 30% survive with major neurological deficits. The highest stroke risk is among those with persistent AF, however paroxysmal AF accounts for 25% of AF associated strokes. The incidence of AF will continue to rise due to improvements in early detection.

#2: Prevalence of subclinical AF is ~ 35% in high-risk patients with no AF history

BACKGROUND: Long-term continuous electrocardiographic monitoring shows a substantial prevalence of asymptomatic, subclinical atrial fibrillation (SCAF) in patients with pacemakers and patients with cryptogenic stroke. Whether SCAF is also common in other patients without these conditions is unknown.
METHODS: We implanted subcutaneous electrocardiographic monitors (St. Jude CONFIRM-AF) in patients ≥65 years of age attending cardiovascular or neurology outpatient clinics if they had no history of atrial fibrillation but had any of the following: CHA2DS2-VASc score of ≥2, sleep apnea, or body mass index >30 kg/m2. Eligibility also required either left atrial enlargement (≥4.4 cm or volume ≥58 mL) or increased (≥290 pg/mL) serum NT-proBNP (N-terminal pro-B-type natriuretic peptide). Patients were monitored for SCAF lasting ≥5 minutes.
RESULTS: Two hundred fifty-six patients were followed up for 16.3±3.8 months. Baseline age was 74±6 years; mean CHA2DS2-VASc score was 4.1±1.4; left atrial diameter averaged 4.7±0.8 cm; and 48% had a prior stroke, transient ischemic attack, or systemic embolism. SCAF ≥5 minutes was detected in 90 patients (detection rate, 34.4%/y; 95% confidence interval [CI], 27.7-42.3). Baseline predictors of SCAF were increased age (hazard ratio [HR] per decade, 1.55; 95% CI, 1.11-2.15), left atrial dimension (HR per centimeter diameter, 1.43; 95% CI, 1.09-1.86), and blood pressure (HR per 10 mm Hg, 0.87; 95% CI, 0.78-0.98), but not prior stroke. The rate of occurrence of SCAF in those with a history of stroke, systemic embolism, or transient ischemic attack was 39.4%/y versus 30.3%/y without (P=0.32). The cumulative SCAF detection rate was higher (51.9%/y) in those with left atrial volume above the median value of 73.5 mL.
CONCLUSIONS: SCAF is frequently detected by continuous electrocardiographic monitoring in older patients without a history of atrial fibrillation who are attending outpatient cardiology and neurology clinics. Its clinical significance is unclear.
REFERENCE: Healey JS et al. Subclinical Atrial Fibrillation in Older Patients. Circulation. 2017 Oct 3;136(14):1276-1283.

In 2017 USPSTF published a draft recommendation entitled “Atrial Fibrillation: Screening With Electrocardiography” and concluded that “…that the current evidence is insufficient to assess the balance of benefits and harms of screening for atrial fibrillation with electrocardiography (ECG).” However as noted in the USPSTF draft statement, “the American Heart Association and the American Stroke Association stated that active screening for atrial fibrillation in the primary care setting among patients older than age 65 years using pulse assessment followed by ECG, as indicated, can be useful.

#3: AF a risk factor for Silent Cerebral Infarcts (SCIs)

BACKGROUND: Atrial fibrillation (AF) is a common cause of stroke. Silent cerebral infarctions (SCIs) are known to occur in the presence and absence of AF, but the association between these disorders has not been well-defined.
PURPOSE: To estimate the association between AF and SCIs and the prevalence of SCIs in stroke-free patients with AF.
DATA SOURCES: Searches of MEDLINE, PsycINFO, Cochrane Library, CINAHL, and EMBASE from inception to 8 May 2014 without language restrictions and manual screening of article references.
STUDY SELECTION: Observational studies involving adults with AF and no clinical history of stroke or prosthetic valves who reported SCIs.
DATA EXTRACTION: Study characteristics and study quality were assessed in duplicate.
DATA SYNTHESIS: Eleven studies including 5317 patients with mean ages from 50.0 to 83.6 years reported on the association between AF and SCIs. Autopsy studies were heterogeneous and low-quality; therefore, they were excluded from the meta-analysis of the risk estimates. When computed tomography (CT) and magnetic resonance imaging (MRI) studies were combined, AF was associated with SCIs in patients with no history of symptomatic stroke (odds ratio, 2.62 [95% CI, 1.81 to 3.80]; I(2) = 32.12%; P for heterogeneity = 0.118). This association was independent of AF type (paroxysmal vs. persistent). The results were not altered significantly when the analysis was restricted to studies that met at least 70% of the maximum possible quality score (odds ratio, 3.06 [CI, 2.24 to 4.19]). Seventeen studies reported the prevalence of SCIs. The overall prevalence of SCI lesions on MRI and CT among patients with AF was 40% and 22%, respectively.
LIMITATION: Most studies were cross-sectional, and autopsy studies were heterogeneous and not sufficiently sensitive to detect small lesions.
CONCLUSION: Atrial fibrillation is associated with more than a 2-fold increase in the odds for SCI.
REFERENCE: Kalantarian S, et al. Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta-analysis. Ann Intern Med. 2014 Nov 4;161(9):650-8.

#4: Anticoagulation assoc with lower dementia rates in AF

In a registry study from Sweden, over 440,000 adults with atrial fibrillation and no history of dementia were identified at baseline and followed for X year. During follow-up, about 6% of the cohort developed dementia (1.73 diagnoses per 100 patient-years). More than 40% of the patients were using anticoagulants at baseline (warfarin and DOACs) and had a 29% lower risk for dementia than those who hadn't been oral anticoagulants at baseline (no difference between NOACs and warfarin). Possible mechanisms include protection against microinfarcts that may lead to dementia.

Aims: The association between atrial fibrillation (AF) and dementia is well documented, but it is not clear if oral anticoagulant treatment offers protection. The aim of the study is therefore to compare the incidence of new dementia in patients with AF with and without oral anticoagulants, and to explore if there is a difference between novel anticoagulants and warfarin in this respect.
Methods and results: Retrospective registry study of all patients with hospital diagnosis of AF and no previous diagnosis of dementia in Sweden between 2006 and 2014. Propensity score matching, falsification endpoints, and analyses according to intention to treat as well as on-treatment principles were used. The study included 444 106 patients and over 1.5 million years at risk. Patients on anticoagulant treatment at baseline was associated with 29% lower risk of dementia than patients without anticoagulant treatment [hazard ratio (HR) 0.71, 95% confidence intervals (95% CI) 0.68-0.74] and 48% lower risk analysed on treatment (HR 0.52, 95% CI 0.50-055). Direct comparison between new oral anticoagulants and warfarin showed no difference (HR 0.97, 95% CI 0.67-1.40).
Conclusion: The risk of dementia is higher without oral anticoagulant treatment in patients with AF. This suggests that early initiation of anticoagulant treatment in patients with AF could be of value in order to preserve cognitive function.
REFERENCE: Friberg L et al. Less dementia with oral anticoagulation in atrial fibrillation. Eur Heart J. 2017 Oct 24. doi: 10.1093/eurheartj/ehx579.

#5: The benefit of anticoagulation is very low in AF patients with CHA2DS2-VASc score of 1

BACKGROUND: Patients with atrial fibrillation (AF) and ≥1 point on the stroke risk scheme CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category) are considered at increased risk for future stroke, but the risk associated with a score of 1 differs markedly between studies.
OBJECTIVES: The goal of this study was to assess AF-related stroke risk among patients with a score of 1 on the CHA2DS2-VASc.
METHODS: We conducted this retrospective study of 140,420 patients with AF in Swedish nationwide health registries on the basis of varying definitions of "stroke events."
RESULTS: Using a wide "stroke" diagnosis (including hospital discharge diagnoses of ischemic stroke as well as unspecified stroke, transient ischemic attack, and pulmonary embolism) yielded a 44% higher annual risk than if only ischemic strokes were counted. Including stroke events in conjunction with the index hospitalization for AF doubled the long-term risk beyond the first 4 weeks. For women, annual stroke rates varied between 0.1% and 0.2% depending on which event definition was used; for men, the corresponding rates were 0.5% and 0.7%.
CONCLUSIONS: The risk of ischemic stroke in patients with AF and a CHA2DS2-VASc score of 1 seems to be lower than previously reported.
REFERENCE: Friberg L et al. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. J Am Coll Cardiol. 2015 Jan 27;65(3):225-32.

#6: Ibutilide (Corvert®) converts AF 50% of the time in an ED setting

Ibutilide is a class III antiarrhythmic agent

STUDY OBJECTIVE: Little is known about the use of ibutilide for cardioversion in atrial fibrillation and flutter outside of clinical trials. We seek to describe patient characteristics, ibutilide administration patterns, cardioversion rates, and adverse outcomes in the community emergency department (ED) setting. We also evaluate potential predictors of cardioversion success.
METHODS: Using a retrospective cohort of adults who received ibutilide in 21 community EDs between January 2009 and June 2015, we gathered demographic and clinical variables from electronic health records and structured manual chart review. We calculated rates of cardioversion and frequency of ventricular tachycardia within 4 hours and estimated adjusted odds ratios (aOR) in a multivariate regression model for potential predictors of cardioversion.
RESULTS: Among 361 patients, the median age was 61 years (interquartile range 53 to 71 years) and most had recent-onset atrial fibrillation and flutter (98.1%). Five percent of the cohort had a history of heart failure. The initial QTc interval was prolonged (>480 ms) in 29.4% of patients, and 3.1% were hypokalemic (<3.5 mEq/L). The mean ibutilide dose was 1.5 mg (SD 0.5 mg) and the rate of ibutilide-related cardioversion within 4 hours was 54.8% (95% confidence interval [CI] 49.6% to 60.1%), 50.5% for atrial fibrillation and 75.0% for atrial flutter. Two patients experienced ventricular tachycardia (0.6%), both during their second ibutilide infusion. Age (in decades) (aOR 1.3; 95% CI 1.1 to 1.5), atrial flutter (versus atrial fibrillation) (aOR 2.7; 95% CI 1.4 to 5.1), and no history of atrial fibrillation and flutter (aOR 2.0; 95% CI 1.2 to 3.1) were associated with cardioversion.
CONCLUSION: The effectiveness and safety of ibutilide in this community ED setting were consistent with clinical trial results despite less stringent patient selection criteria.
REFERENCE: Vinson DR, et al for the Pharm CAFÉ Investigators of the CREST Network. Ibutilide Effectiveness and Safety in the Cardioversion of Atrial Fibrillation and Flutter in the Community Emergency Department. Ann Emerg Med. 2017 Sep 29. pii: S0196-0644(17)31381-1.

#7: Important drug-drug interactions exist with NOACs

Drugs that inhibit the activity of P-glycoprotein and/or cytochrome P450 3A4, such as antiarrhythmics (e.g., amiodarone, diltiazem, verapamil), antiretrovirals, antifungals (fluconazole) and immunosuppressives, can increase OAC levels

Importance: Non-vitamin K oral anticoagulants (NOACs) are commonly prescribed with other medications that share metabolic pathways that may increase major bleeding risk.
Objective: To assess the association between use of NOACs with and without concurrent medications and risk of major bleeding in patients with nonvalvular atrial fibrillation.
Design, Setting, and Participants: Retrospective cohort study using data from the Taiwan National Health Insurance database and including 91 330 patients with nonvalvular atrial fibrillation who received at least 1 NOAC prescription of dabigatran, rivaroxaban, or apixaban from January 1, 2012, through December 31, 2016, with final follow-up on December 31, 2016.
Exposures: NOAC with or without concurrent use of atorvastatin; digoxin; verapamil; diltiazem; amiodarone; fluconazole; ketoconazole, itraconazole, voriconazole, or posaconazole; cyclosporine; erythromycin or clarithromycin; dronedarone; rifampin; or phenytoin.
Main Outcomes and Measures: Major bleeding, defined as hospitalization or emergency department visit with a primary diagnosis of intracranial hemorrhage or gastrointestinal, urogenital, or other bleeding. Adjusted incidence rate differences between person-quarters (exposure time for each person during each quarter of the calendar year) of NOAC with or without concurrent medications were estimated using Poisson regression and inverse probability of treatment weighting using the propensity score.
Results: Among 91 330 patients with nonvalvular atrial fibrillation (mean age, 74.7 years [SD, 10.8]; men, 55.8%; NOAC exposure: dabigatran, 45 347 patients; rivaroxaban, 54 006 patients; and apixaban, 12 886 patients), 4770 major bleeding events occurred during 447 037 person-quarters with NOAC prescriptions. The most common medications co-prescribed with NOACs over all person-quarters were atorvastatin (27.6%), diltiazem (22.7%), digoxin (22.5%), and amiodarone (21.1%). Concurrent use of amiodarone, fluconazole, rifampin, and phenytoin with NOACs had a significant increase in adjusted incidence rates per 1000 person-years of major bleeding than NOACs alone: 38.09 for NOAC use alone vs 52.04 for amiodarone (difference, 13.94 [99% CI, 9.76-18.13]); 102.77 for NOAC use alone vs 241.92 for fluconazole (difference, 138.46 [99% CI, 80.96-195.97]); 65.66 for NOAC use alone vs 103.14 for rifampin (difference, 36.90 [99% CI, 1.59-72.22); and 56.07 for NOAC use alone vs 108.52 for phenytoin (difference, 52.31 [99% CI, 32.18-72.44]; $P < .01$ for all comparisons). Compared with NOAC use alone, the adjusted incidence rate for major bleeding was significantly lower for concurrent use of atorvastatin, digoxin, and erythromycin or clarithromycin and was not significantly different for concurrent use of verapamil; diltiazem; cyclosporine; ketoconazole, itraconazole, voriconazole, or posaconazole; and dronedarone.
Conclusions and Relevance: Among patients taking NOACs for nonvalvular atrial fibrillation, concurrent use of amiodarone, fluconazole, rifampin, and phenytoin compared with the use of NOACs alone, was associated with increased risk of major bleeding. Physicians prescribing NOAC medications should consider the potential risks associated with concomitant use of other drugs.
REFERENCE: Chang SH et al. Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation. JAMA. 2017 Oct 3;318(13):1250-1259.

Bridging

Annually about 10% of patients on oral anticoagulants require treatment interruption for an invasive procedure associated with a bleeding risk, bridging aims to reduce the risk of thrombotic events. The effectiveness and safety of bridging is negligible. Due to the long half-life of warfarin (~42 hours) periprocedural birding is only relevant for warfarin. In my opinion, this issue will likely become less relevant with the increasing use of DOACs (which have shorter half-lives) and the decreasing use of warfarin. According to the ACC “Given the short-half lives of DOACs, bridging with a parenteral agent is rarely, if ever, needed prior to procedures.”

Bridging: The process whereby an OAC is discontinued and replaced by a subcutaneous or intravenous anticoagulant before and/or following an invasive procedure.(ACC)

In abstract #5 below the average CHADS2Vasc score was 2.3 (not included in the abstract), and the rate of thromboembolism in NVAF patients was 0.4% in both bridged and non-bridged patients.

#8: Perioperative bridging associated with more bleeding and no thrombosis prevention

METHODS: In the 108-center North American BRIDGE trial, managed at Duke University, 1,884 adults (mean age, 71.7) with AF and at least one stroke risk factor who required discontinuation of maintenance warfarin for performance of an elective procedure were randomized to perioperative bridging or no bridging. Patients at high risk of thromboembolism were excluded, and most procedures were at relatively low risk for bleeding. Warfarin was discontinued five days before the procedure, and dalteparin or placebo was started three days before the procedure and resumed 12-24 hours or 48-72 hours after procedures associated with a low or high bleeding risk. Warfarin was restarted after the procedure, and dalteparin or placebo was continued until a single INR was 2.0 or higher.
RESULTS: Outcome data were available for 1,813 patients. By 30 days, arterial thromboembolic events (the primary efficacy outcome) occurred in 0.4% of the no-bridging group and 0.3% of the bridging group, and major bleeding (the primary safety outcome) occurred in

1.3% of the no-bridging group but in 3.2% of the bridging group (relative risk [RR] in the no-bridging group 0.41, 95% CI 0.20-0.78, p=0.005). Rates of minor bleeding were 12.0% in the no-bridging group vs. 20.9% in the bridging group (p<0.001). There were no significant differences between the groups in the secondary outcomes of myocardial infarction, deep vein thrombosis or pulmonary embolism, or death.
CONCLUSIONS: In patients with AF who require warfarin discontinuation for elective procedures, perioperative bridging did not significantly reduce the risk of arterial thromboembolism but increased the rate of major and minor bleeding. 46 references (thomas.ortel@duke.edu for reprints)
Reference: Douketis, J.D., et al, PERIOPERATIVE BRIDGING ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION. N Engl J Med 373(9):823, August 27, 2015

#9: Perioperative bridging associated with more bleeding and no thrombosis prevention

BACKGROUND: Periprocedural heparin bridging therapy aims to reduce the risk of thromboembolic events in patients requiring an interruption in their anticoagulation therapy for the purpose of an elective procedure. The efficacy and safety of heparin bridging therapy has not been well established.
OBJECTIVES: To compare through meta-analysis the effects of heparin bridging therapy on the risk of major bleeding and thromboembolic events of clinical significance among patients taking oral anticoagulants.
METHODS: We searched PubMed, EMBASE and the Cochrane library from January 2005 to July 2016. Studies were included if they reported clinical outcomes of patients receiving heparin bridging therapy during interruption of oral anticoagulant for operations. Data were pooled using random-effects modeling.
RESULTS: A total of 25 studies, including 6 randomized controlled trials and 19 observational studies, were finally included in this analysis. Among all the 35,944 patients, 10,313 patients were assigned as heparin bridging group, and the other 25,631 patients were non-heparin bridging group. Overall, compared with patients without bridging therapy, heparin bridging therapy increased the risk of major bleeding (OR = 3.23, 95%CI: 2.06-5.05), minor bleeding (OR = 1.52, 95%CI:1.06-2.18) and overall bleeding (OR = 2.83, 95%CI: 1.86-4.30).While there was no significant difference in thromboembolic events (OR = 0.99,95%CI: 0.49-2.00), stroke or transient ischemic attack(OR = 1.45, 95%CI: 0.93-2.26,) or all-cause mortality (OR = 0.71, 95%CI: 0.31-1.65).
CONCLUSIONS: Heparin-bridging therapy increased the risk of major and minor bleeding without decreasing the risk of thromboembolic events and all cause death compared to non-heparin bridging.
REFERENCE Yong JW et al. Periprocedural heparin bridging in patients receiving oral anticoagulation: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2017 Dec 13;17(1):295.

Managing DOACS (ACC AHH Expert Document)

In 2017, the ACC AHA published 2 Expert Consensus Decision Pathways related to anticoagulation. One provided guidance on the management of bleeding in anticoagulated patients; and the other on the peri- procedural management of anticoagulation. Note that expert consensus documents are "…intended to provide guidance for clinicians in areas in which evidence may be limited or new and evolving"

#10: Oral anticoagulants and Planned Procedures

Reference: Doherty JU, et al.2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017 Feb 21;69(7):871-898
Planned invasive interventions are performed in NOAC-treated patients with a current annual rate of 10% and temporary interruption (TI) is commonly required. NOACs have a rapid onset of action (peak anticoagulant effect occurs within 2 h after oral intake), and the off-set of NOACs is also relatively rapid, *with half-lives of ~ 12 h for patients with normal renal function*, (note these are renally excreted thus will have with prolonged half-lives, particularly for dabigatran, in patients with impaired renal function). The half-life of warfarin is ~ 42 hours, thus periprocedural anticoagulation management differs substantially between these two classes of drugs. Also complicating periprocedural anticoagulation management is the absence of easily available and reliable laboratory tests to quantify residual anticoagulant effects of NOACs.

Temporary Interruption (TI) of Oral Anticoagulants

<u>For Warfarin TI</u>

1. Measure INR 7 days prior to planned procedure
2. DC warfarin:

- 7 days if INR supratherapeutic
- 5 days if INR therapeutic
- 4 days if INR subtherapeutic

3. Recheck INR 24 hours prior to planned procedure

For DOAC TI

1. The duration for which a DOAC should be withheld depends on the:
    a. Procedural bleed risk
    b. Specific DOAC and
    c. Creatinine clearance

Estimating Procedural Risk

Most commonly performed procedures into four bleeding risk levels

1) No clinically important risk
2) Low procedural risk
3) Uncertain risk
4) Intermediate or high risk

Although a bit overwhelming, to obtain the estimated risks of bleeding with almost any procedure click on the document link below:

http://jaccjacc.acc.org/Clinical_Document/PMAC_Online_Appendix.pdf

An example of what appears in this document is identified below

American Academy of Ophthalmology

Procedure Name	Bleed Risk Level				
	Very Low	Low	Intermediate	High	Uncertain
Intravitreal injection with a pharmacologic agent	☒	☐	☐	☐	☐
Cataract Surgery with Intraocular Lens	☒	☐	☐	☐	☐
After-cataract laser surgery	☒	☐	☐	☐	☐
Complex cataract surgery	☒	☐	☐	☐	☐
Closure of tear duct opening	☒	☐	☐	☐	☐
Trabeculoplasty by laser surgery	☒	☐	☐	☐	☐
Revision of eyelashes	☒	☐	☐	☐	☐
Treatment of extensive or progressive retinopathy, photocoagulation	☒	☐	☐	☐	☐
Destruction of localized lesion of retina, photocoagulation	☒	☐	☐	☐	☐
Revision of iris	☒	☐	☐	☐	☐
pars plana vitrectomy (particularly in diabetics)	☐	☒	☐	☐	☐
Orbital surgery	☐	☒	☐	☐	☐
certain eyelid procedures such as blepharoplasty	☐	☒	☐	☐	☐

The Specific DOAC and Creatinine Clearance

DOAC's and planned procedures

Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					**Apixaban, Edoxaban, Rivaroxaban**		
CrCl, mL/min	> 80	50-79	30-49	15-29	< 15	> 30	15-29	< 15
Estimated drug half-life, h	13	15	18	27	30	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban:9	Apixaban: 17 Edoxaban: 10-17 Rivaroxaban:13
Procedural bleed risk								
Low	**≥24**	**≥36**	**≥48**	**≥72**	**No data** Measure dTT and/or withhold > 96 hours	**≥24**	**≥36**	No data Measure agent specific antiXa level and or/ withhold > 48 hours
Uncertain, intermediate or high	**≥48**	**≥72**	**≥96**	**≥120**	**No data** Measure dTT	**≥48**	No data Measure agent specific antiXa level and or/ withhold > 72 hours	

NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

To Bridge or Not (for those on Warfarin)

Bridging Guidance Statements for those on warfarin

Bridging based upon

1. Patients bleeding risk
2. Patients CVA risk

a. CHAD2Ds2-Vasc score or recent history of ischemic stroke, TIA, or SE

1. No bridging
    a. Low risk for thromboembolism (CHA2DS2-VASc score ≤4), AND
    b. No prior history of ischemic stroke, TIA, or SE

2. No bridging
    a. Moderate risk for thromboembolism (CHA2DS2-VASc score 5 - 6), OR
    b. No prior history of ischemic stroke, TIA, or SE (3 months previous)
    c. Increase bleed risk

3. No bridging
    a. Moderate risk for thromboembolism (CHA2DS2-VASc score 5 - 6), OR
    b. Prior history of ischemic stroke, TIA, or SE (3 months previous)
    c. Increase bleed risk“

4. Likely” bridge | No increase bleed risk
    a. Moderate risk for thromboembolism (CHA2DS2-VASc score 5 - 6),
    b. Prior history of ischemic stroke, TIA, or SE (3 months previous)

5. “Likely” DO NOT bridge | | No increase bleed risk
    a. Moderate risk for thromboembolism (CHA2DS2-VASc score 5 - 6),
    b. No prior history of ischemic stroke, TIA, or SE (3 months previous)
6. “Consider” bridging
    a. High risk for thromboembolism (CHA2DS2-VASc score 7-9), OR
    b. Prior history of ischemic stroke, TIA, or SE (3 months previous)

For Bridging

- Start parenteral anticoagulant therapy when the INR is no longer therapeutic (e.g., <2.0 in those with NVAF)
- Unfractionated heparin discontinued 4 to 6 hours prior to the procedure, with guidance using the activated partial thromboplastin time for earlier time points.
- Low Molecular Weight Heparin (LMWH) discontinued at least 24 hours prior to the procedure (earlier in those with renal insufficiency), with the option,

Bridging not relevant with DOACs

- According to the ACC Expert Consensus document “The DOACs have short half-lives that obviate the need to administer an alternative anticoagulant during TI in the majority of situations.”

#11: Major bleeds with DOACS

REFERENCE: Tomaselli GF et al.2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Dec 19;70(24):3042-3067. (no abstract)

Major bleeds are defined as one or more of the following: 1) Critical site bleed (e.g. ICH, intraocular, spinal, retroperitoneal, intra thoracic or intraabdominal, intraarticular and intramuscular sites). All of these can compromise an organs function. 2) Hemodynamic instability (e.g. SBP < 90 or a decrease

in BP of > 40 mmHg or 20 mmHg decrease in orthostatic BP, or MAP < 65). 3) Overt bleeding with a Hgb decrease of 2 g/dL or need for > 2 u PRBcs

Pearls: (from the ACC/AHA Guideline)

No specific antidotes available for reversal of FXa inhibitors (apixiban, edoxaban or rivaroxaban) Dabigitran specific reversal agent is idarucizumab 5 grams IV | Also dabigatran is the only OAC that can be removed by hemodialysis

For major bleeding and recent ingestion (within 2 – 4 hours), consider activated charcoal
For reversal for FXa inhibitors (or for Dabigitran if idarucizumab is not available) use **prothrombin complex concentrates (PCCs)**

There are three types of PCCs

- Nonactivated 3-factor PCCs contain FII (i.e. prothrombin), FIX, and FX with negligible FVII, protein C, and S,
- Nonactivated 4F-PCCs contain FII, **FVII**, FIX, FX, and protein C and S.
- Activated PCC (aPCC) contain 4 coagulation factors (both inactive and active forms of II, VII IX and X)
    - (aPCCs (are PCCs that contain at least 1 factor in the activated form mostly developed and used for patients with hemophilia who have bleeding in the setting of a factor inhibitor factor eight inhibitor bypassing activity) - contain 4 coagulation factors (both inactive and active forms of II, VII IX and X))
- PCCs contain purified vitamin K–dependent clotting factors, they:
    - Do not require ABO compatibility (fresh frozen plasma does)
    - Can be rapidly reconstituted and infused (FFP needs to be thawed)
    - Can be infused with lower volumes (FFP requires larger volumes)
    - Dosed (for warfarin reversal) at 25 - 50 units/kg or fixed dose 1000 units for any manor bleed or 1500 units for ICH; OR 50 units/kg for FXa (apixiban, edoxaban or rivaroxaban) reversal

Reversal Agent	Vitamin K Antagonists (Warfarin)	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, Edoxaban and Rivaroxaban)
4F-PCC	First Line	Second line	First Line
aPCC	Not indicated	Second line	Second line
Idarucizumab	Not indicated	First Line	Not indicated
Plasma	If 4F-PCC is not available	Not indicated	Not indicated
4F-PCC = 4 factor prothrombin complex; **aPCC** = activated prothrombin complex concentrate			

#12: Watchman device = warfarin after 5 years for VTE prevention and better for ↓ bleeding

BACKGROUND: The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, St. Paul, Minnesota) was equivalent to warfarin for preventing stroke in atrial fibrillation, but had a high rate of complications. In a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term

Warfarin Therapy), the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy endpoints inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time.
OBJECTIVES: The final results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF trial, are reported with patients in both trials followed for 5 years.
METHODS: PREVAIL and PROTECT AF are prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 patients for 4,343 patient-years. Analyses are by intention-to-treat, and rates are events per 100 patient-years.
RESULTS: For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; p = 0.27), as were all-stroke/SE (HR: 0.961; p = 0.87). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p = 0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; p = 0.0022; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively).
CONCLUSIONS: These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial; demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; NCT00129545; and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; NCT01182441).
REFERENCE: Reddy VY et al PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials.J Am Coll Cardiol. 2017 Dec 19;70(24):2964-2975.

Bottom Lines

1. For AF, the AAFP recommends lenient rate control, (vs rhythm control and strict rate control), use of chronic anticoagulation for AF patient with a CHADS score $\geq$ 2 and recommends against DAPT
2. Subclinical atrial fibrillation (AF) is common and AF is a risk factor for silent cerebral infarcts and anticoagulation for AF is associated with lower dementia
3. Ibutilide (Corvert®) converts AF 50% of the time in an ED setting
4. Periprocedural heparin bridging in patients receiving oral anticoagulation is not effective for those with an average CHADS score of 2-3
5. Direct Acting Oral Anticoagulants (DOACs) have several important drug-drug interactions
6. Periprocedural management of patients on DOACS includes understand the bleeding risk of the procedure and the patients creatinine clearance
7. The ACC Expert Consensus Decision Pathways on managing bleeding in many patients on factor Xa inhibitors includes prothrombin complex concentrate

Useful Tools for the Point of Care Diagnosis

Mark Ebell, MD, MS

Objectives

1. Learn a framework for evaluating point of care tests, and when to use them
2. Understand how to interpret c-reactive protein tests in patients with acute infection
3. Understand how to integrate the history and physical with point of care testing.

When thinking about tests for the point of care, it's helpful to use the following framework (thanks to my friends Dave Slawson of UNC-Charlotte and Allen Shaughnessy of Tufts):

1. How accurate is the test/exam/procedure?
2. If we order the test, will it change the diagnosis of the patient?
3. If we order the test, will it change the treatment of the patient?
4. Finally, and most importantly, if we order the test will patient outcomes be improved?

Usually, we're lucky just to know how accurate the test is in a primary care population! If diagnosis is improved, you have to ask: is that a good thing? Does it lead to better targeted therapy, known to improve patient outcomes (an indirect chain of evidence)? Or just one more diagnosis, more worry, and the like? Unfortunately direct evidence of improved patient oriented outcomes from a study randomizing patients to test or no test is incredibly rare.

A useful framework for clinical decision making is to think of patients with an undifferentiated symptom like sore throat, chest pain, or leg pain as falling in one of three groups:

- Disease is so unlikely that we can rule it out (for now, at least)
- Disease is so likely that we can rule it in and initiate therapy
- The likelihood of disease lies somewhere in the middle, and we need more information before we are comfortable ruling-in or ruling-out

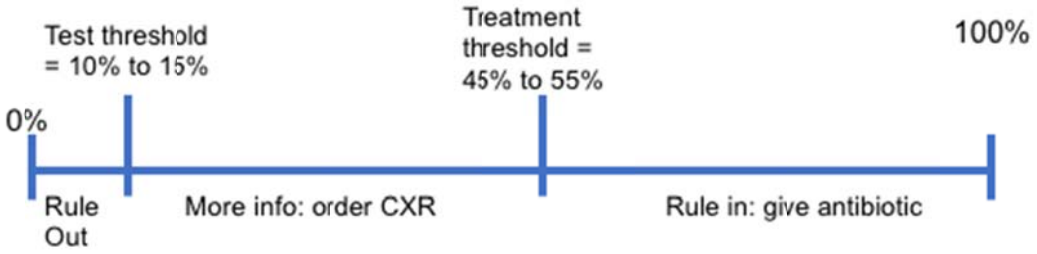
This the threshold theory of decision making in a nutshell, and is summarized graphically below:

So, how are these magical test and treatment thresholds determined? It depends on:

- The accuracy of diagnostic tests
- The risk of treatment (if we over-treat, will that cause harm?)
- The risk of testing (if we order more tests, will that cause harm?)
- The benefit of treatment

There are fancy formulas, but physicians never use them, and it's not clear that other factors don't come into play like culture, risk avoidance, patient preference, and the like. You usually will be setting the thresholds implicitly, rather than explicitly, in the real world. That's OK, it likely varies with your risk tolerance and whether or not the patient is a malpractice attorney.

From research that we have done using simulated patient cases with known probabilities of disease, a sample threshold diagram for patients presenting with acute cough, with options of rule-out, CXR, or rule-in, are shown below:



With this as background, let's discuss some common clinical scenarios.

Cough

Scenario: A patient presents with a 3-day history of cough productive of yellowish green sputum and a runny nose. He is not short of breath, his measured temp is 100.6 F, his heart rate is 80 bpm, and his lung exam reveals crackles (rales) but breath sounds are not decreased. What is the likelihood of community-acquired pneumonia? What should you do?

Heckerling Score

This is an older clinical decision rule, developed in one center and validated in two others. You count up the total number of signs and symptoms ("predictors") and then find the likelihood of pneumonia:

				Posttest Probability of pneumonia (%)	
Signs and Symptoms		**Total # predictors**	**LR**	**Primary care (pretest prob 5%)**	**ED (pretest prob 15%)**
Temp > 37.8 C (100 F)		0	0.12	1%	2%
HR > 100		1	0.2	1%	3%
Rales		2	0.7	4%	11%
Decreased breath sounds		3	1.6	8%	22%
No h/o asthma		4	7.2	27%	56%
# of predictors:		5	17	47%	75%

Hecklering PS, Tape TG, Wigton RS, et al. Clinical prediction rule for pulmonary infiltrates. Ann Intern Med 1990; 113: 664-70

Pneumonia Rule Out Score

Sometimes, ruling out is as helpful as ruling in. A systematic review (Marchello, in press) identified four studies of patients with cough or clinically suspected pneumonia. It found that normal vitals and a normal chest exam was very good at ruling out pneumonia (LR- 0.10). Among patients with CAP, 96% had at least one abnormal vital sign or chest finding on exam.

Primary care overall CAP risk = 5% → with normal vitals and chest exam risk of CAP = 0.5%

ED overall CAP risk = 20% → with normal vitals and chest exam risk of CAP = 2.4%

The c-reactive protein is a general measure of inflammation. It has been well studied for the diagnosis of pneumonia in patients with cough, bacterial sinusitis in patients with sinus symptoms, and for the identification of patients with cough likely to have a benign course.

GRACE pneumonia score

This score was developed from a large European primary care study that enrolled 2820 patients with acute cough and got a chest radiograph on all of them:

Sign or symptom	Points
No runny nose	1

Risk group	LR	CAP/total (%)
0 (low)	0.13	4/572 (0.7%)

Breathlessness	1
Crackles	1
Diminished breath sounds	1
HR > 100/min	1
Temp > 37.8C	1
CRP > 30 mg/L	1

1 -2 (intermediate)	0.76	73/1902 (3.8%)
3+ (high)	4.3	63/346 (18.2%)

Van Vugt S, et al. BMJ 2013; 346: f2450

Steurer/Held low risk cough score

C-reactive protein is also part of a simple heuristic developed by Steurer, Held and colleagues. They developed it in Switzerland, and validated it in Germany.

Low risk for CAP: **CRP < 10 mcg/ml** OR **CRP 11 – 50 mcg/ml, no dyspnea, and no daily fever since onset**

	CAP / total
CRP < 10 mcg/ml	0/123 (0%)
CRP 11 – 50 mcg/ml, no dyspnea, and no daily fever since onset	0/67 (0%)
CRP 11-50 and either dyspnea or daily fever	25/191 (13%)
CRP > 50 mcg/ml	102/240 (42%)

CRB-65 Score for Prognosis of CAP

This is a widely used and recommended score that is simple enough to memorize.

Characteristic	**Points**		**Score**	**Recommendation (British Thoracic Society)**
Confusion	1		**0**	Very low risk, do not normally require hospitalization
Respiratory rate >= 30/min	1		**1 to 2**	Increased risk of death – consider hospitalization
S**B**P < 90 or DBP < 60	1		**3 or 4**	High risk of death, urgent hospitalization
65 years	1			
Total:				

We are doing a meta-analysis of over and found the following overall estimates of accuracy:

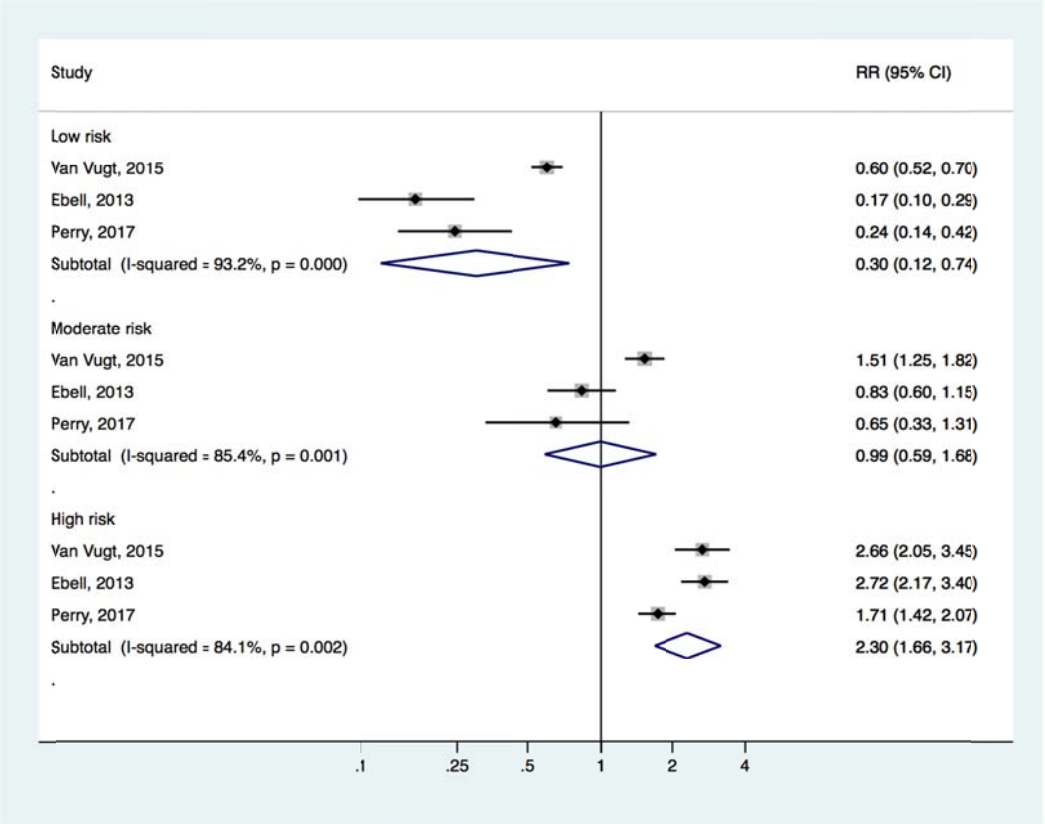
Risk group	**LR**	**3% overall mortality**	**5% overall mortality**	**10% overall mortality**
Low (0)	0.16	0.5%	0.8%	1.7%
Moderate (1-2)	0.96	2.8%	4.8%	9.6%
High (3-4)	4.3	11%	18%	32%

Influenza

We developed a simple score using 4 symptoms or combinations of symptoms (no physical exam needed) to determine the likelihood of influenza. It has been evaluated in two new populations:

Symptom(s)	**Points**		**Risk group**	**% flu**	**Action**
Fever and cough	2		Low (0-2)	6%	Flu ruled out
Myalgias	2		Mod (3)	26%	Consider rapid test
Chills or sweats	1		High (4-6)	58%	Treat
Onset < 48 hours	1				

Meta-analysis of original study, plus prospective validation in 280 college students with influenza-like illness (50% flu prevalence) and retrospectively in large European cohort of patients with (10% flu prevalence):



Summary estimates of likelihood ratios

Low risk: 0.30

Moderate risk: 0.99

High risk: 2.30

Advantage of Flu Score is that it can be used over the phone or by medical assistants, as it is symptom only, for triage.

Sore throat

Strep score

The classic! Developed almost 30 years ago by Robert Centor, MD at UAB:

Clinical finding	Points
Fever (Subj or objective)	1
Adenopathy	1
Absence of cough	1
Purulent or enlarged tonsils	1
Age	
< 15 years	1
15 to 45 years	0
> 45 years	-1
Total points:	

Points	Probability of strep
< 1	2%
1, 2 or 3	18%
4 or 5	52%

A newer option is the FeverPAIN score, which predicts both Group A and C strep:

Finding	Points		Score	Group A or C strep	Treatment
Fever in past 24 hrs	1		0 or 1	18%	Symptomatic
No cough or coryza	1		2 or 3	40%	Rapid test
Symptom onset <= 3 d.	1		>= 4	65%	Antibiotics
Purulent tonsils	1				
Severe tonsil inflammation	1				

Chest pain

This is a consortium of researchers, who combined 6 datasets and came up with the best clinical decision rule for evaluating chest pain in the primary care setting:

Clinical predictor	Points		Risk Group	CAD/total (%)
Pain reproduced by palpating chest wall	-1		Low risk (-1 - 0)	1/295
Older age (male ≥ 55 years; female ≥ 65 years)	+1		Mod risk (1 - 2)	17/245
Physician initially suspected a serious condition	+1		High risk (3+)	67/104
Chest discomfort feels like “pressure”	+1			
Chest pain related to effort	+1			
History of CAD	+1			
Total:				

Urinary tract infection

The aptly named DUTY (as in do your) score predicts the likelihood of UTI in kids. It is nice because you begin without requiring a urine specimen (never fun to get from the little ones). Only if high risk do you then go on to get the urine specimen, which is very practical in primary care.

TABLE 1

The DUTY Clinical Decision Rules

Signs and symptoms model

Clinical characteristic	Points
Pain/crying when passing urine	2
Smelly urine (parental report)	2
Previous UTI	1
Absence of severe cough*	2
Severe illness present†	2
Total:	____

Total points	UTI diagnoses/ total patients (%)	LR‡
0 to 2	9/2,003 (0.45%)	0.20
3 or 4	20/562 (3.6%)	1.6
5 or more	31/175 (17.7%)	9.6

Signs, symptoms, and dipstick model

Clinical characteristic	Points
Pain/crying when passing urine	2
Smelly urine (parental report)	2
Previous UTI	1
Absence of severe cough*	2
Severe illness present†	2
Dipstick urine analysis positive for:	
Leukocytes	2
Nitrites	3
Blood	1
Total:	____

Total points	UTI diagnoses/ total patients (%)	LR‡
0 to 5	13/2,444 (0.53%)	0.24
6 to 8	18/240 (7.5%)	3.6
9 or more	29/56 (51.8%)	48.0

DUTY = Diagnosis of Urinary Tract Infection in Young Children; LR = likelihood ratio; UTI = urinary tract infection.

*—Parents were given four levels to choose from for severity of cough: no problem, slight problem, moderate problem, or severe problem.
†—Defined as a score of 6 or more on the clinician global illness severity scale, with a range of 0 (child completely well) to 10 (child extremely unwell).
‡—An LR less than 1 reduces the likelihood of UTI, and an LR more than 1 increases the likelihood of UTI.

Information from reference 1.

Take Home Points

1. It is helpful to think in terms of patients in whom you can rule out disease, patients in whom you need more information, and patients that you can initiate treatment in.
2. Clinical decision rules can improve diagnosis of influenza, sore throat, cough, community-acquired pneumonia, and UTI.
3. Point of care tests such as CRP, rapid strep test, and rapid flu test should be used selectively and not for all patients.

Vitamins: to take or not to take, that is the question John Hickner MD, MSc

Objectives

1. Know the value of a variety of vitamins for prevention and disease treatment

2. Know the conditions for which Vitamin D supplementation is effective or ineffective or unknown

Vitamin supplementation other than Vitamin D

Vitamins are a multi-billion dollar business. Unfortunately, solid evidence from RCTs for effectiveness of vitamin therapy is scarce. Here are a few studies about vitamins published in the past few years. There is not a whole lot that is new, other than Vitamin D, which is the current darling child of vitamin researchers.

1. B vitamins produce small increase in sustained depression remission

Clinical question: Does B vitamin supplementation enhance response to antidepressants?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Drawing on epidemiologic research that found a relationship between B vitamin deficiency and anemia with depression, the authors of this Australian study tested a B vitamin supplement on 153 patients. The patients were referred by their primary care physician or were drawn from a survey of adults who were found to have moderate depression but were not yet being treated. The patients were randomly assigned, using concealed allocation, to treatment with citalopram plus a combination of 0.5 mg vitamin B12, 2 mg folic acid, and 25 mg vitamin B6, or to citalopram plus placebo. Citalopram doses were adjusted to a maximum of 40 mg daily. Citalopram was continued, or the antidepressant was changed, for 9 months in patients who achieved remission, at the discretion of the treating physician, and B vitamin or placebo was continued. Remission (resolution of depression scores) within 3 months occurred in approximately 78% of patients in both groups. However, more patients who were taking the supplement were in remission after 1 year (85.5% vs 75.8%). A few caveats: The study was small, patients had more severe depression than typically seen in primary care, and the response to the antidepressant in both groups was higher than is typical.
Bottom line: The addition of B vitamins -- cyanocobalamin, thiamine, and folate -- to antidepressant medication in patients with moderate depression does not improve the initial response rate but increases the percentage of patients in remission after 1 year. This effect was more pronounced in patients with higher baseline homocysteine levels, a marker of low B vitamin status. The effect in this study was small, but given their low expense and low risk B vitamin supplements could be tried in some patients.
Almeida OP, Ford AH, Hirani, V, et al. B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. Br J Psychiatry 2014;205(6):450-457. doi: 10.1192/bjp.bp.114.145177.

2. Nicotinamide reduces recurrent non-melanoma skin cancers in high-risk patients

Clinical question: Does nicotinamide reduce the likelihood of new nonmelanoma skin cancers in high-risk patients?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: Previous studies have shown that nicotinamide (vitamin B3) may improve cell repair and can reduce the likelihood of actinic keratoses. In this Australian study (Australia, with its combination of pale inhabitants and lots of sun, is the epicenter of skin cancer), 386 adults with at least 2 previous nonmelanoma skin cancers (NMSC) were randomized to receive nicotinamide 500 mg twice daily or matching placebo. Patients who were immunosuppressed, pregnant, who had significant comorbidities, or were currently taking medications for actinic keratosis (eg, fluorouracil) were excluded. The patients' mean age at enrollment was 66 years, 63% were men, and 47% were never smokers. These folks had a lot of skin cancers: a mean of 8 NMSC (6 basal cell and 2 squamous cell) in the previous 5 years. Clearly, this was a very high-risk group. They were evaluated every 3 months by dermatologists masked to treatment assignment, and followed up for 12 months. The mean number of new NMSC during the year of active treatment was lower with nicotinamide (1.8 vs 2.4; P = .02), with a trend toward both fewer basal cell cancers (1.3 vs 1.7; P = .12) and squamous cell cancers (0.5 vs 0.7; P = .05). The relative reduction was 23%. During the 6 months after the intervention the benefit went away, with no differences between groups. There was no difference between groups in melanomas or serious adverse events.
Bottom line: For patients at very high risk of nonmelanoma skin cancers (NMSC), with a mean of 8 such cancers in the previous 5 years, nicotinamide 500 mg twice daily provides a modest reduction of 0.6 fewer lesions in 12 months of treatment.
Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 2015;373(17):1618-1626.

3. Carotenoids and omega-3 fatty acids do not effect rate of cognitive function decline

Clinical question: Can an increased dietary intake of carotenoids (lutein plus zeaxanthin), omega-3 fatty acids, or both, reduce the rate of cognitive function decline in adults with age-related macular degeneration?
Study design: Systematic review
Setting: Outpatient (specialty)

Synopsis: Previous studies from the Age-Related Eye Disease Study (AREDS) reported that adding the carotenoids lutein and zeaxanthin and/or omega-3 fatty acids as daily oral supplements to standard antioxidant vitamins and minerals did not further reduce the risk of advanced AMD. As part of the AREDS these investigators identified adults, aged 50 to 85 years, at high risk for progression to advanced AMD with either bilateral large drusen or large drusen in one eye and advanced AMD in the other eye. Consenting patients (N = 3741) eligible for an add-on cognitive function study randomly received assignment (concealed allocation assignment) to 1 of 4 treatment groups: (1) omega-3 fatty acids (1g), (2) the carotenoids lutein (10 mg) and zeaxanthin (2 mg), (3) both the omega-3s and the carotenoids, or (4) matched placebo. All patients were also given varying combinations of vitamins C, E, beta carotene, and zinc. Individuals who assessed outcomes using a standard cognitive function battery test remained masked to treatment group assignment. Testing occurred 3 months after randomization and then approximately every 2 years. Follow-up with at least 2 interviews occurred for 93% of participants. Using intention-to-treat analysis, the authors found no significant differences between the treatment groups in the rate of cognitive function decline for a mean of 4.9 years. Similarly, no significant difference in cognitive function decline occurred in high-zinc versus low-zinc groups nor in groups with or without beta carotene. Multiple analyses were performed to adjust for potential confounding factors, including age, sex, race, education, depression, and history of hypertension. No clinically significant differences in reported serious adverse events occurred. The study was adequately powered to have a 85% chance of detecting a pre-determined clinically significant difference between the treatment groups.
Bottom line: Adding the carotenoids lutein and zeaxanthin and/or omega-3 fatty acids as daily oral supplements to standard antioxidant vitamins and minerals did not reduce the rate of cognitive function decline in adults with advanced age-related macular degeneration (AMD). A similar study in the same issue also found no benefit to moderate-intensity physical activity in reducing cognitive function decline in the elderly.
Chew EY, Clemons TE, Agron E, et al, for the Age-Related Eye Disease Study 2 (AREDS2) Research Group. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function. The AREDS2 randomized clinical trial. JAMA 2015;314(8):791-801.

4. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration: Cochrane

Background: It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption. Higher dietary levels of antioxidant vitamins and minerals may reduce the risk of progression of age-related macular degeneration (AMD).
Objectives: The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD.
Search methods: We searched CENTRAL (2017, Issue 2), MEDLINE Ovid (1946 to March 2017), Embase Ovid (1947 to March 2017), AMED (1985 to March 2017), OpenGrey (System for Information on Grey Literature in Europe, the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 29 March 2017.
Selection criteria: We included randomised controlled trials (RCTs) that compared antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention, in people with AMD.
Data collection and analysis: Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5; the other author checked the data entry. We graded the certainty of the evidence using GRADE.
Main results: We included 19 studies conducted in USA, Europe, China, and Australia. We judged the trials that contributed data to the review to be at low or unclear risk of bias.Nine studies compared multivitamins with placebo (7 studies) or no treatment (2 studies) in people with early and moderate AMD. The duration of supplementation and follow-up ranged from nine months to six years; one trial followed up beyond two years. Most evidence came from the Age-Related Eye Disease Study (AREDS) in the USA. People taking antioxidant vitamins were less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 2445 participants; 3 RCTs; moderate-certainty evidence). In people with very early signs of AMD, who are at low risk of progression, this would mean that there would be approximately 4 fewer cases of progression to late AMD for every 1000 people taking vitamins (1 fewer to 6 fewer cases). In people at high risk of progression (i.e. people with moderate AMD) this would correspond to approximately 8 fewer cases of progression for every 100 people taking vitamins (3 fewer to 13 fewer). In one study of 1206 people, there was a lower risk of progression for both neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; moderate-certainty evidence) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; moderate-certainty evidence) and a lower risk of losing 3 or more lines of visual acuity (OR 0.77, 95% CI 0.62 to 0.96; 1791 participants; moderate-certainty evidence). Low-certainty evidence from one study of 110 people suggested higher quality of life scores (National Eye Institute Visual Function Questionnaire) in treated compared with the non-treated people after 24 months (mean difference (MD) 12.30, 95% CI 4.24 to 20.36). Six studies compared lutein (with or without zeaxanthin) with placebo. The duration of supplementation and follow-up ranged from six months to five years. Most evidence came from the AREDS2 study in the USA. People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94, 95% CI 0.87 to 1.01; 6891 eyes; low-certainty evidence), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 6891 eyes; low-certainty evidence), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15 or more letters was seen in the lutein and control groups (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; low-certainty evidence). Quality of life (measured with Visual Function Questionnaire) was similar between groups in one study of 108 participants (MD 1.48, 95% -5.53 to 8.49, moderate-certainty evidence). One study, conducted in Australia, compared vitamin E with placebo. This study randomised 1204 people to vitamin E or placebo, and followed up for four years. Participants were enrolled from the general population; 19% had AMD. The number of late AMD events was low (N = 7) and the estimate of effect was uncertain (RR 1.36, 95% CI 0.31 to 6.05, very low-certainty evidence). There were no data on neovascular AMD or geographic atrophy.There was no evidence of any effect of treatment on visual loss (RR 1.04, 95% CI 0.74 to 1.47, low-certainty evidence). There were no data on quality of life. Five studies compared zinc with placebo. The duration of supplementation and follow-up ranged from six months to seven years. People taking zinc supplements may be less likely to progress to late AMD (OR 0.83, 95% CI 0.70 to 0.98; 3790 participants; 3 RCTs; low-certainty evidence),

neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 2442 participants; 1 RCT; moderate-certainty evidence), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 2442 participants; 1 RCT; moderate-certainty evidence), or visual loss (OR 0.87, 95% CI 0.75 to 1.00; 3791 participants; 2 RCTs; moderate-certainty evidence). There were no data reported on quality of life.Very low-certainty evidence was available on adverse effects because the included studies were underpowered and adverse effects inconsistently reported.
Authors' conclusions: People with AMD may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation. This finding was largely drawn from one large trial, conducted in a relatively well-nourished American population. We do not know the generalisability of these findings to other populations. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed. Supplements containing lutein and zeaxanthin are heavily marketed for people with age-related macular degeneration but our review shows they may have little or no effect on the progression of AMD.
Reference: Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD000254.

5. Vitamin E for Alzheimer's dementia and mild cognitive impairment

Background: Vitamin E occurs naturally in the diet. It has several biological activities, including functioning as an antioxidant to scavenge toxic free radicals. Evidence that free radicals may contribute to the pathological processes behind cognitive impairment has led to interest in the use of vitamin E supplements to treat mild cognitive impairment (MCI) and Alzheimer's disease (AD). This is an update of a Cochrane Review first published in 2000, and previously updated in 2006 and 2012.
Objectives: To assess the efficacy of vitamin E in the treatment of MCI and dementia due to AD.
Search methods: We searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (ALOIS), the Cochrane Library, MEDLINE, Embase, PsycINFO, CINAHL, LILACS as well as many trials databases and grey literature sources on 22 April 2016 using the terms: "Vitamin E", vitamin-E, alpha-tocopherol.
Selection criteria: We included all double-blind, randomised trials in which treatment with any dose of vitamin E was compared with placebo in people with AD or MCI.
Data collection and analysis: We used standard methodological procedures according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We rated the quality of the evidence using the GRADE approach. Where appropriate we attempted to contact authors to obtain missing information.
Main results: Four trials met the inclusion criteria, but we could only extract outcome data in accordance with our protocol from two trials, one in an AD population (n = 304) and one in an MCI population (n = 516). Both trials had an overall low to unclear risk of bias. It was not possible to pool data across studies owing to a lack of comparable outcome measures. In people with AD, we found no evidence of any clinically important effect of vitamin E on cognition, measured with change from baseline in the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) over six to 48 months (mean difference (MD) -1.81, 95% confidence interval (CI) -3.75 to 0.13, P = 0.07, 1 study, n = 272; moderate quality evidence). There was no evidence of a difference between vitamin E and placebo groups in the risk of experiencing at least one serious adverse event over six to 48 months (risk ratio (RR) 0.86, 95% CI 0.71 to 1.05, P = 0.13, 1 study, n = 304; moderate quality evidence), or in the risk of death (RR 0.84, 95% CI 0.52 to 1.34, P = 0.46, 1 study, n = 304; moderate quality evidence). People with AD receiving vitamin E showed less functional decline on the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory than people receiving placebo at six to 48 months (mean difference (MD) 3.15, 95% CI 0.07 to 6.23, P = 0.04, 1 study, n = 280; moderate quality evidence). There was no evidence of any clinically important effect on neuropsychiatric symptoms measured with the Neuropsychiatric Inventory (MD -1.47, 95% CI -4.26 to 1.32, P = 0.30, 1 study, n = 280; moderate quality evidence). We found no evidence that vitamin E affected the probability of progression from MCI to probable dementia due to AD over 36 months (RR 1.03, 95% CI 0.79 to 1.35, P = 0.81, 1 study, n = 516; moderate quality evidence). Five deaths occurred in each of the vitamin E and placebo groups over the 36 months (RR 1.01, 95% CI 0.30 to 3.44, P = 0.99, 1 study, n = 516; moderate quality evidence). We were unable to extract data in accordance with the review protocol for other outcomes. However, the study authors found no evidence that vitamin E differed from placebo in its effect on cognitive function, global severity or activities of daily living . There was also no evidence of a difference between groups in the more commonly reported adverse events.
Authors' conclusions: We found no evidence that the alpha-tocopherol form of vitamin E given to people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD. Vitamin E was not associated with an increased risk of serious adverse events or mortality in the trials in this review. These conclusions have changed since the previous update, however they are still based on small numbers of trials and participants and further research is quite likely to affect the results.
***Reference**: Farina N, Llewellyn D, Isaac MGEKN, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD002854. DOI: 10.1002/14651858.CD002854.pub5.*

6. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial

CONTEXT: Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.
OBJECTIVE: To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men.
DESIGN, SETTING, AND PARTICIPANTS: A large-scale, randomized, double-blind, placebo controlled trial (Physicians" Health Study II) of 14 641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.
INTERVENTION: Daily multivitamin or placebo.

MAIN OUTCOME MEASURES: Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.
RESULTS: During a median (interquartile range) follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years; hazard ratio [HR], 0.92; 95% CI, 0.86-0.998; P=.04). There was no significant effect of a daily multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; P=.76), colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; P=.39), or other site-specific cancers. There was no significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI, 0.77-1.01; P=.07). Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; P=.02), but this did not differ significantly from that among 13 329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; P=.15; P for interaction=.07).
CONCLUSION: In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.
***Reference**: Gaziano JM1, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2012 Nov 14;308(18):1871-80.*

7. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement

DESCRIPTION: Update of the 2003 U.S. Preventive Services Task Force (USPSTF) recommendation on vitamin supplementation to prevent cardiovascular disease and cancer.
METHODS: The USPSTF reviewed the evidence on the efficacy of multivitamin or mineral supplements in the general adult population for the prevention of cardiovascular disease and cancer.
POPULATION: This recommendation applies to healthy adults without special nutritional needs (typically aged 50 years or older). It does not apply to children, women who are pregnant or may become pregnant, or persons who are chronically ill or hospitalized or have a known nutritional deficiency.
RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of multivitamins for the prevention of cardiovascular disease or cancer. (I statement). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of single- or paired-nutrient supplements (except β-carotene and vitamin E) for the prevention of cardiovascular disease or cancer. (I statement). The USPSTF recommends against β-carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. (D recommendation).
***Reference**: Moyer VA; U.S. Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement. Ann Intern Med. 2014 Apr 15;160(8):558-64.*

Vitamin D as a Medication

Vitamin D's popularity as a therapy is booming. A PubMed search of "vitamin D supplementation" in December of 2017 yielded 5,776 clinical studies and 683 systematic reviews. The good news is that, although the benefits are small, there is evidence that Vitamin D therapy is useful for more than bone health. Following are some of the new findings, both positive and negative. These studies are not so much about achieving an adequate vitamin D level ("adequate level" is controversial) but about using vitamin D as a medication to improve outcomes of specific conditions. There is hardly an affliction that affects humans for which Vitamin D has not been tested. I have not included all the negative trials, such as those for liver disease (no effects). Vitamin D therapy for vascular disease and cancer has not yet been adequately studied, but most RCTs to date have been negative. The very large trial underway should have definitive results in about 5 years. Vitamin D combined with calcium has very modest effects on fracture prevention, but we will not present data about bones in this chapter.

Respiratory Tract Infections and Asthma

8. Bolus dosing of Vitamin D does not prevent ARTI or asthma exacerbation in vitamin D–deficient patients

Clinical question: Does vitamin D supplementation improve asthma symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Ah, vitamin D. You are such a good marker of bad health, yet supplementing you seems to have so little effect. For example, lots of observational studies have found an association between low vitamin D levels and a high rate of acute respiratory tract infections (ARTI). This is the first randomized trial to test the hypothesis that vitamin D supplementation would reduce the likelihood of ARTI or asthma exacerbation in adults with corticosteroid-treated asthma. The authors identified 590 patients with asthma: 297 were

then screened for inclusion and 250 met the inclusion criteria. All were between the ages of 16 and 80 years, had smoked less than 15 pack-years, were using an inhaled corticosteroid, and had evidence of reversible airway obstruction. The 250 participants were randomized to receive either 120,000 IU vitamin D every 2 months for 1 year, or matching placebo. The mean age of participants was 48 years, 44% were male, most had received a flu vaccine, and most had moderately severe asthma. Most (82%) had a low vitamin D level at enrollment (serum 25(OH)D level < 75 nmol/L [30 ng/mL]). Unfortunately, the intervention had no effect. The intervention group experienced a significant increase in vitamin D levels (23 nmol/L [10 ng/mL]), but there was no difference between groups in the time to first exacerbation or time to first ARTI. The study was powered to detect a 60-day difference in the time to event.
Bottom line: Vitamin D supplementation does nothing to prevent exacerbations or improve clinical outcomes in a group of adults with asthma, most of whom were also vitamin D deficient.
Martineau AR, MacLaughlin BD, Hooper RL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax 2015;70(5): 451-457.

9. High-dose vitamin D does not reduce wintertime URIs in healthy children

Clinical question: Does high-dose vitamin D reduce the incidence of wintertime upper respiratory infections in otherwise healthy children?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: Vitamin D increases the synthesis of antimicrobial peptides in respiratory epithelium and may thus reduce viral replication and subsequent URIs. These investigators enrolled 703 healthy children, 1 year to 5 years old, who presented for a scheduled well-child visit prior to the wintertime viral season in Toronto, Ontario, Canada. Eligible children randomly received (concealed allocation assignment) liquid vitamin D in a standard dose (400 IU daily) or a high-dose (2000 IU daily). Drops were identical in taste, volume, and color. Throughout the winter months parents completed a symptom checklist and collected viral nasal swabs for suspected URIs. The individuals who assessed outcomes remained masked to treatment group assignment. Follow-up occurred for 99.4% of participants for approximately 6 months (winter lasts a LONG time up there). Mean baseline serum 25-hydroxyvitamin D levels were comparable in the standard-dose and high-dose groups (36.9 ng/mL and 35.9 ng/mL, respectively). Using intention-to-treat analysis, no significant differences occurred between the 2 groups in the mean number of infections per child based on both parent-reported URIs and laboratory confirmed upper respiratory virus infections from nasal smears. There was a statistically significant difference in serum 25-hydroxyvitamin D levels between the standard-dose and high-dose groups after treatment (36.8 ng/mL vs 48.7 ng/mL, respectively). The study was 90% powered to detect a reduction of at least 1 URI per winter season between the 2 treatment groups.
Bottom line: Daily administration of high-dose vitamin D (2000 IU) did not reduce the incidence of wintertime upper respiratory infections (URIs) compared with standard dose vitamin D (400 IU) in otherwise healthy children residing in Toronto, Canada.
Aglipay M, Birken CS, Parkin PC, et al, for the TARGet Kids! Collaboration. Effect of high-dose vs standard-dose wintertime vitamin D supplementation on viral upper respiratory tract infections in young healthy children. JAMA 2017;318(3):245-255.

10. Vitamin D does not reduce URIs in children age 1 to 5

IMPORTANCE: Epidemiological studies support a link between low 25-hydroxyvitamin D levels and a higher risk of viral upper respiratory tract infections. However, whether winter supplementation of vitamin D reduces the risk among children is unknown.
OBJECTIVE: To determine whether high-dose vs standard-dose vitamin D supplementation reduces the incidence of wintertime upper respiratory tract infections in young children.
DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial was conducted during the winter months between September 13, 2011, and June 30, 2015, among children aged 1 through 5 years enrolled in TARGet Kids!, a multisite primary care practice-based research network in Toronto, Ontario, Canada.
INTERVENTIONS: Three hundred forty-nine participants were randomized to receive 2000 IU/d of vitamin D oral supplementation (high-dose group) vs 354 participants who were randomized to receive 400 IU/d (standard-dose group) for a minimum of 4 months between September and May.
MAIN OUTCOME MEASURES: The primary outcome was the number of laboratory-confirmed viral upper respiratory tract infections based on parent-collected nasal swabs over the winter months. Secondary outcomes included the number of influenza infections, noninfluenza infections, parent-reported upper respiratory tract illnesses, time to first upper respiratory tract infection, and serum 25-hydroxyvitamin D levels at study termination.
RESULTS: Among 703 participants who were randomized (mean age, 2.7 years, 57.7% boys), 699 (99.4%) completed the trial. The mean number of laboratory-confirmed upper respiratory tract infections per child was 1.05 (95% CI, 0.91-1.19) for the high-dose group and 1.03 (95% CI, 0.90-1.16) for the standard-dose group, for a between-group difference of 0.02 (95% CI, -0.17 to 0.21) per child. There was no statistically significant difference in number of laboratory-confirmed infections between groups (incidence rate ratio [RR], 0.97; 95% CI, 0.80-1.16). There was also no significant difference in the median time to the first laboratory-confirmed infection: 3.95 months (95% CI, 3.02-5.95 months) for the high-dose group vs 3.29 months (95% CI, 2.66-4.14 months) for the standard-dose group, or number of parent-reported upper respiratory tract illnesses between groups (625 for high-dose vs 600 for standard-dose groups, incidence RR, 1.01; 95% CI, 0.88-1.16). At study termination, serum 25-hydroxyvitamin D levels were 48.7 ng/mL (95% CI, 46.9-50.5 ng/mL) in the high-dose group and 36.8 ng/mL (95% CI, 35.4-38.2 ng/mL) in the standard-dose group.
CONCLUSIONS AND RELEVANCE: Among healthy children aged 1 to 5 years, daily administration of 2000 IU compared with 400 IU of vitamin D supplementation did not reduce overall wintertime upper respiratory tract infections. These findings do not support the routine use of high-dose vitamin D supplementation in children for the prevention of viral upper respiratory tract infections.
Aglipay M, Birken CS, Parkin PC, Loeb MB, Thorpe K, Chen Y, Laupacis A, Mamdani M, Macarthur C, Hoch JS, Mazzulli T, Maguire JL; TARGet Kids! Collaboration. Effect of High-Dose vs Standard-Dose Wintertime Vitamin D Supplementation on Viral Upper Respiratory Tract Infections in Young Healthy Children. JAMA. 2017 Jul 18;318(3):245-254.

11. No Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals

OBJECTIVE: Vitamin D supplementation may be a simple preventive measure against respiratory tract infections (RTIs) but evidence from randomized controlled trials is inconclusive. We aimed to systematically summarize results from interventions studying the protective effect of vitamin D supplementation on clinical and laboratory confirmed RTIs in healthy adults and children.
METHODS: Medline, EMBASE, CENTRAL, and CINAHL were screened from inception until present (last updated in January 2016) completed by a search of the grey literature, clinical trial registers and conference abstracts. We included randomized trials comparing vitamin D versus placebo or no treatment. Two independent reviewers were responsible for study selection and data extraction. Cochrane's risk of bias tool and the GRADE approach were used for quality assessment. Estimates were pooled with random-effects models. Heterogeneity was explored by sub-group and meta-regression analyses.
RESULTS: Of 2627 original hits, 15 trials including 7053 individuals were ultimately eligible. All used oral cholecalciferol. We found a 6% risk reduction with vitamin D3 supplementation on clinical RTIs, but the result was not statistically significant (RR 0.94; 95% CI 0.88 to 1.00). Heterogeneity was large (I-square 57%) and overall study quality was low. There were too few studies to reliably assess a potential risk reduction of laboratory confirmed RTI. Evidence was insufficient to demonstrate an association between vitamin D supplementation and risk of clinical RTI in sub-groups with vitamin D deficiency.
CONCLUSIONS: In previously healthy individuals vitamin D supplementation does not reduce the risk of clinical RTIs. However, this conclusion is based on a meta-analysis where the included studies differed with respect to population, baseline vitamin D levels and study length. This needs to be considered when interpreting the results. Future trials should focus on vitamin D deficient individuals and apply more objective and standardized outcome measurements.
Vuichard Gysin D, Dao D, Gysin CM, Lytvyn L, Loeb M. Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One. 2016 Sep 15;11(9):e0162996.

12. Vitamin D reduces the frequency of respiratory tract infections

Objectives To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.
Design Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.
Data sources Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry from inception to December 2015.
Eligibility criteria for study selection Randomised, double blind, placebo controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.
Results 25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. IPD were obtained for 10 933 (96.6%) participants. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; P for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83). The body of evidence contributing to these analyses was assessed as being of high quality.
Conclusions Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.
Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583.

13. Vitamin D supplementation during pregnancy does not prevent wheezing in the infant

Clinical question: Does vitamin D supplementation during pregnancy reduce the risk of asthma or recurrent wheezing in children up to 3 years of age?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: These investigators identified 623 consenting and eligible Danish women within pregnancy weeks 22 through 26 with no history of endocrine, cardiovascular, or nephrological disorders. Patients randomly received (concealed allocation assignment) a daily dose of 2400 IU vitamin D3 supplementation or matching placebo from pregnancy week 24 to postpartum week 1. All women also took an additional 400 IU per day of vitamin D3 supplementation. Participating clinicians masked to treatment group assignment assessed children at periodic scheduled visits for a total of 36 months. Parents, also masked to treatment group, assessed their children's daily symptom burden between scheduled visits using daily diary cards. Complete follow-up occurred for 94% of children at 3 years. The authors used intention-to-treat analysis and found that, although the intervention resulted in a significant increase in maternal serum vitamin D levels in the treatment group, no significant differences occurred between the 2 groups in the risk of the primary outcome: persistent wheeze in offspring during the first 3 years of life. No confounding effect was found after controlling for sex, season of birth, or maternal vitamin D3 level at baseline. A secondary analysis found a significant reduction in episodes of "troublesome lung symptoms" in the vitamin D group, but no significant differences occurred in the risk of asthma diagnosis, upper or lower respiratory tract infections, or eczema diagnoses. The study was underpowered (< 80%) to detect a clinically significant effect in the primary end point of wheezing.
Bottom line: Vitamin D supplementation (2800 IU/day) during the third trimester of pregnancy compared with a standard prenatal dose

of 400 IU per day in average-risk women did not significantly reduce the risk of wheezing-related illness in offspring through the age of 3 years. A similar study of supplementation with a higher vitamin D dose (4400 IU/day) in pregnant women at high risk of allergic disease also reported no reduced risk of wheezing-related illness in offspring through age 3 years (Litonjua AA, et al. JAMA 2016;315(4):362-370).
Chawes BL, Bonnelykke K, Stokholm J. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring. A randomized clinical trial. JAMA 2016;315(4):353-361.

14. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood

BACKGROUND: We recently published two independent randomized controlled trials of vitamin D supplementation during pregnancy, both indicating a >20% reduced risk of asthma/recurrent wheeze in the offspring by 3 years of age. However, neither reached statistical significance.
OBJECTIVE: To perform a combined analysis of the two trials and investigate whether maternal 25-hydroxy-vitamin D (25(OH)D) level at trial entry modified the intervention effect.
METHODS: VDAART (N = 806) and COPSAC2010. (N = 581) randomized pregnant women to daily high-dose vitamin D3 (4,000 IU/d and 2,400 IU/d, respectively) or placebo. All women also received a prenatal vitamin containing 400 IU/d vitamin D3. The primary outcome was asthma/recurrent wheeze from 0-3yrs. Secondary end-points were specific IgE, total IgE, eczema and lower respiratory tract infections (LRTI). We conducted random effects combined analyses of the treatment effect, individual patient data (IPD) meta-analyses, and analyses stratified by 25(OH)D level at study entry.
RESULTS: The analysis showed a 25% reduced risk of asthma/recurrent wheeze at 0-3yrs: adjusted odds ratio (aOR) = 0.74 (95% CI, 0.57-0.96), p = 0.02. The effect was strongest among women with 25(OH)D level ≥30ng/ml at study entry: aOR = 0.54 (0.33-0.88), p = 0.01, whereas no significant effect was observed among women with 25(OH)D level <30ng/ml at study entry: aOR = 0.84 (0.62-1.15), p = 0.25. The IPD meta-analyses showed similar results. There was no effect on the secondary end-points.
CONCLUSIONS: This combined analysis shows that vitamin D supplementation during pregnancy results in a significant reduced risk of asthma/recurrent wheeze in the offspring, especially among women with 25(OH)D level ≥ 30 ng/ml at randomization, where the risk was almost halved. Future studies should examine the possibility of raising 25(OH)D levels to at least 30 ng/ml early in pregnancy or using higher doses than used in our studies.
Wolsk HM, Chawes BL, Litonjua AA, Hollis BW, Waage J, Stokholm J, Bønnelykke K, Bisgaard H, Weiss ST. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: A combined analysis of two randomized controlled trials. PLoS One. 2017 Oct 27;12(10):e0186657.

15. Vitamin D Reduces the Risk of Asthma Exacerbations Requiring systemic steroids

BACKGROUND: A previous aggregate data meta-analysis of randomised controlled trials showed that vitamin
D supplementation reduces the rate of asthma exacerbations requiring treatment with systemic corticosteroids. Whether this effect is restricted to patients with low baseline vitamin D status is unknown.
METHODS: For this systematic review and one-step and two-step meta-analysis of individual participant data, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for double-blind, placebo-controlled, randomised controlled trials of vitamin D_3 or vitamin D_2 supplementation in people with asthma that reported incidence of asthma exacerbation, published between database inception and Oct 26, 2016. We analysed individual participant data requested from the principal investigator for each eligible trial, adjusting for age and sex, and clustering by study. The primary outcome was the incidence of asthma exacerbation requiring treatment with systemic corticosteroids. Mixed-effects regression models were used to obtain the pooled intervention effect with a 95% CI. Subgroup analyses were done to determine whether effects of vitamin D on risk of asthma exacerbation varied according to baseline 25-hydroxyvitamin D (25[OH]D) concentration, age, ethnic or racial origin, body-mass index, vitamin D dosing regimen, use of inhaled corticosteroids, or end-study 25(OH)D levels; post-hoc subgroup analyses were done according to sex and study duration. This study was registered with PROSPERO, number CRD42014013953.
FINDINGS: Our search identified 483 unique studies, eight of which were eligible randomised controlled trials (total 1078 participants). We sought individual participant data for each and obtained it for seven studies (955 participants). Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio [aIRR] 0·74, 95% CI 0·56-0·97; p=0·03; 955 participants in seven studies; high-quality evidence). There were no significant differences between vitamin D and placebo in the proportion of participants with at least one exacerbation or time to first exacerbation. Subgroup analyses of the rate of asthma exacerbations treated with systemic corticosteroids revealed that protective effects were seen in participants with baseline 25(OH)D of less than 25 nmol/L (aIRR 0·33, 0·11-0·98; p=0·046; 92 participants in three studies; moderate-quality evidence) but not in participants with higher baseline 25(OH)D levels (aIRR 0·77, 0·58-1·03; p=0·08; 764 participants in six studies; moderate-quality evidence; $p_{interaction}$=0·25). p values for interaction for all other subgroup analyses were also higher than 0·05; therefore, we did not show that the effects of this intervention are stronger in any one subgroup than in another. Six studies were assessed as being at low risk of bias, and one was assessed as being at unclear risk of bias. The two-step meta-analysis did not reveal evidence of heterogeneity of effect (I^2=0·0, p=0·56).
INTERPRETATION: Vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids overall. We did not find definitive evidence that effects of this intervention differed across subgroups of patients.
Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, Jensen ME, Mauger D, Stelmach I, Urashima M, Martineau AR. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med. 2017 Nov;5(11):881-890.

Pain

16. Vitamin D does not reduce pain in adults with symptomatic knee osteoarthritis

Clinical question: Does vitamin D supplementation reduce pain in adults with symptomatic knee osteoarthritis and low vitamin D levels?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: These investigators identified adults, aged 50 to 79 years, in otherwise good health with at least 6 months of symptomatic knee osteoarthritis (based on standard diagnostic criteria) and a pain score of 20 mm to 80 mm on a 100-mm visual analog scale. Eligibility criteria also included a low serum 25-hydroxyvitamin D level (12.5 nmol/L to 60 nmol/L). Study patients randomly received (concealed allocation assignment) a monthly capsule of 50,000 IU vitamin D3 or identical placebo for 24 months. The primary outcomes of knee pain and tibial cartilage volume were assessed using standard evaluation tools by individuals masked to treatment group assignment. Complete follow-up occurred for 82.4% of participants at 24 months. Serum 25-hydroxyvitamin D levels increased significantly more in the vitamin D group than in the placebo group, with 79% versus 43% of patients, respectively, who reached a 25-hydroxyvitamin D level of greater than 60 nmol/L at month 3. Although pain scores significantly decreased from baseline over 24 months in both groups, there was no difference in change of pain scores from baseline to 24 months between the 2 groups using intention-to-treat and per-protocol analyses. Tibial cartilage volume loss also occurred similarly between both groups. The study was 80% powered to detect predetermined clinically significant differences in pain scores and cartilage loss.
Bottom line: Vitamin D supplementation did not significantly reduce pain or prevent cartilage loss compared with placebo in adults with symptomatic knee osteoarthritis and low vitamin D levels over 2 years.
Jin X, Jones G, Cicuttini F, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis. A randomized clinical trial. JAMA 2016;315(10):1005-1013.

17. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoarthritis

BACKGROUND: The aim of this study was to describe whether maintaining sufficient serum vitamin D levels in people with knee osteoarthritis and baseline vitamin D insufficiency has an association with change in knee structures and symptoms over 2 years.
METHODS: Participants (n = 413, mean age 63.2 years) with symptomatic knee osteoarthritis and vitamin D insufficiency were enrolled in a clinical trial. In all, 340 participants (82.3%) completed the study, with 25-hydroxyvitamin D [25(OH)D] measurements at baseline and months 3 and 24. Participants were classified as consistently insufficient [serum 25(OH)D ≤50 nmol/L at months 3 and 24, n = 45], fluctuating [25(OH)D >50 nmol/L at either point, n = 68), and consistently sufficient [25(OH)D >50 nmol/L at months 3 and 24, n = 226] groups. Knee cartilage volume, cartilage defects, bone marrow lesions, and effusion-synovitis volume were assessed using MRI at baseline and month 24. Knee symptoms were assessed at baseline and months 3, 6, 12, and 24 using the Western Ontario and McMaster Universities Arthritis Index.
RESULTS: The consistently sufficient group had significantly less loss of tibial cartilage volume (β 2.1%; 95% confidence interval [CI], 0.3%, 3.9%), less increase in effusion-synovitis volume (β -2.5 mL; 95 CI%, -4.7, -0.2 mL), and less loss of Western Ontario and McMaster Universities Arthritis Index physical function (β -94.2; 95% CI, -183.8, -4.5) compared with the consistently insufficient group in multivariable analyses. In contrast, there were no significant differences in these outcomes between the fluctuating and consistently insufficient groups. Changes in cartilage defects, bone marrow lesions, and knee pain were similar between groups.
CONCLUSION: This post hoc analysis suggests beneficial effects of maintaining vitamin D sufficiency on cartilage loss, effusion-synovitis, and physical function in people with knee osteoarthritis.
***Reference**: Am J Med. Zheng S1, Jin X1, Cicuttini F2, Wang X1, Zhu Z1, Wluka A2, Han W3, Winzenberg T4, Antony B1, Aitken D1, Blizzard L1, Jones G1, Ding C5. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoarthritis. 2017 Oct;130(10):1211-1218. doi: 10.1016/j.amjmed.2017.04.038. Epub 2017 May 24.*

18. Vitamin D for the treatment of chronic painful conditions in adults

Background: This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2010) on 'Vitamin D for the treatment of chronic painful conditions in adults'. Vitamin D is produced in the skin after exposure to sunlight and can be obtained through food. Vitamin D deficiency has been linked with a range of conditions, including chronic pain. Observational and circumstantial evidence suggests that there may be a role for vitamin D deficiency in the aetiology of chronic painful conditions.
Objectives: To assess the efficacy and safety of vitamin D supplementation in chronic painful conditions when tested against placebo or against active comparators.
Search methods: For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE to February 2015. This was supplemented by searching the reference lists of retrieved articles, reviews in the field, and online trial registries.
Selection criteria: We included studies if they were randomised double-blind trials of vitamin D supplementation compared with placebo or with active comparators for the treatment of chronic painful conditions in adults.
Data collection and analysis: Two review authors independently selected the studies for inclusion, assessed methodological quality, and extracted data. We did not undertake pooled analysis due to the heterogeneity of the data. Primary outcomes of interest were pain responder outcomes, and secondary outcomes were treatment group average pain outcomes and adverse events.
Main results: We included six new studies (517 participants) in this review update, bringing the total of included studies to 10 (811 participants). The studies were heterogeneous with regard to study quality, the chronic painful conditions that were investigated, the dose of vitamin D given, co-interventions, and the outcome measures reported. Only two studies reported responder pain outcomes; the other studies reported treatment group average outcomes only. Overall, there was no consistent pattern that vitamin D treatment

was associated with greater efficacy than placebo in any chronic painful condition (low quality evidence). Adverse events and withdrawals were comparatively infrequent, with no consistent difference between vitamin D and placebo (good quality evidence).
Authors' conclusions: The evidence addressing the use of vitamin D for chronic pain now contains more than twice as many studies and participants than were included in the original version of this review. Based on this evidence, a large beneficial effect of vitamin D across different chronic painful conditions is unlikely. Whether vitamin D can have beneficial effects in specific chronic painful conditions needs further investigation.
Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD007771. DOI: 10.1002/14651858.CD007771.pub3.

19. Vitamin D supplementation improves pain symptoms in patients with chronic widespread pain (aka fibromyalgia)

Chronic non-specific widespread pain (CWP) including fibromyalgia (FMS) is characterized by widespread pain, reduced pain threshold, and multiple tender points on examination, causing disability and decreased quality of life. Vitamin D has been proposed as an associated factor in CWP. This meta-analysis aimed to explore the benefit of vitamin D supplementation in the management of CWP. A comprehensive search of the CENTRAL, MEDLINE, and Embase databases was performed from inception through January 2017. The inclusion criterion was the randomized clinical trials' evaluating the effects of vitamin D treatment in adult subjects with CWP or FMS. CWP was defined as chronic recurrent musculoskeletal pain without secondary causes; FMS patients met the American College of Rheumatology criteria for FMS. Study outcome was assessed using visual analog scale (VAS) of pain intensity. Pooled mean difference (MD) of VAS and 95% confidence interval (CI) were calculated using a random-effect meta-analysis. Meta-regression analysis using a random-effects model was performed to explore the effects of change in vitamin D in the treatment group on difference in the mean of VAS. Sensitivity analysis was performed to evaluate the robustness of results. The between-study heterogeneity of effect size was quantified using the Q statistic and I 2. Data were extracted from four randomized controlled trials involving 287 subjects. Pooled result demonstrated a significantly lower VAS in CWP patients who received vitamin D treatment compared with those who received placebo (MD = 0.46; 95% CI 0.09-0.89, I 2 = 48%). Meta-regression analysis revealed no significant relationship between the changes of vitamin D and VAS (coefficient = 0.04 (95% CI -0.01 to 0.08), p = 0.10). In this meta-analysis, we conclude that vitamin D supplementation is able to decrease pain scores and improve pain despite no significant change in VAS after increasing serum vitamin D level. Further studies need to be conducted in order to explore the improvement of functional status, quality of life, and the pathophysiological change that improves chronic widespread pain.
Yong WC, Sanguankeo A, Upala S. Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis. Clin Rheumatol. 2017 Dec;36(12):2825-2833.

20. The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis

Background: Type 2 diabetes is a global health concern, with an increased prevalence and high cost of treatment.
Objective: The aim of this systematic review and meta-analysis was to determine the effect of vitamin D supplementation and improved vitamin D status on glycemia and insulin resistance in type 2 diabetic patients.
Data Source: We searched PUBMED/Medline, Cumulative Index to Nursing and Allied Health, and Cochrane Library (until January 2017).
Study Selection: Prospective clinical trials were selected evaluating the impact of vitamin D supplementation on glycosylated hemoglobin (HbA1c), serum fasting plasma glucose (FPG), and homeostatic model assessment of insulin resistance (HOMA-IR) in diabetic patients. Data Extraction and Synthesis: We used a random-effects model to synthesize quantitative data, followed by a leave-one-out method for sensitivity analysis. The systematic review registration was CRD42017059555. From a total of 844 entries identified via literature search, 24 controlled trials (1528 individuals diagnosed with type 2 diabetes) were included. The meta-analysis indicated a significant reduction in HbA1c [mean difference: -0.30%; 95% confidence interval (CI): -0.45 to -0.15, P < 0.001], FPG [mean difference: -4.9 mg/dL (-0.27 mmol/L); 95% CI: -8.1 to -1.6 (-0.45 to -0.09 mmol/L), P = 0.003], and HOMA-IR (mean difference: -0.66; 95% CI: -1.06 to -0.26, P = 0.001) following vitamin D supplementation and significant increase in serum 25-hydroxyvitamin D levels [overall increase of 17 ± 2.4 ng/mL (42 ± 6 nmol/L)].
Conclusions: Vitamin D supplementation, a minimum dose of 100 μg/d (4000 IU/d), may significantly reduce serum FPG, HbA1c, and HOMA-IR index, and helps to control glycemic response and improve insulin sensitivity in type 2 diabetic patients.
***Reference**: Mirhosseini N1, Vatanparast H2, Mazidi M3,4, Kimball SM1,5. The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3097-3110. doi: 10.1210/jc.2017-01024.*

21. Vitamin D does not improve symptoms of bipolar disorder

OBJECTIVE: Bipolar depression is difficult to treat. Vitamin D supplementation is well tolerated and may improve mood via its neurotransmitter synthesis regulation, nerve growth factor enhancement and antioxidant properties. Vitamin D adjunct reduces unipolar depression, but has not been tried in bipolar depression.
METHODS: 18-70yos with DSM IV bipolar depression and Vitamin D deficiency (<30 ng/ml) were randomized in a controlled double blind trial of 5000IU Vitamin D_3 po qday supplementation versus placebo for twelve weeks. Change in Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Young Mania Rating Scale (YMRS), medication, and tolerance were assessed q2weeks.
RESULTS: 16 VitD vs 17 placebo subjects did not differ in baseline characteristics (mean = 44 yo, SD = 13), VitD level (19.2 ± 65.8 g/ml vs 19.3 ± 5.5 ng/ml respectively) or mood ratings (MADRS 21.3 ± 6.4 vs 22.8 ± 6.9 respectively). At 12wks, the placebo group VitD levels remained unchanged, while the VitD group levels increased to 28 ng/ml. MADRS score decreased

significantly in both placebo (mean = 6.42 (95% CI [2.28 to 10.56]) and VitD groups (mean = 9.54 (95% CI[3.51 to 15.56]) (p = 0.031), but there were no differences between treatment groups (time by treatment interaction estimate: 0.29, $t_{(23)}$ = 0.14, p = 0.89); VitD and placebo groups had similar reductions in YMRS and HAM-A. Vitamin D_3 was well tolerated.
CONCLUSIONS: In this small study, despite a greater rise in Vitamin D levels in the VitD supplementation group, there was no significant difference reduction in depressive symptoms. However both groups' VitD levels remained deficient. Vitamin D_3 supplementation vs placebo did not improve reduction in mood elevation or anxiety symptoms.
Marsh WK, Penny JL, Rothschild AJ. Vitamin D supplementation in bipolar depression: A double blind placebo controlled trial. J Psychiatr Res. 2017 Dec;95:48-53.

22. Vitamin D plus calcium does not reduce cancer risk in postmenopausal women

Clinical question: Does dietary supplementation with vitamin D and calcium reduce the risk of cancer in postmenopausal women?
Study design: Randomized controlled trial (double-blinded)
Setting: Population-based
Synopsis: These investigators enrolled 2303 postmenopausal women, 55 years and older, who consented to random (concealed) allocation to either the treatment group (2000 IU vitamin D3 once daily and 500 mg calcium carbonate 3 times daily) or identical placebos. Individuals masked to treatment group assignments assessed cancer diagnosis outcomes (excluding nonmelanoma skin cancer) using medical records and death certificates. The mean baseline serum 25-hydroxyvitamin D level for all women was 32.8 ng/mL (81.8 nmol/L) and the values did not differ significantly between groups. Complete follow-up occurred for 89.6% of patients at 4 years. Using intention-to-treat analysis, the authors found no significant difference between the treatment group and the control group in the incidence of cancers diagnosed (3.89% vs 5.58%, respectively, difference not significant). In particular, there was no significant difference in the incidence of breast cancer diagnoses, with all other individual cancers occurring too infrequently to analyze separately. All serum 25-hydroxyvitamin D levels after baseline were significantly higher in the treatment group than in the control group. No serious adverse events occurred more frequently in the treatment group, including renal calculi. The study was 94.4% powered to detect a 50% reduction in cancer incidence, assuming an annual incidence rate of 2% in the control group.
Bottom line: Among healthy postmenopausal women, 55 years and older, with normal baseline serum vitamin D levels, supplementation with vitamin D3 and calcium did not significantly reduce the risk of all-type cancers at 4 years.
Lappe J, Watson P, Travers Gustafson D, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women. A randomized clinical trial. JAMA 2017;317(12):1234-1243.

23. High Dose Bolus Vitamin D does NOT prevent cardiovascular disease

IMPORTANCE: Cohort studies have reported increased incidence of cardiovascular disease (CVD) among individuals with low vitamin D status. To date, randomized clinical trials of vitamin D supplementation have not found an effect, possibly because of using too low a dose of vitamin D.
OBJECTIVE: To examine whether monthly high-dose vitamin D supplementation prevents CVD in the general population.
DESIGN, SETTING, AND PARTICIPANTS: The Vitamin D Assessment Study is a randomized, double-blind, placebo-controlled trial that recruited participants mostly from family practices in Auckland, New Zealand, from April 5, 2011, through November 6, 2012, with follow-up until July 2015. Participants were community-resident adults aged 50 to 84 years. Of 47 905 adults invited from family practices and 163 from community groups, 5110 participants were randomized to receive vitamin D3 (n = 2558) or placebo (n = 2552). Two participants retracted consent, and all others (n = 5108) were included in the primary analysis.
INTERVENTIONS: Oral vitamin D3 in an initial dose of 200 000 IU, followed a month later by monthly doses of 100 000 IU, or placebo for a median of 3.3 years (range, 2.5-4.2 years).
MAIN OUTCOMES AND MEASURES: The primary outcome was the number of participants with incident CVD and death, including a prespecified subgroup analysis in participants with vitamin D deficiency (baseline deseasonalized 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL). Secondary outcomes were myocardial infarction, angina, heart failure, hypertension, arrhythmias, arteriosclerosis, stroke, and venous thrombosis.
RESULTS: Of the 5108 participants included in the analysis, the mean (SD) age was 65.9 (8.3) years, 2969 (58.1%) were male, and 4253 (83.3%) were of European or other ethnicity, with the remainder being Polynesian or South Asian. Mean (SD) baseline deseasonalized 25(OH)D concentration was 26.5 (9.0) ng/mL, with 1270 participants (24.9%) being vitamin D deficient. In a random sample of 438 participants, the mean follow-up 25(OH)D level was greater than 20 ng/mL higher in the vitamin D group than in the placebo group. The primary outcome of CVD occurred in 303 participants (11.8%) in the vitamin D group and 293 participants (11.5%) in the placebo group, yielding an adjusted hazard ratio of 1.02 (95% CI, 0.87-1.20). Similar results were seen for participants with baseline vitamin D deficiency and for secondary outcomes.
CONCLUSIONS AND RELEVANCE: Monthly high-dose vitamin D supplementation does not prevent CVD. This result does not support the use of monthly vitamin D supplementation for this purpose. The effects of daily or weekly dosing require further study.
Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, Camargo CA Jr. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. JAMA Cardiol. 2017 Jun 1;2(6):608-616.

Slow S, Florkowski CM, Chambers ST, Priest PC, Stewart AW, Jennings LC, Livesey JH, Camargo CA Jr, Scragg R, Murdoch DR. Effect of monthly vitamin D3 supplementation in healthy adults on adverse effects of earthquakes: randomized controlled trial. BMJ. 2014 Dec 15;349:g7260.

Sorry; Vitamin D did not help earthquake survivors

Bottom Lines

1. Consider augmenting depression treatment with a multi-B vitamin.

2. Prescribe nicotinamide for patients with multiple non-melanoma skin cancers.

3. People with acute macular degeneration may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation.

4. Vitamin E may slow cognitive decline in patients with Alzheimer's dementia but does not prevent cardiovascular disease.

5. The jury is out on whether any vitamins reduce risk of cancer or cardiovascular disease. So far there is no strong evidence to support benefit.

6. Vitamin D decreases frequency of acute respiratory infections, though perhaps not in young children.

7. Vitamin D decreases asthma exacerbations requiring steroids, but not the rate of exacerbations.

8. Vitamin D does not reduce pain from knee arthritis but does decrease the pain of chronic widespread pain syndrome.

9. Vitamin D decreases A1C slightly in type 2 diabetes; the clinical significance is unknown

10. Vitamin D does not decrease symptoms of manic depression.

Dementia/End-of- Life Care Gary Ferenchick MD MS

Objectives:

1. Recognize that mild cognitive impairment normalizes over time in a large percentage of patients
2. Anti-cholinergic medication use is associated with dementia
3. PPIs are not associated with dementia
4. The general conclusions from 2 major reports on dementia published in 2017
5. The evidence for cognitive training, medications/OTCs, and physical activity for preventing dementia is insufficient
6. Advanced care planning (ACP) occurs more commonly with an easy to use interactive web site
7. Percutaneous endoscopic gastrostomy (PEG) tube use does not improve any outcome in patients with dementia
8. Melatonin may help improve sleep in patients with dementia

Dementia represents a decline from a previously attained cognitive level AND affects activities of daily living or social functioning
Mild cognitive impairment (MCI) represents a decline from a previously attained cognitive level, but the individual can still engage in complex activities (e.g paying bills, taking meds)

MCI is described as an intermediate phase between normal cognition and dementia; it is associated with an objective deficit and cognitive abilities but does not yet affect the patient's functional independence. MCI is considered a relevant risk factor for the development of dementia. However, the first abstract notes a substantial percentage of patients with MCI normalize over time

1. Mild cognitive impairment (MCI) appears reversible

BACKGROUND: Although mild cognitive impairment often precedes dementia, it can also resolve spontaneously.
METHODS: These Italian and French authors performed a systematic review and meta-analysis to determine the proportion of subjects who revert from mild cognitive impairment to normal cognition. A literature search for 1999-2015 identified 25 longitudinal studies on 6914 patients with mild cognitive impairment (mean age 75; 51% female) who had at least two-year follow-up. The primary outcome was the percentage of patients who reverted to normal cognition.
RESULTS: Subjects were derived from population cohorts (15 studies; mean 3.9 years of follow-up) or clinical settings (10 studies; 3.2 years of follow-up). Reversion from mild cognitive impairment to normal cognition occurred in 1243 subjects overall (18%; 95% CI, 14-22%), with high heterogeneity (I^2=96.1%; $p<0.001$). Meta-regression showed a significant association between effect size and study setting, whereby the reversion rate was 8% (95% CI, 4-11%) in clinical settings and 25% (95% CI, 19-30%) in population cohorts. When only high-quality studies were included, the reversion rate was 26%. Reversion rates did not depend on participant age or duration of follow-up. Reasons for the discrepant results were hypothesized to include mis-classification of subjects, wide variation in definitions of mild cognitive impairment, and the unstable and fluctuating nature of MCI.
CONCLUSIONS: Mild cognitive impairment appears to normalize over time in a fairly large percentage of patients, and thus should not be considered as the first manifestation of dementia. Physicians must be aware of the bidirectionality of cognitive impairment to avoid overdiagnosis and overtreatment. 52 references (marco.canevelli@gmail.com – no reprints)
REFERENCE: Canevelli, M., et al. SPONTANEOUS REVERSION OF MILD COGNITIVE IMPAIRMENT TO NORMAL COGNITION: A SYSTEMATIC REVIEW OF LITERATURE AND META-ANALYSIS. J Am Med Dir Assoc 17(10):943, October 1, 2016

Factors associated (or not) with dementia

2. Anticholinergic medication use associated with dementia risk

IMPORTANCE: Many medications have anticholinergic effects. In general, anticholinergic-induced cognitive impairment is considered reversible on discontinuation of anticholinergic therapy. However, a few studies suggest that anticholinergics may be associated with an increased risk for dementia.
OBJECTIVE: To examine whether cumulative anticholinergic use is associated with a higher risk for incident dementia.
DESIGN, SETTING, AND PARTICIPANTS: Prospective population-based cohort study using data from the Adult Changes in Thought study in Group Health, an integrated health care delivery system in Seattle, Washington. We included 3434 participants 65 years or older with no dementia at study entry. Initial recruitment occurred from 1994 through 1996 and from 2000 through 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants were followed up every 2 years. Data through September 30, 2012, were included in these analyses.

EXPOSURES: Computerized pharmacy dispensing data were used to ascertain cumulative anticholinergic exposure, which was defined as the total standardized daily doses (TSDDs) dispensed in the past 10 years. The most recent 12 months of use was excluded to avoid use related to prodromal symptoms. Cumulative exposure was updated as participants were followed up over time.
MAIN OUTCOMES AND MEASURES: Incident dementia and Alzheimer disease using standard diagnostic criteria. Statistical analysis used Cox proportional hazards regression models adjusted for demographic characteristics, health behaviors, and health status, including comorbidities.
RESULTS: The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. During a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia (637 of these [79.9%] developed Alzheimer disease). A 10-year cumulative dose-response relationship was observed for dementia and Alzheimer disease (test for trend, P < .001). For dementia, adjusted hazard ratios for cumulative anticholinergic use compared with nonuse were 0.92 (95% CI, 0.74-1.16) for TSDDs of 1 to 90; 1.19 (95% CI, 0.94-1.51) for TSDDs of 91 to 365; 1.23 (95% CI, 0.94-1.62) for TSDDs of 366 to 1095; and 1.54 (95% CI, 1.21-1.96) for TSDDs greater than 1095. A similar pattern of results was noted for Alzheimer disease.
Results were robust in secondary, sensitivity, and post hoc analyses.
CONCLUSIONS AND RELEVANCE: Higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.
REFERENCE: Gray SL et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015 Mar;175(3):401-7.

Medications associated with dementia in this study included: antihistamines, antidepressants (amitriptyline, paroxetine), antiemetic (meclizine, prochlorperazine), antiparkinsons agents (benztropine); antipsychotics (olanzapine), bladder antimuscarinics (oxybutynin, tolteradine), skeletal muscle relaxants (cyclobenzaprine), GI antispasmodics (hyocyamine, scopolamine)

3. No association between PPIs and Dementia

OBJECTIVES: The objective of the study was to investigate whether proton pump inhibitor (PPI) use is associated with an increased risk of clinically verified Alzheimer's disease (AD).
METHODS: A Finnish nationwide nested case-control study MEDALZ includes all community-dwelling individuals with newly diagnosed AD during 2005-2011 (N=70,718), and up to four age-, sex-, and region of residence-matched comparison individuals for each case (N=282,858). Data were extracted from Finnish nationwide health-care registers. PPI use was derived from purchases recorded in the Prescription register data since 1995 and modeled to drug use periods with PRE2DUP method. AD was the outcome measure.
RESULTS: PPI use was not associated with risk of AD with 3-year lag window applied between exposure and outcome (adjusted odds ratio (OR) 1.03, 95% confidence interval (CI) 1.00-1.05). Similarly, longer duration of use was not associated with risk of AD (1-3 years of use, adjusted OR 1.01 (95% CI 0.97-1.06); ≥3 years of use adjusted OR 0.99 (95% CI 0.94-1.04)). Higher dose use was not associated with an increased risk (≥1.5 defined daily doses per day, adjusted OR 1.03 (95% CI 0.92-1.14)).
CONCLUSIONS: In conclusion, we found no clinically meaningful association between PPI use and risk of AD. The results for longer duration of cumulative use or use with higher doses did not indicate dose-response relationship.
REFERENCE: Taipale H et al. No Association Between Proton Pump Inhibitor Use and Risk of Alzheimer's Disease. Am J Gastroenterol. 2017 Jul 11. doi: 10.1038/ajg.2017.196.

4. No association between PPIs and Dementia (again)

OBJECTIVES: To examine the risk associated with the use of proton pump inhibitors (PPIs) of conversion to mild cognitive impairment (MCI), dementia, and specifically Alzheimer's disease (AD).
DESIGN: Observational, longitudinal study.
SETTING: Tertiary academic Alzheimer's Disease Centers funded by the National Institute on Aging.
PARTICIPANTS: Research volunteers aged 50 and older with two to six annual visits; 884 were taking PPIs at every visit, 1,925 took PPIs intermittently, and 7,677 never reported taking PPIs. All had baseline normal cognition or MCI.
MEASUREMENTS: Multivariable Cox regression analyses evaluated the association between PPI use and annual conversion of baseline normal cognition to MCI or dementia or annual conversion of baseline MCI to dementia, controlling for demographic characteristics, vascular comorbidities, mood, and use of anticholinergics and histamine-2 receptor antagonists.
RESULTS: Continuous (always vs never) PPI use was associated with lower risk of decline in cognitive function (hazard ratio (HR) = 0.78, 95% confidence interval (CI) =0.66-0.93, P = .005) and lower risk of conversion to MCI or AD (HR = 0.82, 95% CI = 0.69-0.98, P = .03). Intermittent use was also associated with lower risk of decline in cognitive function (HR = 0.84, 95% CI = 0.76-0.93, P = .001) and risk of conversion to MCI or AD (HR = 0.82, 95% CI = 0.74-0.91, P = .001).This lower risk was found for persons with normal cognition or MCI.
CONCLUSION: Proton pump inhibitors were not associated with greater risk of dementia or of AD, in contrast to recent reports. Study limitations include reliance on self-reported PPI use and lack of dispensing data. Prospective studies are needed to confirm these results to guide empirically based clinical treatment recommendations.
REFERENCE: Goldstein FC et al. Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia. J Am Geriatr Soc. 2017 Sep;65(9):1969-1974.

Lancet Commission and the AHA/ASA 2017 reports

In 2017 2 large reports related to dementia were published

- Defining Optimal Brain Health in Adults by the American Heart Association and American Stroke Association
- Lancet Commission Report on “Dementia prevention, intervention and care”

5. Defining optimal brain health in adults AHA ASA advisory

Cognitive function is an important component of aging and predicts quality of life, functional independence, and risk of institutionalization. Advances in our understanding of the role of cardiovascular risks have shown them to be closely associated with cognitive impairment and dementia. Because many cardiovascular risks are modifiable, it may be possible to maintain brain health and to prevent dementia in later life. The purpose of this American Heart Association (AHA)/American Stroke Association presidential advisory is to provide an initial definition of optimal brain health in adults and guidance on how to maintain brain health. We identify metrics to define optimal brain health in adults based on inclusion of factors that could be measured, monitored, and modified. From these practical considerations, we identified 7 metrics to define optimal brain health in adults that originated from AHA's Life's Simple 7: 4 ideal health behaviors (nonsmoking, physical activity at goal levels, healthy diet consistent with current guideline levels, and body mass index <25 kg/m2) and 3 ideal health factors (untreated blood pressure <120/<80 mm Hg, untreated total cholesterol <200 mg/dL, and fasting blood glucose <100 mg/dL). In addition, in relation to maintenance of cognitive health, we recommend following previously published guidance from the AHA/American Stroke Association, Institute of Medicine, and Alzheimer's Association that incorporates control of cardiovascular risks and suggest social engagement and other related strategies. We define optimal brain health but recognize that the truly ideal circumstance may be uncommon because there is a continuum of brain health as demonstrated by AHA's Life's Simple 7. Therefore, there is opportunity to improve brain health through primordial prevention and other interventions. Furthermore, although cardiovascular risks align well with brain health, we acknowledge that other factors differing from those related to cardiovascular health may drive cognitive health. Defining optimal brain health in adults and its maintenance is consistent with the AHA's Strategic Impact Goal to improve cardiovascular health of all Americans by 20% and to reduce deaths resulting from cardiovascular disease and stroke by 20% by the year 2020. This work in defining optimal brain health in adults serves to provide the AHA/American Stroke Association with a foundation for a new strategic direction going forward in cardiovascular health promotion and disease prevention.
REFERENCE: Gorelick PB et al. Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association. Stroke. 2017 Oct;48(10):e284-e303.

6. Lancet Commission Report

REFERENCE: Dementia prevention, intervention and care” (Livingston G et al. Dementia prevention, intervention, and care. Lancet. 2017 Dec 16;390(10113):2673-2734

The general theme of both documents is that that dementia has an important proportion of modifiable risk factors.

My major conclusions from the AHA/ASA document | the focus is primarily on CV risk reduction

- The definition of “optimal brain health” is optimal capacity to function adaptively in the environment.
    1. This could be assessed in terms of competencies across the domains of “thinking, moving, and feeling,” encompassing, for example, the abilities pay attention, perceive, and recognize sensory input; to learn and remember; to communicate; to problem solve and make decisions; to have mobility; and to regulate emotional status.
    2. A healthy brain is one that can perform all the mental processes that encompass cognition such as the ability to learn and judge, use language, and remember
- Many brain disorders manifest later in life but, in fact, *are life-course illnesses*.
    1. Cumulative exposure to vascular risk factors throughout life, perhaps starting as early as in utero (and certainly from the fourth decade onward), affects the risk of … stroke and dementia
- Research has convincingly demonstrated that cardiovascular risk factors are major contributors to late-life cognitive health and risk of stroke and AD.
    1. Of all major cognitively impairing disorders, including AD, there is a vascular component in up to 80%.
    2. Cardiovascular risks are important targets for strategies to prevent or delay cognitive impairments and factors such as uncontrolled hypertension, diabetes mellitus, obesity,

physical inactivity, smoking, and depression *are associated with compromised brain health*

- A strategy of using AHA Life's Simple 7 helps preserve cognition

  Health-Related Behaviors

  1. Nonsmoking status
  2. Physical activity at goal levels
  3. BMI <25 kg/m2
  4. Healthy diet consistent with current guidelines

  Health-Related Factors

  5. Untreated BP <120/<80 mm Hg
  6. Untreated total cholesterol <200 mg/dL
  7. Fasting blood glucose <100 mg/dL

7. Improvements in Life's Simple 7 associated with healthy vascular aging

Hypertension and increased vascular stiffness are viewed as inevitable parts of aging. To elucidate whether the age-related decrease in vascular function is avoidable, we assessed the prevalence, correlates, and prognosis of healthy vascular aging (HVA) in 3196 Framingham Study participants aged ≥50 years. We defined HVA as absence of hypertension and pulse wave velocity <7.6 m/s (mean+2 SD of a reference sample aged <30 years). Overall, 566 (17.7%) individuals had HVA, with prevalence decreasing from 30.3% in people aged 50 to 59 to 1% in those aged ≥70 years. In regression models adjusted for physical activity, caloric intake, and traditional cardiovascular disease (CVD) risk factors, we observed that lower age, female sex, lower body mass index, use of lipid-lowering drugs, and absence of diabetes mellitus were cross-sectionally associated with HVA (P<0.001 for all). A unit increase in a cardiovascular health score (Life's Simple 7) was associated with 1.55-fold (95% confidence interval, 1.38-1.74) age- and sex-adjusted odds of HVA. During a follow-up of 9.6 years, 391 CVD events occurred. In Cox regression models adjusted for traditional CVD risk factors, including blood pressure, HVA was associated with a hazard ratio of 0.45 (95% confidence interval, 0.26-0.77) for CVD relative to absence of HVA. Although HVA is achievable in individuals acculturated to a Western lifestyle, maintaining normal vascular function beyond 70 years of age is challenging. Although our data are observational, our findings support prevention strategies targeting modifiable factors and behaviors and obesity, in particular, to prevent or delay vascular aging and the associated risk of CVD.
REFERENCE: Niiranen TJ et al. Prevalence, Correlates, and Prognosis of Healthy Vascular Aging in a Western Community-Dwelling Cohort: The Framingham Heart Study. Hypertension. 2017 Aug;70(2):267-274.

Major conclusions from the Lancet document

35% of dementia is attributable to a combination of the following nine risk factors:

1. smoking
2. physical inactivity
3. midlife obesity
4. midlife hypertension
5. diabetes
6. education to a maximum of age 11–12 years
7. hearing loss
8. late life depression
9. social isolation

Conversely, completely eliminating the apolipoprotein E (ApoE) ε4 allele as the major *genetic risk factor* is calculated to produce a 7% reduction in incidence

Modifiable risk factors for dementia

The population attributable fraction (PAF) is the percentage reduction in new cases over a given time if a particular risk factor were eliminated.

	Relative risk for dementia (95% CI)	Prevalence	Communality	PAF	Weighted PAF*
Early life (age <18 years)					
Less education (none or primary school only)	1·6 (1·26–2·01)	40·0%	64·6%	19·1%	7·5%
Midlife (age 45–65 years)					
Hypertension	1·6 (1·16–2·24)	8·9%	57·3%	5·1%	2·0%
Obesity	1·6 (1·34–1·92)	3·4%	60·4%	2·0%	0·8%
Hearing loss	1·9 (1·38–2·73)	31·7%	46·1%	23·0%	9·1%
Later life (age >65 years)					
Smoking	1·6 (1·15–2·20)	27·4%	51·1%	13·9%	5·5%
Depression	1·9 (1·55–2·33)	13·2%	58·6%	10·1%	4·0%
Physical inactivity	1·4 (1·16–1·67)	17·7%	26·6%	6·5%	2·6%
Social isolation	1·6 (1·32–1·85)	11·0%	45·9%	5·9%	2·3%
Diabetes	1·5 (1·33–1·79)	6·4%	70·3%	3·2%	1·2%

Data are relative risk (95% CI) or %. Total weighted PAF adjusted for communality=35·0%. PAF=population attributable fraction. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 1: **Potentially modifiable risk factors for dementia**

According to the Lancet Commission report "The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER study) provided four intensive lifestyle-based strategies (diet, exercise, cognitive training, and vascular management) to more than 600 people who were older than 60 years and at high risk of dementia according to their age, sex, education, systolic blood pressure, total cholesterol, and physical activity. The study compared cognition in the intervention group versus controls who received general health advice. This highly intensive intervention consisted of about 200 meetings (300 h) with health professionals and trainers over 2 years. Participants in the intervention group showed a mean improvement versus the control group in a composite measure of cognition (d=0·13) on executive function and processing speed, but not memory. Despite the intervention's intensity, the effect was small, although this outcome shows potential for lifestyle modification to improve cognitive function in people at risk of dementia. Pragmatic multimodal models for dementia prevention should be tested in other populations and settings. Earlier intervention and longer followup will determine whether these approaches reduce dementia risk." (Abstract #8)

8. Multidomain interventions improve cognitive functioning in at-risk elderly people

BACKGROUND: Modifiable vascular and lifestyle-related risk factors have been associated with dementia risk in observational studies. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a proof-of-concept randomised controlled trial, we aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population.
METHODS: In a double-blind randomised controlled trial we enrolled individuals aged 60-77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989.
FINDINGS: Between Sept 7, 2009, and Nov 24, 2011, we screened 2654 individuals and randomly assigned 1260 to the intervention group (n=631) or control group (n=629). 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total Z score at 2 years was 0·20 (SE 0·02, SD 0·51) in the intervention group and 0·16 (0·01, 0·51) in the control group. Between-group difference in the change of NTB total score per year was 0·022 (95% CI 0·002-0·042, p=0·030). 153 (12%) individuals dropped out overall. Adverse events occurred in 46 (7%) participants in the intervention group compared with six (1%) participants in the control group; the most common adverse event was musculoskeletal pain (32 [5%] individuals for intervention vs no individuals for control).
INTERPRETATION: Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.
REFERENCE: Ngandu T et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015 Jun 6;385(9984):2255-63.

9. Mediterranean diet is associated with improved cognitive function

IMPORTANCE: Oxidative stress and vascular impairment are believed to partly mediate age-related cognitive decline, a strong risk factor for development of dementia. Epidemiologic studies suggest that a Mediterranean diet, an antioxidant-rich cardioprotective dietary pattern, delays cognitive decline, but clinical trial evidence is lacking.
OBJECTIVE: To investigate whether a Mediterranean diet supplemented with antioxidant-rich foods influences cognitive function compared with a control diet.
DESIGN, SETTING, AND PARTICIPANTS: Parallel-group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona, Spain (233 women [52.1%]; mean age, 66.9 years), at high cardiovascular risk were enrolled into the Prevención con Dieta Mediterránea nutrition intervention trial from October 1, 2003, through December 31, 2009. All patients underwent neuropsychological assessment at inclusion and were offered retesting at the end of the study.
INTERVENTIONS: Participants were randomly assigned to a Mediterranean diet supplemented with extravirgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat).
MAIN OUTCOMES AND MEASURES: Rates of cognitive change over time based on a neuropsychological test battery: Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from the Wechsler Memory Scale, and the Color Trail Test. We used mean z scores of change in each test to construct 3 cognitive composites: memory, frontal (attention and executive function), and global.
RESULTS: Follow-up cognitive tests were available in 334 participants after intervention (median, 4.1 years). In multivariate analyses adjusted for confounders, participants allocated to a Mediterranean diet plus olive oil scored better on the RAVLT (P = .049) and Color Trail Test part 2 (P = .04) compared
with controls; no between-group differences were observed for the other cognitive tests. Similarly adjusted cognitive composites (mean z scores with 95% CIs) for changes above baseline of the memory composite were 0.04 (-0.09 to 0.18) for the Mediterranean diet plus olive oil, 0.09 (-0.05 to 0.23; P = .04 vs controls) for the Mediterranean diet plus nuts, and -0.17 (-0.32 to -0.01) for the control diet. Respective changes from baseline of the frontal cognition composite were 0.23 (0.03 to 0.43; P = .003 vs controls), 0.03 (-0.25 to 0.31), and -0.33 (-0.57 to -0.09). Changes from baseline of the global cognition composite were 0.05 (-0.11 to 0.21; P = .005 vs controls) for the Mediterranean diet plus olive oil,
-0.05 (-0.27 to 0.18) for the Mediterranean diet plus nuts, and -0.38 (-0.57 to -0.18) for the control diet. All cognitive composites significantly (P < .05) decreased from baseline in controls.
CONCLUSIONS AND RELEVANCE: In an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function.
TRIAL REGISTRATION: isrctn.org Identifier: ISRCTN35739639.
REFERENCE: Valls-Pedret C et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015 Jul;175(7):1094-103.

Findings from RCTS on interventions to prevent Alzheimer disease and related dementias

The following four abstracts reflect the work of the Minnesota Evidence-based Practice Center (EPC) summarizing findings from RCTS on interventions to prevent Alzheimer disease and related dementias (ADRD). These were published in a series in early 2018. Funded by the Agency for

Healthcare Research and Quality (AHPQ), EPC systematic reviews provide an evidence base and help inform the USPSTF. In an editorial concerning these reviews, Eric Larson stated, “Although we found some intriguing positive results ... nothing even approached the evidence level required for a USPSTF recommendation.

10. Insufficient evidence for MindGames in preventing dementia

Background: Structured activities to stimulate brain function-that is, cognitive training exercises-are promoted to slow or prevent cognitive decline, including dementia, but their effectiveness is highly debated.
Purpose: To summarize evidence on the effects of cognitive training on cognitive performance and incident dementia outcomes for adults with normal cognition or mild cognitive impairment (MCI).
Data Sources: Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and PsycINFO through July 2017, supplemented by hand-searches.
Study Selection: Trials (published in English) lasting at least 6 months that compared cognitive training with usual care, waitlist, information, or attention controls in adults without dementia.
Data Extraction: Single-reviewer extraction of study characteristics confirmed by a second reviewer; dual-reviewer risk-of-bias assessment; consensus determination of strength of evidence. Only studies with low or medium risk of bias were analyzed.
Data Synthesis: Of 11 trials with low or medium risk of bias, 6 enrolled healthy adults with normal cognition and 5 enrolled adults with MCI. Trainings for healthy older adults were mostly computer based; those for adults with MCI were mostly held in group sessions. The MCI trials used attention controls more often than trials with healthy populations. For healthy older adults, training improved cognitive performance in the domain trained but not in other domains (moderate-strength evidence). Results for populations with MCI suggested no effect of training on performance (low-strength and insufficient evidence). Evidence for prevention of cognitive decline or dementia was insufficient. Adverse events were not reported.
Limitation: Heterogeneous interventions and outcome measures; outcomes that mostly assessed test performance rather than global function or dementia diagnosis; potential publication bias.
Conclusion: In older adults with normal cognition, training improves cognitive performance in the domain trained. Evidence regarding prevention or delay of cognitive decline or dementia is insufficient.
Primary Funding Source: Agency for Healthcare Research and Quality.
Reference: Butler M et al. Does Cognitive Training Prevent Cognitive Decline?: A Systematic Review. Ann Intern Med. 2018 Jan 2;168(1):63-68.

11. No evidence for pharmacological treatments for cognitive protection

Background: Optimal treatment to prevent or delay cognitive decline, mild cognitive impairment (MCI), or dementia is uncertain.
Purpose: To summarize current evidence on the efficacy and harms of pharmacologic interventions to prevent or delay cognitive decline, MCI, or dementia in adults with normal cognition or MCI.
Data Sources: Several electronic databases from January 2009 to July 2017, bibliographies, and expert recommendations.
Study Selection: English-language trials of at least 6 months' duration enrolling adults without dementia and comparing pharmacologic interventions with placebo, usual care, or active control on cognitive outcomes.
Data Extraction: Two reviewers independently rated risk of bias and strength of evidence; 1 extracted data, and a second checked accuracy.
Data Synthesis: Fifty-one unique trials were rated as having low to moderate risk of bias (including 3 that studied dementia medications, 16 antihypertensives, 4 diabetes medications, 2 nonsteroidal anti-inflammatory drugs [NSAIDs] or aspirin, 17 hormones, and 7 lipid-lowering agents). In persons with normal cognition, estrogen and estrogen-progestin increased risk for dementia or a combined outcome of MCI or dementia (1 trial, low strength of evidence); high-dose raloxifene decreased risk for MCI but not for dementia (1 trial, low strength of evidence); and antihypertensives (4 trials), NSAIDs (1 trial), and statins (1 trial) did not alter dementia risk (low to insufficient strength of evidence). In persons with MCI, cholinesterase inhibitors did not reduce dementia risk (1 trial, low strength of evidence). In persons with normal cognition and those with MCI, these pharmacologic treatments neither improved nor slowed decline in cognitive test performance (low to insufficient strength of evidence). Adverse events were inconsistently reported but were increased for estrogen (stroke), estrogen-progestin (stroke, coronary heart disease, invasive breast cancer, and pulmonary embolism), and raloxifene (venous thromboembolism).
Limitation: High attrition, short follow-up, inconsistent cognitive outcomes, and possible selective reporting and publication.
Conclusion: Evidence does not support use of the studied pharmacologic treatments for cognitive protection in persons with normal cognition or MCI.
Primary Funding Source: Agency for Healthcare Research and Quality.
Reference: Fink HA et al. Pharmacologic Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review. Ann Intern Med. 2018 Jan 2;168(1):39-51.

12. Insufficient evidence for OTC supplements for cognitive protection

Background: Optimal interventions to prevent or delay cognitive decline, mild cognitive impairment (MCI), or dementia are uncertain.
Purpose: To summarize the evidence on efficacy and harms of over-the-counter (OTC) supplements to prevent or delay cognitive decline, MCI, or clinical Alzheimer-type dementia in adults with normal cognition or MCI but no dementia diagnosis.
Data Sources: Multiple electronic databases from 2009 to July 2017 and bibliographies of systematic reviews.
Study Selection: English-language trials of at least 6 months' duration that enrolled adults without dementia and compared cognitive outcomes with an OTC supplement versus placebo or active controls.

Data Extraction: Extraction performed by a single reviewer and confirmed by a second reviewer; dual-reviewer assessment of risk of bias; consensus determination of strength of evidence.
Data Synthesis: Thirty-eight trials with low to medium risk of bias compared ω-3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C or β-carotene, multi-ingredient supplements, or other OTC interventions with placebo or other supplements. Few studies examined effects on clinical Alzheimer-type dementia or MCI, and those that did suggested no benefit. Daily folic acid plus vitamin B12 was associated with improvements in performance on some objectively measured memory tests that were statistically significant but of questionable clinical significance. Moderate-strength evidence showed that vitamin E had no benefit on cognition. Evidence about effects of ω-3 fatty acids, soy, ginkgo biloba, folic acid alone or with other B vitamins, β-carotene, vitamin C, vitamin D plus calcium, and multivitamins or multi-ingredient supplements was either insufficient or low-strength, suggesting that these supplements did not reduce risk for cognitive decline. Adverse events were rarely reported.
Limitation: Studies had high attrition and short follow-up and used a highly variable set of cognitive outcome measures.
Conclusion: Evidence is insufficient to recommend any OTC supplement for cognitive protection in adults with normal cognition or MCI.
Primary Funding Source: Agency for Healthcare Research and Quality.
Reference: Butler M et al. Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review. Ann Intern Med. 2018 Jan 2;168(1):52-62.

13. PubMed: Physical Activity interventions to prevent cognitive decline or AD is insufficient

Background: The prevalence of cognitive impairment and dementia is expected to increase dramatically as the population ages, creating burdens on families and health care systems.
Purpose: To assess the effectiveness of physical activity interventions in slowing cognitive decline and delaying the onset of cognitive impairment and dementia in adults without diagnosed cognitive impairments.
Data Sources: Several electronic databases from January 2009 to July 2017 and bibliographies of systematic reviews.
Study Selection: Trials published in English that lasted 6 months or longer, enrolled adults without clinically diagnosed cognitive impairments, and compared cognitive and dementia outcomes between physical activity interventions and inactive controls.
Data Extraction: Extraction by 1 reviewer and confirmed by a second; dual-reviewer assessment of risk of bias; consensus determination of strength of evidence.
Data Synthesis: Of 32 eligible trials, 16 with low to moderate risk of bias compared a physical activity intervention with an inactive control. Most trials had 6-month follow-up; a few had 1- or 2-year follow-up. Evidence was insufficient to draw conclusions about the effectiveness of aerobic training, resistance training, or tai chi for improving cognition. Low-strength evidence showed that multicomponent physical activity interventions had no effect on cognitive function. Low-strength evidence showed that a multidomain intervention comprising physical activity, diet, and cognitive training improved several cognitive outcomes. Evidence regarding effects on dementia prevention was insufficient for all physical activity interventions.
Limitation: Heterogeneous interventions and cognitive test measures, small and underpowered studies, and inability to assess the clinical significance of cognitive test outcomes.
Conclusion: Evidence that short-term, single-component physical activity interventions promote cognitive function and prevent cognitive decline or dementia in older adults is largely insufficient. A multidomain intervention showed a delay in cognitive decline (low-strength evidence).
Primary Funding Source: Agency for Healthcare Research and Quality.
Reference: Brasure M et al. Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review. Reference: Ann Intern Med. 2018 Jan 2;168(1):30-38.

As Larson stated “To put it simply, all evidence indicates that there is no magic bullet.”

Advanced Care Planning (ACP)

An easy to use interactive website designed to help older adults engage in advanced care planning through a simple 5-step process and videos has been shown to increase ACP documentation by 10% (www.prepareforyourcare.org)

14. Advanced care planning website associated with ↑ ACP documentation

Importance: Documentation rates of patients' medical wishes are often low. It is unknown whether easy-to-use, patient-facing advance care planning (ACP) interventions can overcome barriers to planning in busy primary care settings.
Objective: To compare the efficacy of an interactive, patient-centered ACP website (PREPARE) with an easy-to-read advance directive (AD) to increase planning documentation.
Design, Setting, and Participants: This was a comparative effectiveness randomized clinical trial from April 2013 to July 2016 conducted at multiple primary care clinics at the San Francisco VA Medical Center. Inclusion criteria were age of a least 60 years; at least 2 chronic and/or serious conditions; and 2 or more primary care visits; and 2 or more additional clinic, hospital, or emergency room visits in the last year.
Interventions: Participants were randomized to review PREPARE plus an easy-to-read AD or the AD alone. There were no clinician and/or system-level interventions or education. Research staff were blinded for all follow-up measurements.
Main Outcomes and Measures: The primary outcome was new ACP documentation (ie, legal forms and/or discussions) at 9 months. Secondary outcomes included patient-reported ACP engagement at 1 week, 3 months, and 6 months using validated surveys of behavior change process measures (ie, 5-point knowledge, self-efficacy, readiness scales) and action measures (eg, surrogate

designation, using a 0-25 scale). We used intention-to-treat, mixed-effects logistic and linear regression, controlling for time, health literacy, race/ethnicity, baseline ACP, and clustering by physician.
Results: The mean (SD) age of 414 participants was 71 (8) years, 38 (9%) were women, 83 (20%) had limited literacy, and 179 (43%) were nonwhite. No participant characteristic differed significantly among study arms at baseline. Retention at 6 months was 90%. Advance care planning documentation 6 months after enrollment was higher in the PREPARE arm vs the AD-alone arm (adjusted 35% vs 25%; odds ratio, 1.61 [95% CI, 1.03-2.51]; P = .04). PREPARE also resulted in higher self-reported ACP engagement at each follow-up, including higher process and action scores; P <.001 at each follow-up).
Conclusions and Relevance: Easy-to-use, patient-facing ACP tools, without clinician- and/or system-level interventions, can increase planning documentation 25% to 35%. Combining the PREPARE website with an easy-to-read AD resulted in higher planning documentation than the AD alone, suggesting that PREPARE may increase planning documentation with minimal health care system resources.
Trial Registration: clinicaltrials.gov Identifier: NCT01550731.
Reference: Sudore RL et al. Effect of the PREPARE Website vs an Easy-to-Read Advance Directive on Advance Care Planning Documentation and Engagement Among Veterans: A Randomized Clinical
Trial.JAMA Intern Med. 2017 Aug 1;177(8):1102-1109.

Miscellaneous

15. Melatonin helpful for sleep disorders in dementia

BACKGROUND: Sleep disturbance may affect up to half of elderly patients with dementia and is a possible contributor to cognitive impairment. Melatonin replacement may improve both sleep and cognition.
METHODS: These authors, from China and the USA, performed a literature review and meta-analysis to determine whether melatonin has therapeutic benefit for patients with dementia. The investigators identified seven randomized controlled trials that included 520 patients with dementia treated with melatonin versus placebo or light therapy. Primary outcomes were the effects of melatonin on sleep disturbance and on cognitive function as assessed by the Mini-Mental State Examination (MMSE).
RESULTS: Melatonin given for more than four weeks (but not shorter durations) improved sleep efficacy (four trials; p=0.02), and four weeks of melatonin also lengthened total sleep time by 28 minutes (six trials; p=0.02). Results on the MMSE (five trials) did not change significantly after melatonin treatment and there was, likewise, no significant effect of melatonin on cognitive function as assessed using the Alzheimer's Disease Assessment-Cognitive subscale (two trials). For subgroups with Alzheimer's disease, melatonin significantly improved sleep efficacy but had no effect on total sleep time or cognition. Adverse events, when reported, did not differ significantly between the melatonin and placebo groups. Study limitations included the wide range of sleep measures and melatonin doses.
CONCLUSIONS: Melatonin may help improve sleep in patients with dementia but appears to have no impact on cognitive function. 34 references.
REFERENCE: Xu, J., et al MELATONIN FOR SLEEP DISORDERS AND COGNITION IN DEMENTIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. Am J Alzheimers Dis Other Demen 30(5):439, August 2015

There exist in no randomize trials comparing the difference in mortality quality-of-life in dementia patients who have been provided PEG feeding versus regular oral feedings; **all studies have been observational**. A 2009 Cochran review demonstrated there was no evidence for increased survival in dementia patients who received enteral tube feedings. Abstract # 16 was a retrospective analysis from a prospect of database of 392 patient who underwent PEG placement between 2008 and 2013 The patient's were classified into 3 categories 1) dementia, 2) CVA, and 3) other indications (including oropharyngeal cancer and motor neuron disease). Outcome data included biochemical markers of nutritional status, rehospitalization rates and survival rates, measured 18 months after PEG insertion The group with dementia (n = 165; mean age 83) was compared to the group with a CVA (n=124; mean age 79) and a group with other PEG indications (n=103; mean age 77). Clinical reasons for PEG placement included: refusing to eat, dysphasia, recurrent aspiration, altered mental status, and others.

- Rehospitalization rates 6 months post procedure were 2.45 vs 1.86 vs 1.65
- Mortality within the first year post PEG placement was 75% vs 58% vs 38%
- 1 month mortality post procedure was 15% vs 3.3% vs 7.8%
- The presence of dementia was associated the mean time to death 7.2 vs 8.9 vs 8 months

- Additionally a 2.3 gram/dL decrease in albumin was noted in the dementia group whereas the other 2 groups a slightly smaller decreases in albumin

Thus, there was no increased survival, rehospitalization or improved albumin patients with dementia receiving a PEG vs those with a PEG for other reasons

16. PEG Placement has no effect on dementia outcomes

BACKGROUND: Percutaneous endoscopic gastrostomy (PEG) tubes are commonly utilized as a method of enteral feeding in patients unable to obtain adequate oral nutrition. Although some studies have shown improved mortality in select populations, the safety and effectiveness of PEG insertion in patients with dementia compared with those with other neurological diseases or head and neck malignancy remains less well defined.
OBJECTIVE: To evaluate the nutritional effectiveness, rate of rehospitalization, and risk of mortality among patients with dementia compared with patients with other neurological diseases or head and neck cancers who undergo PEG placement.
MATERIALS AND METHODS: We conducted a retrospective analysis from a prospective database of patients who underwent PEG placement at an academic tertiary center between 2008 and 2013. The following data were collected: indication for PEG, patient demographics, biochemical markers of nutritional status rehospitalization, and survival rates.
RESULTS: During the study period, 392 patients underwent PEG tube placement. Indications for PEG were dementia (N=165, group A), cerebrovascular accident (N=124, group B), and other indications such as oropharyngeal cancers and motor neuron disease (N=103, group C). The mean follow-up time after PEG was 18 months (range, 3 to 36 mo). No differences in baseline demographics were noted. PEG insertion in the dementia (group A) neither reduced the rehospitalization rate 6 months' postprocedure compared with groups B and C (2.45 vs. 1.86 and 1.65, respectively; P=0.05), nor reduced the mortality rate within the first year post-PEG placement (75% vs. 58% and 38% for groups A, B, and C, respectively=0.001), as well, it did not improve survival at 1 month after the procedure (15% vs. 3.26% and 7.76%, for groups A, B, C, respectively, P<0.01). The presence of dementia was also associated with shorter mean time to death (7.2 vs. 8.85 and 8 mo for groups A, B, C, respectively, P<0.05). The rate of improvement of the nutritional biomarker albumin was lower in the dementia group [3.1. to 2.9 vs. 3.2 to 3.3 and 3 to 3.3 g/dL for groups A, B, and C, respectively (P<0.02)]. Multivariate regression analysis showed that the presence of dementia was an independent predictor for mortality rate within the first year and 1-month mortality rate in patients undergoing PEG insertion with odds ratio 3.22 (95% confidence interval, 1.52-4.32) and odds ratio 2.52 (95% confidence interval, 1.22-3.67).
CONCLUSIONS: PEG insertion in patients with dementia neither improve short-term and long-term mortality nor rehospitalization rate as compared with patients who underwent PEG placement for alternate indications such as other neurological diseases or head and neck malignancy and even was associated with shorter time to death. Furthermore, PEG insertion in patients with dementia did not improve albumin. Therefore, careful selection of patients with dementia is warranted before PEG placement weighing the risks and benefits on a personalized basis.
REFERENCE: Abu R A et al. PEG Insertion in Patients With Dementia Does Not Improve Nutritional Status and Has Worse Outcomes as Compared With PEG Insertion for Other Indications. J Clin Gastroenterol. 2016 Aug 8. [Epub ahead of print]

17. PEG Placement associated with worse dementia outcomes

BACKGROUND: Percutaneous endoscopic gastrostomy (PEG) is often performed to provide long-term nutritional support. There is some evidence to suggest that its benefits are limited in elderly patients with dementia.
METHODS: The authors, from Hadassah-Hebrew University in Israel and Harvard Medical School, compared selected outcomes following PEG placement in a retrospective cohort of 165 patients in whom the indication for placement was dementia (mean age 83), 124 stroke patients (mean age 79), and 103 patients with other indications including oropharyngeal cancer and motor neuron disease (mean age 77).
RESULTS: Within six months after placement, nutritional status, as reflected by albumin and hemoglobin levels, was worse in the dementia patients than in the other two groups. There was a greater decline in albumin in the dementia cohort than in the other two groups, and hemoglobin improved in the latter two groups but decreased in the dementia cohort. The six-month rehospitalization rate was significantly greater in the dementia cohort than in the other groups (2.45 vs. 1.86 in the CVA group and 1.65 in patients undergoing PEG placement for other indications, p<0.05), and the one-year mortality rate was also significantly higher (75% vs. 58% and 38%, p<0.001). Death occurred within one month in 15% of the dementia group vs. 3.3% and 7.8% of the other groups (p<0.01). The mean time to death was 7.2 months in the dementia group vs. 8.85 and 8 months in the other two groups (p<0.05).
CONCLUSIONS: PEG placement for nutritional support in elderly patients with dementia did not improve outcomes when compared with patients undergoing PEG placement for other indications. 28 references (dtawfikkhoury1@hotmail.com – no reprints)
REFERENCE: Ayman, A.R., et al. PEG INSERTION IN PATIENTS WITH DEMENTIA DOES NOT IMPROVE NUTRITIONAL STATUS AND HAS WORSE OUTCOMES AS COMPARED WITH PEG INSERTION FOR OTHER INDICATIONS. J Clin Gastroenterol 51(5):417, May/June 2017

Conclusions

1. Mild cognitive impairment (MCI) appears reversible
2. Cumulative anticholinergic use is associated with an increased risk for dementia
3. No association exists between proton pump inhibitor use and risk of Alzheimer's Disease
4. Many brain disorders manifest later in life but, in fact, are life-course illnesses and there is a vascular component in up to 80%.
5. About 35% of the risk of dementia is potentially modifiable with lifestyle modification
6. Certain interventions (including resource intensive multidomain interventions) and the Mediterranean diet are associated with improved cognitive function

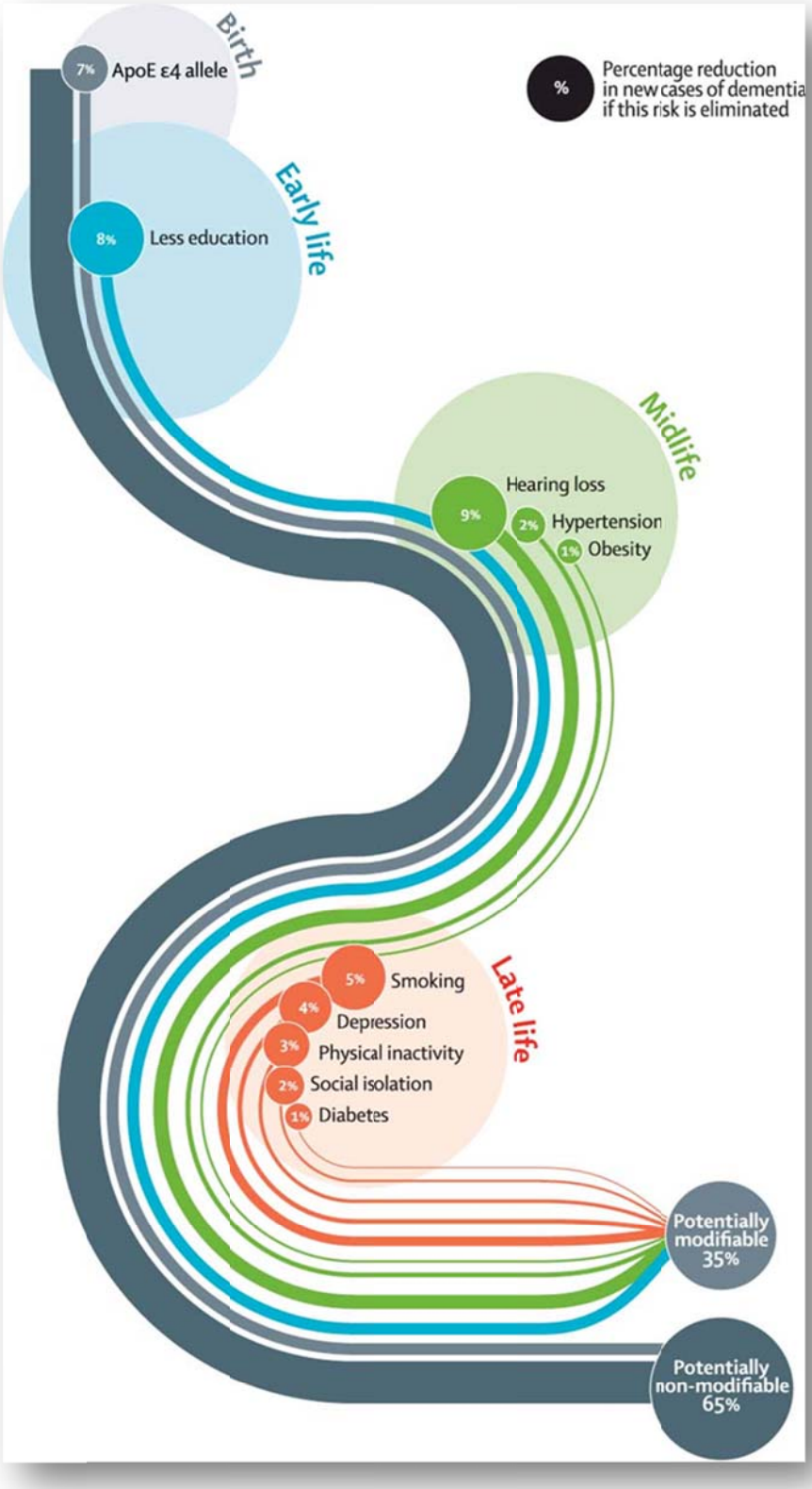
7. There is no evidence that single interventions (such as cognitive training, pharmacological treatments, OT supplements and exercise) are not associated with improved cognitive outcomes
8. Advanced care planning is facilitated with an easy to use online resource
9. PEG placement has no effect on dementia outcomes

Appendix

Note that The Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 has stopped using the word dementia (phrase associated with stigma) and instead uses the phrase “major neurocognitive disorders”.

10 ways to love your brain (from the Alzheimer’s Association)

1. Break a sweat.
    a. Engage in regular cardiovascular exercise that elevates your heart rate and increases blood flow to the brain and body. Several studies have found an association between physical activity and reduced risk of cognitive decline.
2. Hit the books.
    a. Formal education in any stage of life will help reduce your risk of cognitive decline and dementia. For example, take a class at a local college, community center or online.
3. Butt out.
    a. Evidence shows that smoking increases risk of cognitive decline. Quitting smoking can reduce that risk to levels comparable to those who have not smoked.
4. Follow your heart.
    a. Evidence shows that risk factors for cardiovascular disease and stroke — obesity, high blood pressure and diabetes — negatively impact your cognitive health. Take care of your heart, and your brain just might follow.
5. Heads up!
    a. Brain injury can raise your risk of cognitive decline and dementia. Wear a seat belt, use a helmet when playing contact sports or riding a bike, and take steps to prevent falls.
6. Fuel up right.
    a. Eat a healthy and balanced diet that is lower in fat and higher in vegetables and fruit to help reduce the risk of cognitive decline. Although research on diet and cognitive function is limited, certain diets, including Mediterranean and Mediterranean-DASH (Dietary Approaches to Stop Hypertension), may contribute to risk reduction.
7. Catch some zzz's.
    a. Not getting enough sleep due to conditions like insomnia or sleep apnea may result in problems with memory and thinking.
8. Take care of your mental health.
    a. Some studies link a history of depression with increased risk of cognitive decline, so seek medical treatment if you have symptoms of depression, anxiety or other mental health concerns. Also, try to manage stress.
9. Buddy up.
    a. Staying socially engaged may support brain health. Pursue social activities that are meaningful to you. Find ways to be part of your local community — if you love animals, consider volunteering at a local shelter. If you enjoy singing, join a local choir or help at an afterschool program. Or, just share activities with friends and family.
10. Stump yourself.
    a. Challenge and activate your mind. Build a piece of furniture. Complete a jigsaw puzzle. Do something artistic. Play games, such as bridge, that make you think strategically. Challenging your mind may have short and long-term benefits for your brain.



Life-course model of contribution of modifiable risk factors to dementia (from the Lancet Commission Article)

Written by: Steven R. Brown, MD

Objectives

1. Summarize clinical approaches to fever in a pediatric patient
2. Discuss updates in well-child preventive care including vision screening and screening for hip dysplasia
3. Review evidence for use of tympanostomy tubes

What is a reasonable approach to the febrile infant? Is clinical diagnosis reliable? Are any blood tests helpful?

#1: Clinical diagnosis of serious infection in children is difficult

Clinical question: How reliable is the history and physical in determining if a child has a serious infection?
Study design: Meta-analysis (other) **Funding source:** Government
Setting: Various (meta-analysis)
Synopsis: These authors searched several databases looking for studies in ambulatory settings that evaluated clinical features of children (1 month to 18 years of age) with suspected serious infection. The studies had to include an appropriate spectrum of illness severity and a reference standard. The authors defined serious infection as sepsis (including bacteremia), meningitis, pneumonia, osteomyelitis, cellulitis, gastroenteritis with dehydration, complicated urinary tract infection (positive urine culture and systemic signs such as fever), and viral respiratory tract infections complicated by hypoxia (eg, bronchiolitis). One can argue about whether some of these are truly serious. Two authors independently assessed the quality of each study, finding most only fair to poor. They found 30 studies evaluating clinical features. The studies included from 72 to 3981 children! The positive likelihood ratios (LR+) for individual elements of the history ranged from 1 to 23 and the negative likelihood ratios (LR-) ranged from 0.26 to 1.3. (Remember: Tests with likelihood ratios of 1 provide no useful information and that an LR+ near 10 and an LR- near 0.1 have the greatest discriminatory capacity.) In most of the studies, the value of the history and physical ranged widely on the basis of the rate of illness in the sick children (less than 5%, 5% to 20%, or more than 20%). Among all of the tested history and physical findings, 4 were predictive for serious infections: cyanosis (LR+ range = 2.66 - 52.2); rapid breathing (LR+ range = 1.26 - 9.78); poor peripheral perfusion (LR+ range = 2.39 - 38.8); and petechial rash (LR+ range = 6.18 - 83.7). In one primary care study, parental concern and clinician instinct were also strong red flags. The negative likelihood ratios, however, were too high to be useful to rule out serious infection. Clinical decision rules, such as the Yale Observational Scale, were also quite variable with the LR+ ranging from 1.1 to 7 and the LR- from 0.2 to 1. There are a couple of "Aunt Fannie" findings in this study (everyone has an Aunt Fannie who can be recognized from 100 feet away because of her easily recognized and eccentric manner of dress). For example, the presence of petechiae, nuchal rigidity, or coma had a LR+ of 395. I think most of us would recognize that a comatose child is seriously ill!
Bottom line: In this systematic review, each element of the history and physical has a wide enough range of reliability that they should not be used independently to evaluate sick children. Specifically, they are not reliable enough to rule out serious infection. (LOE = 1a-)
Reference: *Van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mant D; European Research Network on Recognising Serious Infection investigators. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. Lancet 2010;375(9717):834-845.*

#2: Pediatric SIRS criteria not accurate for predicting which children will require critical care

Clinical question: How useful are pediatric SIRS vital signs in predicting which children require critical care resuscitation?
Study design: Cohort (retrospective) **Funding source:** Unknown/not stated
Setting: Emergency department
Synopsis: Pediatric SIRS vital signs require the presence of 2 or more of the following criteria, one of which must be abnormal temperature or leukocyte count: Core temperature less than 36C or greater than 38.5C, tachycardia (or bradycardia in infants), tachypnea, abnormal leukocyte count for age, or greater than 10% immature neutrophils. Despite consensus agreement on these criteria, their effectiveness as a screening test for detecting critically ill children is unknown. These investigators retrospectively analyzed data from all visits by patients younger than 18 years to the emergency department (ED) of a tertiary academic pediatric hospital between April 2011 and March 2012. Eligible patients (N = 40,356) included those presenting to the ED for the first time within the preceding 72 hours with nontrauma-related diagnoses and for whom SIRS vital signs were recorded. A temperature-heart rate correction was performed: For each 1 degree Celsius above 38.5C, 10 beats per minute was subtracted from the heart rate. Outcomes included requirement for critical care within 24 hours of ED arrival, intensive care unit admission, 30-day in-hospital mortality, 72-hour readmission, ED laboratory evaluation, and ED intravenous therapy. A total of 6122 patients (15.2%) met SIRS criteria. Of these, 4993 (81.6%) were discharged from the ED without the need for intravenous therapy and without 72-hour readmission. Only 99 children (0.25%) required critical care within the first 24 hours, including 23 patients with and 76 without SIRS vital signs. Those children meeting SIRS criteria had a significantly increased risk of critical care requirement, intensive care unit admission, and intravenous therapy, but the sensitivity of meeting the SIRS criteria for critical care requirement was only 23.2% (95% CI 15.3%-32.8%). The pair of SIRS vital signs with the highest positive likelihood ratio was temperature and corrected heart rate (LR+ = 2.74; 95% CI 1.87-4.01).

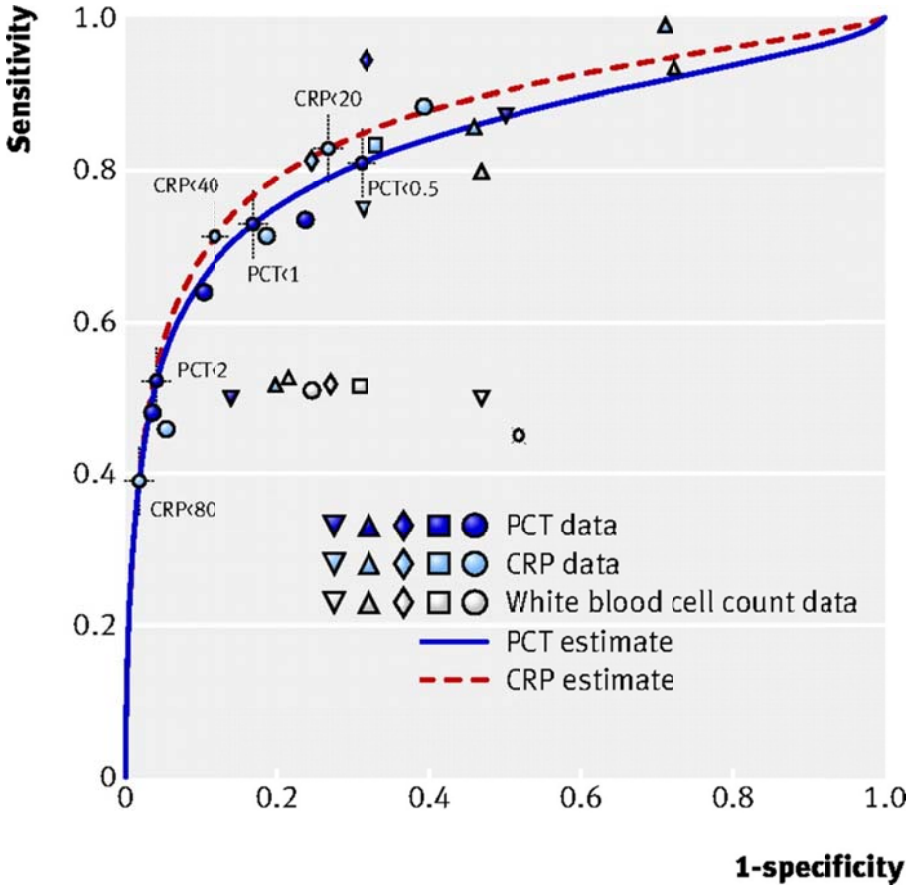
Positive likelihood ratios of less than 5 are generally felt not to be clinically useful. No differences in results were detected in any specific age subgroups.
Bottom line: Pediatric systemic inflammatory response syndrome (SIRS) vital signs are minimally, if at all, accurate in predicting which acutely ill children will require critical care resuscitation. (LOE = 2c)
Reference: *Scott HF, Deakyne SJ, Woods JM, Bajaj L. The prevalence and diagnostic utility of systemic inflammatory response syndrome vital signs in a pediatric emergency department. Acad Emerg Med 2015:22(4):382-389.*

#3: Gut feelings have good negative predictive value for serious infection in children

Clinical question: What is the accuracy of a clinician's gut feelings about the seriousness of illness in children without overt symptoms of serious infection?
Study design: Diagnostic test evaluation **Funding source**: Foundation
Setting: Outpatient (primary care)
Synopsis: Cognitive researchers have found that experienced clinicians make diagnoses using 2 different approaches: either a slow, logical, step-by-step reasoning process, or (more often) a fast, intuitive approach based on recognition of patterns of illness seen in previous cases. This study, conducted in Belgium, evaluated the role of the latter approach, which they called "gut feeling," in the diagnosis of children with possible serious infections. The researchers evaluated 3890 consecutive children aged 0 to 16 years presenting to primary care physicians with acute illness. For each child the doctors recorded clinical features along with their overall clinical impression and whether the doctor had a gut feeling, based on intuition, suggesting the child had something more serious than was suggested by the clinical features. The report doesn't tell us anything about the clinicians but they all seem to be practicing in primary care. After this initial assessment the children were cared for in the usual manner. Serious infection -- defined as requiring hospitalization for pneumonia, sepsis, meningitis, or other infections -- occurred in 21 children (0.54%). Physicians' gut feeling of seriousness was present in 62% of these children but also in 2.7% of children without a serious illness, resulting in a sensitivity of 61.9% and a specificity of 97%. Given the low likelihood of serious infection in the group, though, the positive predictive value was only 10.8% and the negative predictive value was 99.8%. An accurate gut feeling of seriousness was present for 2 the 6 seriously ill children whose clinical features suggested a nonserious illness (positive predictive value = 4.4%; negative predictive value = 99.8%). Individual clinical features strongly associated with a gut feeling of serious illness were the child's lack of responsiveness, abnormal breathing, weight loss, convulsions, and parents' concern.
Bottom line: An intuitive feeling that the objective clinical assessment of a sick child misrepresents the seriousness of his or her illness usually overidentifies serious infection. But, in some cases, this gut feeling is correct. In this study, a parent's concern and nonspecific symptoms in the child (such as drowsiness, abnormal breathing, weight loss, and convulsions) were linked to clinicians' gut feelings of a more serious illness. The authors suggest that you can hone the accuracy of these gut feelings by reflecting on the triggers in the clinical presentation that make you suspicious of something more serious. (LOE = 1c)
Reference: Van den Bruel A, Thompson M, Buntinx F, Mant D. Clinicians' gut feelings about serious infections in children: observational study. BMJ 2012;345:e6144.

#4: CRP and procalcitonin best for dx in febrile children

Clinical question: What is the diagnostic value of laboratory tests for the diagnosis of serious infections in febrile children?
Study design: Meta-analysis (other) **Funding source:** Government
Setting: Outpatient (any)
Synopsis: To conduct this systematic review, the authors searched 4 databases, including DARE, to find studies that evaluated the diagnostic accuracy of tests in febrile outpatient children at least 30 days of age. They identified 14 studies, all of moderate quality or low quality. The prevalence of serious infection ranged from 4.5% to 29.3%. The tests best at ruling in serious infection were C-reactive protein, using a cut-off of 80 mg/L (positive likelihood ratio [LR+] = 8.4; 95% CI, 5.1 - 14.1), and procalcitonin greater than 2 ng/mL (LR+ [from 2 studies] = 3.6 and 13.7; 95% CIs, 7.4 - 25.3 and 1.4 - 8.9). Using a C-reactive protein cutoff of 20 mg/L (negative likelihood ratio [LR-] = .19 - .25) and a procalcitonin cutoff of .5 ng/mL (LR- = .08 - .25) is effective in ruling out serious infection. An elevated white blood cell count is not effective at ruling in or ruling out disease. Combinations of tests did not appreciably improve diagnostic accuracy.
Bottom line: C-reactive protein and procalcitonin are the most effective laboratory tests for ruling in or ruling out serious infections in febrile children. Both tests are better at ruling out than ruling in disease. A white blood cell count is not useful, and other markers of inflammation do not provide good sensitivity or specificity. (LOE = 2a)
Reference: *Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ 2011;342:d3082.*
From the authors:
What this study adds
C reactive protein and procalcitonin may be useful measures, but different cut-off values should be used for ruling in or ruling out serious infections
White blood cell counts are less useful
MAJOR CAVEATS:
No evidence from primary care was identified
No studies of high methodologic quality



#5: Risk-based use of CRP preferred for acutely ill children

Clinical question: Should C-reactive protein be used for all acutely ill children, or only for those at high risk of serious infection?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Government
Allocation: Unconcealed **Setting:** Outpatient (primary care)
Synopsis: CRP is an inflammatory biomarker available as a rapid point-of-care test in many countries (it is not CLIA-waived in the United States, though). It has been shown in previous studies to be a good predictor of pneumonia, acute sinusitis, and other bacterial infections. In this study, 133 general practitioners in 78 practices in Belgium were randomized to use universal or selective CRP for acutely ill children. Children aged 1 month to 16 years were eligible for the study if they had been sick for less than 5 days, and if the illness was not due to a traumatic, neurologic, or psychiatric condition, or to poisoning or intoxication. The universal group always ordered a CRP, while the selective group only ordered a CRP when one of the following was present: shortness of breath, fever 40 °C or higher, diarrhea (in children 12 to 30 months old), or "physician concern." The primary outcome was whether the child was hospitalized for a serious infection between 1 and 5 days after the index visit. In the selective testing group, 285 of 1417 patients met the criteria for testing, of whom 30 were referred to the hospital and 4 had a serious infection. In the comparison group, 50 were referred to the hospital, of whom 7 had a serious infection. These small differences between groups were not statistically significant. In the selective testing group, a cutoff of 5 mg/L or higher would not have missed any serious infections, but would have resulted in a 57% false positive rate. Among the 24 children with a CRP of less than 5 mg/L who were referred to the hospital, 13 received a final diagnosis of viral upper respiratory tract infection, 3 had a urinary tract infection, and 8 had viral gastroenteritis. Only one of these 24 children were admitted.
Bottom line: Restricting the use of C-reactive protein (CRP) to children with shortness of breath, fever of 40 °C or higher, or diarrhea (in 12- to 30-month-olds), or because of "physician concern" is a safe strategy. Of the 24 children who met these criteria and had a CRP level of less than 5 mg/L, 3 had a urinary tract infection and the remainder had a self-limited viral infection. (LOE = 1b-)
Reference: *Verbakel JY, Lemiengre MB, De Burghgraeve T, et al. Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial. BMC Medicine 2016;14(1)131.*

#6: Useful signs and symptoms for diagnosing pneumonia in children younger than 5 years

Clinical question: Are there useful signs and symptoms for diagnosing pneumonia in children younger than 5 years?
Study design: Other **Funding source**: Unknown/not stated
Setting: Population-based
Synopsis: These investigators sourced MEDLINE and Embase, as well as pertinent references for articles evaluating the accuracy of the medical history and physical examination for the diagnosis of pneumonia in children younger than 5 years. Additional eligibility criteria included the use of chest radiography as the reference standard for diagnosis. Two individuals evaluated potential articles for study inclusion and assessed methodologic quality using a standard scoring tool. Disagreements were resolved by consensus discussion with a third reviewer. Only studies of medium or high quality were included. A total of 23 prospective cohort studies (N =

13,833 patients) met inclusion criteria. The presence of chest pain was the only symptom with a positive likelihood ratio approximating at least 2.0 (LR+ = 1.9; 95% CI 1.1 - 3.4). Cough, difficulty breathing, vomiting, and diarrhea all had positive likelihood ratios that were not useful (95% CI that included 1.0). Absence of cough was the only finding with a negative likelihood ratio of less than 0.5 (LR- = 0.47; 0.24 - 0.70). The finding of hypoxemia varied with oxygen saturation thresholds: hypoxemia at 96% or less (LR+ = 2.8; 2.1 - 3.6) and hypoxemia at 95% or less (LR+ = 3.5; 2.0 - 6.4). More severe hypoxemia (oxygen saturation < 90%) was actually less useful (LR+ = 1.5; 1.1 - 1.9). A normal oxygenation saturation (> 96%) was useful for ruling out pneumonia (LR- = 0.47; 0.32 - 0.67). The presence of fever was not useful for ruling in pneumonia, but the absence of fever decreased the likelihood of pneumonia (LR- range = 0.17 - 0.37). Tachypnea (respiratory rate at least 40 breaths per minute), the physicians general assessment of the presence or absence of tachypnea, and tachypnea defined by age-specific rates all had positive likelihood rates of less than 2.0 or with 95% CI that included 1.0 or less). However, a respiratory rate less than or equal to 40 breaths per minute decreased the likelihood of pneumonia (LR- = 0.41; 0.17 - 0.99). No auscultatory findings—including crackles, rales, crepitations, wheeze and rhonchi—were useful in ruling pneumonia in or out. Signs of increased work of breathing were the most useful physical examination findings, including grunting (LR+ = 2.7; 1.5 - 5.1), nasal flaring (LR+ = 2.2; 1.3 - 3.1), and chest retractions (LR+ = 1.9; 1.2 - 2.5).
Bottom line: No single symptom or physical examination finding is reliably useful (positive likelihood ratio [LR+] > 10.0; negative likelihood ratio [LR-] < 0.1) for diagnosing pneumonia in children younger than 5 years. Hypoxia (oxygen saturation < 96%) and physical findings of increased work of breathing (grunting, nasal flaring, and chest retractions) are the most useful for the diagnosis of pneumonia. Tachypnea and auscultation are not useful. (LOE = 3a)
Reference: *Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia? The rational clinical examination systematic review. JAMA 2017;318(5):462-471.*

#7: Clinical signs and symptoms of pneumonia unreliable in children

Clinical question: Which clinical features are useful for the accurate diagnosis of pneumonia in children younger than 5 years?
Study design: Systematic review **Funding source:** Government
Setting: Various (meta-analysis)
Synopsis: These investigators searched multiple databases including MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, as well as performed manual searches of reference lists from eligible articles, for studies evaluating the diagnostic accuracy of clinical signs and symptoms of pneumonia in children aged between 2 months and 6 years. Studies included otherwise healthy children with acute respiratory infections from both the ambulatory and inpatient hospital settings. No language restrictions were applied. Two reviewers used standard risk of bias assessment tools to independently assess articles for inclusion criteria and methodological quality. Disagreements were resolved by consensus discussion. Chest radiography served as the reference standard for the diagnosis of pneumonia. Of the 18 studies that met the inclusion criteria, most were of low to moderate risk of bias. No clinical signs or symptoms reached the level for commonly accepted clinical usefulness (positive likelihood ratio [LR+] > 5 or negative likelihood ratio [LR?] < 0.2). The most useful signs and symptoms for ruling in pneumonia included respiratory rate higher than 50 breaths per minute (LR+ = 1.90; 95% CI 1.45-2.48); grunting (LR+ = 1.78; 1.10-2.88), chest retractions (LR+ = 1.76; 0.86-3.58), and nasal flaring (LR+ = 1.75; 1.20-2.56). The most useful signs and symptoms (when absent) for excluding the diagnosis of pneumonia included cough (LR? = 0.30; 0.09-0.96), history of fever (LR? = 0.53; 0.41-0.69), and respiratory rate higher than 40 breaths per minute (LR? = 0.43; 0.23-0.83).
Bottom line: Standard clinical signs and symptoms are minimally useful in accurately diagnosing pneumonia in children younger than 5 years. The most useful signs and symptoms for ruling in pneumonia included a respiratory rate higher than 50 breaths per minute, grunting, chest retractions, and nasal flaring. The most useful signs and symptoms (when absent) for excluding the diagnosis of pneumonia included cough, history of fever, and a respiratory rate higher than 40 breaths per minute. (LOE = 2a)
Reference: *Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: A systematic review and meta-analysis. Lancet Infect Dis 2015;15(4):439-450.*

What's new with the well child exam?

#8: American Academy of Pediatrics guidelines for hip dysplasia screening and treatment

Clinical question: How should infants be screened and treated for hip dysplasia?
Study design: Practice guideline **Funding source:** Foundation
Setting: Various (guideline)
Synopsis: These guidelines, largely in line with guidelines from the Canadian Task Force and other groups, recommend screening for developmental hip dysplasia through physical examination that includes leg length comparison, examination for asymmetric thigh/gluteal creases, the Ortolani maneuver around the time of birth, and observation for limited abduction after 3 months of age. Though they recommend against universal ultrasonography, they suggest that it be considered between the ages of 6 weeks and 6 months for "high-risk" infants without positive physical findings (though they go on to say that most hip dysplasia occurs in children without risk factors). Evaluation for possible hip dislocation should be performed by an orthopedist. The authors also suggest counseling parents to swaddle the infant in a way that does not restrict hip motion. The guideline developers acknowledge these guidelines are very conservative and err on the side of overdiagnosis; the US Preventive Services Task Force has concluded there is insufficient evidence to support screening. If you find a click or clunk on examination, remember that only 1 in 8 children with positive findings will have dysplasia (Arch Dis Child Fetal Neonatal Ed 2005;90:F25-30).
Bottom line: The American Academy of Pediatrics continues to recommend physical examination for the screening of newborns for developmental hip dysplasia, reserving ultrasound screening for infants at "high risk." A video showing an abnormal Barlow-Ortolani test result can be downloaded at www2.aap.org/sections/ortho/BarlowOrtolani.avi. The authors also suggest counseling parents to swaddle infants in a way that does not restrict hip motion. (LOE = 5)

Reference: Shaw BA, Segal LS, SECTION ON ORTHOPAEDICS. Evaluation and referral for developmental dysplasia of the hip in infants. Pediatrics 2016;138(6):e20163107.

#9: USPSTF 2017 recommends vision screening for all children aged 3 years to 5 years

Clinical question: Should primary care clinicians screen for vision abnormalities in children younger than 6 years?
Study design: Practice guideline **Funding source:** Government
Setting: Population-based
Synopsis: In this updated review the USPSTF evaluated current evidence that assessed the accuracy of vision screening tests and the benefits and harms of vision screening and treatment in children younger than 6 years. The prevalence of amblyopia or its risk factors in this age group is 1% to 6%. No eligible randomized clinical trials directly compared screening with no screening. In addition, no studies evaluated patient-oriented outcomes, such as school performance or quality of life. The task force found adequate evidence that vision-screening tools are accurate for detecting vision abnormalities. Treatment of amblyopia is associated with improved visual acuity in children aged 3 to 5 years. Potential harms of screening include psychosocial problems due to labeling and anxiety (eg, if wearing a patch or eyeglasses is necessary), unnecessary referrals due to false-positive results, and unnecessary treatments. Overall, the task force considered the potential harms of screening and subsequent treatment as small. Trials that examined the benefits and harms of treatment did not enroll children younger than 3 years. The Academy of Pediatrics and Ophthalmology recommend vision assessment in children aged 6 months to 3 years. The American Academy of Family Physicians recommends vision screening in all children at least once between the age of 3 years and 5 years.
Bottom line: The US Preventive Services Task Force (USPSTF) recommends that primary care clinicians perform visual screening at least once for all children aged 3 to 5 years to detect amblyopia or its risk factors (B recommendation). Current evidence is insufficient to assess the benefits and harms of vision screening in children younger than 3 years (I statement). This updated recommendation is essentially unchanged from the previous recommendation in 2011. (LOE = 2b)
Reference: US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Vision screening in children aged 6 months to 5 years. US Preventive Services Task Force recommendation statement. JAMA 2017;318(9):836-844.

#10: Screening for and treating iron deficiency in children: no evidence of benefit or harm

Clinical question: Is there a benefit to screening for iron deficiency in infants and children and in subsequently giving supplements to those found to be deficient?
Study design: Systematic review
Funding source: Government **Setting:** Various (meta-analysis)
Synopsis: Here's the logic trail: Iron deficiency can be identified in approximately 8% of infants and toddlers in the United States; approximately one-third of these children (and 1% to 2% of all children) will have iron-deficiency anemia. However, there is no research that demonstrates either the harm or the benefit of treating iron deficiency or anemia. The researchers searched Medline and the Cochrane databases, as well as reference lists of systematic reviews, to identify English-language clinical trials and observational studies performed in developed countries regarding the screening for iron deficiency and the benefits and harms of iron supplementation in children aged 6 to 24 months. Two investigators evaluated identified studies for inclusion and 2 investigators evaluated included research for quality. They found no studies that evaluated the effect of screening on growth, development, mortality, or quality of life. Iron supplementation had an inconsistent effect on hematologic measures (10 studies). No studies of iron supplementation evaluated the effect on neurodevelopment. Five of 6 weak studies found no clear benefit on growth. No studies have evaluated the harm of iron supplementation.
Bottom line: There is no evidence to support screening for iron deficiency or iron-deficiency anemia in infants and toddlers, and no good research showing a benefit to iron supplementation in identified children. Limited evidence does not show significant harm with supplementation. In both cases -- benefit and harm -- absence of proof is not proof of absence. It would be great to have research that explores these common interventions in children. (LOE = 1a)
Reference: *McDonagh MS, Blazina I, Dana T, Cantor A, Bougatsos C. Screening and routine supplementation for iron deficiency anemia: a systematic review. Pediatrics 2015;135(4):723-733.*

#11: USPSTF: Prevention of dental caries in children

DESCRIPTION: Update of the 2004 US Preventive Services Task Force (USPSTF) recommendation on prevention of dental caries in preschool-aged children.
METHODS: The USPSTF reviewed the evidence on prevention of dental caries by primary care clinicians in children 5 years and younger, focusing on screening for caries, assessment of risk for future caries, and the effectiveness of various interventions that have possible benefits in preventing caries.
POPULATION: This recommendation applies to children age 5 years and younger.
RECOMMENDATION: The USPSTF recommends that primary care clinicians prescribe oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride. (B recommendation) The USPSTF recommends that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of routine screening examinations for dental caries performed by primary care clinicians in children from birth to age 5 years. (I Statement).
Moyer VA; US Preventive Services Task Force. Prevention of dental caries in children from birth through age 5 years: US Preventive Services Task Force recommendation statement. Pediatrics. 2014 Jun;133(6):1102-11.

#12: USPSTF: Screening for speech and language delay and disorders

BACKGROUND: This report is an update of the US Preventive Services Task Force (USPSTF) 2006 recommendation on screening for speech and language delay in preschool-aged children.
METHODS: The USPSTF reviewed the evidence on screening for speech and language delay and disorders in children aged 5 years or younger, including the accuracy of screening in primary care settings, the role of surveillance by primary care clinicians, whether screening and interventions lead to improved outcomes, and the potential harms associated with screening and interventions.
POPULATION: This recommendation applies to asymptomatic children aged 5 years or younger whose parents or clinicians do not have specific concerns about their speech, language, hearing, or development.
RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for speech and language delay and disorders in children aged 5 years or younger (I statement).
Siu AL; US Preventive Services Task Force. Screening for Speech and Language Delay and Disorders in Children Aged 5 Years or Younger: US Preventive Services Task Force Recommendation Statement. Pediatrics. 2015 Aug;136(2):e474-81.

#13: USPSTF: Screening for autism spectrum disorder in young children

DESCRIPTION: New US Preventive Services Task Force (USPSTF) recommendation on screening for autism spectrum disorder (ASD) in young children.
METHODS: The USPSTF reviewed the evidence on the accuracy, benefits, and potential harms of brief, formal screening instruments for ASD administered during routine primary care visits and the benefits and potential harms of early behavioral treatment for young children identified with ASD through screening.
POPULATION: This recommendation applies to children aged 18 to 30 months who have not been diagnosed with ASD or developmental delay and for whom no concerns of ASD have been raised by parents, other caregivers, or health care professionals.
RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician. (I statement).
Siu AL; US Preventive Services Task Force (USPSTF), Screening for Autism Spectrum Disorder in Young Children: US Preventive Services Task Force Recommendation Statement. JAMA. 2016 Feb 16;315(7):691-6.

#14: Editorial: What to Do at Well-Child Visits: The AAFP's Perspective

Evidence supports the following clinical interventions:

Newborns	Congenital hypothyroidism, screening
	Hearing loss, screening
	Ocular gonorrhea infection, preventive medication
	Phenylketonuria, screening
	Sickle cell disease, screening
Children six months and older	Fluoride supplementation in areas where the primary water source is deficient in fluoride
Children three to five years of age	Visual impairment, screening
School-aged children	Tobacco use, counseling to prevent initiation
Children six years and older	Obesity, screening
Children 10 years and older	Skin cancer, counseling to reduce risk
Children 12 years and older	Depression, screening
Sexually active adolescents	Sexually transmitted infections, counseling to reduce risk
Sexually active adolescent females	Gonorrhea and chlamydia infections, screening
Children at high risk of infection	Hepatitis B virus, screening

“The current AAP Bright Futures guideline includes three screening tests that were not recommended for all children in previous versions: autism screening at 18 and 24 months of age, cholesterol screening between nine and 11 years of age, and annual screening for high blood pressure beginning at three years of age.”
“Time is a precious clinical resource. Clinicians who spend time delivering unproven or ineffective interventions at health maintenance visits risk “crowding out” effective services. For example, a national survey of family and internal medicine physicians regarding adult well-male examination practices found that physicians spent an average of five minutes discussing prostate-specific antigen screening (a service that the AAFP and the USPSTF recommend against because the harms outweigh the benefits), but one minute or less each on nutrition and smoking cessation counseling. Similarly, family physicians have limited time at well-child visits and therefore should prioritize preventive services that have strong evidence of net benefit.”
KENNETH W. LIN, MD, MPH, : Editorial: What to Do at Well-Child Visits: The AAFP's Perspective. Am Fam Physician. 2015 Mar 15;91(6):362-364.

When are tympanostomy tubes recommended for otitis media with effusion? How strong is the evidence they are beneficial?

#15: AHRQ: Otitis Media With Effusion: Comparative Effectiveness of Treatments

Objectives: To compare benefits and harms of strategies currently in use for managing otitis media with effusion (OME). Treatment for OME may include single approaches alone or combinations of two or more approaches. We compared benefits and harms among these treatments: tympanostomy tubes (TT), myringotomy (myr), adenoidectomy (adenoid), autoinflation (auto), oral or nasal steroids, complementary and alternative medicine (CAM), and watchful waiting (WW). We included comparisons of treatment effectiveness in subgroups of patients with OME, and whether outcome differences were related to factors affecting health care delivery or the receipt of pneumococcal vaccine inoculation.
Data sources: We identified five recent systematic reviews a priori and searched MEDLINE, Embase, the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from root through August 13, 2012, for additional studies. Eligible studies included randomized controlled trials (RCTs), nonrandomized trials, and cohort studies.
Review methods: Eligible studies included at least two arms comparing the treatments described above. Pairs of reviewers independently selected, extracted data from, and rated the risk of bias of relevant studies; they graded the strength of evidence using established criteria. We incorporated meta-analyses from the earlier reviews and synthesized additional evidence qualitatively.
Results: We identified 59 studies through the earlier reviews and our independent searches. Generally, studies examined interventions in otherwise healthy, noninfant children. We did not find any eligible studies covering CAM. Findings are reported for clinical and functional outcomes, and harms. Variation in length of TT retention corresponded to whether TT were designed to be short versus long term, but variation in TT type was not related to improved OME and hearing outcomes. TT decreased OME for 2 years compared with WW or myr, and improved hearing for 6 months compared with WW. OME resolution was more likely with adenoid than no treatment at 12 months. Adenoid and myr were superior to myr alone in relation to OME and hearing outcomes at 24 months. Adenoid and TT were superior to WW for hearing outcomes at 24 months. Auto was superior to standard treatment at improving OME at 1 month. We found no benefits from oral steroids at 2 months, or topical steroids at 9 months. In relation to functional outcomes, TT and WW did not differ in long-term language, cognitive or academic outcomes. Tympanosclerosis and otorrhea were more common in ears with TT. Adenoid increased the risk of postsurgical hemorrhage. In one study of a subgroup, adults receiving auto were more likely to recover from OME than those in the control group at one month. We found no studies examining the influence of any health care factors on treatment effectiveness.
Conclusions: There is evidence that both TT and adenoid reduce OME and improve hearing in the short term, but both treatments also have associated harms. Large, well-controlled studies could help resolve the risk-benefit ratio by measuring AOM recurrence, functional outcomes, quality of life measures, and long-term outcomes. Finally, additional research is needed to support treatment decisions in subpopulations, particularly those with comorbidities and those who have received a pneumococcal vaccine inoculation.Reference: Berkman ND, Wallace IF, Steiner MJ, Harrison M, Greenblatt AM, Lohr KN, Kimple A, Yuen A. Otitis Media With Effusion: Comparative Effectiveness of Treatments. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 May. Report No.: 13-EHC091-EF. AHRQ Comparative Effectiveness Reviews.

#16: Clinical practice guideline: Tympanostomy tubes in children.

Objective: Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States. Tympanostomy tubes are most often inserted because of persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy. Despite the frequency of tympanostomy tube insertion, there are currently no clinical practice guidelines in the United States that address specific indications for surgery. This guideline is intended for any clinician involved in managing children, aged 6 months to 12 years, with tympanostomy tubes or being considered for tympanostomy tubes in any care setting, as an intervention for otitis media of any type.
Purpose: The primary purpose of this clinical practice guideline is to provide clinicians with evidence-based recommendations on patient selection and surgical indications for and management of tympanostomy tubes in children. The development group broadly discussed indications for tube placement, perioperative management, care of children with indwelling tubes, and outcomes of tympanostomy tube surgery. Given the lack of current published guidance on surgical indications, the group focused on situations in which tube insertion would be optional, recommended, or not recommended. Additional emphasis was placed on opportunities for quality improvement, particularly regarding shared decision making and care of children with existing tubes.
ACTION STATEMENTS: The development group made a strong recommendation that clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea. The panel made recommendations that (1) clinicians should not perform tympanostomy tube insertion in children with a single episode of otitis media with effusion (OME) of less than 3 months' duration; (2) clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer (chronic OME) or prior to surgery when a child becomes a candidate for tympanostomy tube insertion; (3) clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer (chronic OME) and documented hearing difficulties; (4) clinicians should reevaluate, at 3- to 6-month intervals, children with chronic OME who did not receive tympanostomy tubes until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected; (5) clinicians should not perform tympanostomy tube insertion in children with recurrent acute otitis media (AOM) who do not have middle ear effusion in either ear at the time of assessment for tube candidacy; (6) clinicians should offer bilateral tympanostomy tube insertion to children with recurrent AOM who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy; (7) clinicians should determine if a child with recurrent AOM or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors; (8) in the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications; (9) clinicians

should not encourage routine, prophylactic water precautions (use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes. The development group provided the following options: (1) clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) and symptoms that are likely attributable to OME including, but not limited to, vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life and (2) clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME).
Reference: Rosenfeld RM[1], Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM, Hackell JM, Harrison MF, Haskell H, Haynes DS, Kim TW, Lafreniere DC, LeBlanc K, Mackey WL, Netterville JL, Pipan ME, Raol NP, Schellhase KG. *Clinical practice guideline: Tympanostomy tubes in children.* Otolaryngol Head Neck Surg. *2013 Jul;149(1 Suppl):S1-35. doi: 10.1177/0194599813487302.*

#17: Prompt tympanostomy tube insertion doesn't improve 9 yr outcomes

Clinical question: Does the delayed insertion of tympanostomy tubes impair the long-term outcomes in children with persistent middle-ear effusion?
Study design: Randomized controlled trial (single-blinded) **Setting:** Outpatient (any)
Synopsis: Many parents and clinicians still believe that there is a significant risk of permanent harm if tympanostomy tubes are not promptly inserted for children with persistent middle-ear effusion. In this study, which is a follow-up to a previously published POEM (N Engl J Med 2005;353:576), 429 children between the ages of 2 months and 3 years with middle-ear effusion for at least 90 days (bilateral) or 135 days (unilateral) were randomized to receive either prompt or delayed tympanostomy tube insertion. The delay was 6 months for bilateral effusion and 9 months for unilateral effusion. Allocation was concealed, groups were balanced at the start of the study, and analysis was by intention to treat. The researchers did an excellent job of following up: 195 of 216 in the early treatment group and 196 of 213 in the delayed treatment group underwent developmental testing between the ages of 9 years and 11 years. At the time of this final evaluation, 86% in the early treatment group had received tympanostomy tubes compared with only 49% in the delayed treatment group. There was no differences between groups in the results of a broad range of tests including evaluation of hearing, reading, oral fluency, auditory processing, phonological processing, behavior, or intelligence. There was also no difference between these groups and a group of children with ear problems that weren't bad enough to qualify them for the study.
Bottom line: Delayed tympanostomy tube insertion successfully helps many children avoid tubes and does not result in any developmental or other impairment. (LOE = 1b)
Reference: *Paradise JL, Feldman HM, Campbell TF, et al. Tympanostomy tubes and developmental outcomes at 9 to 11 years of age. N Engl J Med 2007;356:248-261.*

There is evidence that tympanostomy tubes are substantially overused. According to a 2008 cohort study in the BMJ (Keyhani, et al, Oct 3 2008), only 30% of tube insertions met criteria based on any guideline in the New York City metropolitan area. The authors concluded:

"A significant majority of tympanostomy tube insertions in the largest and most populous metropolitan area in the United States were inappropriate according to the explicit criteria and not recommended according to both guidelines. Regardless of whether current practice represents a substantial overuse of surgery or the guidelines are overly restrictive, the persistent discrepancy between guidelines and practice cannot be good for children or for people interested in improving their health care."

#18: Tubes ineffective for treating otitis media in children

Clinical question: In children with recurrent otitis media or chronic effusion, do tympanostomy tubes decrease further episodes, improve hearing, or improve language acquisition?
Study design: Meta-analysis (other) **Funding source:** Government
Setting: Various (meta-analysis)
Synopsis: These researchers searched 4 databases, including Cochrane CENTRAL, to find randomized controlled trials and other comparative research studies that evaluated the effectiveness of tympanostomy tubes. They included research written in any language. Citations were selected by 2 independent researchers. Study details were abstracted by one researcher and checked by a second researcher. In 16 randomized controlled trials of treating children with otitis media with effusion, the insertion of tubes with or without adenoidectomy decreased (improved) hearing threshold within the first 1 month to 3 months by an average 9.1 dB to 10.0 dB as compared with no treatment. However, there was no effect on hearing thresholds at 12 months to 24 months for tympanostomy alone or combined with adenoidectomy, prophylactic antibiotic treatment, or myringotomy as compared with no treatment. Overall, there was no effect on cognitive, language, and behavioral outcomes. In 3 small studies of children with recurrent acute otitis media the effect of tympanostomy tubes was inconsistent regarding recurrences. This analysis was a Bayesian network analysis, a statistical approach that still has some kinks in it, and the study report itself was somewhat incomplete, as is the evidence base for this common intervention.
Bottom line: Tympanostomy tubes, with or without other interventions, do not produce sustained improved hearing as compared with no treatment, and has not been shown to improve language acquisition, cognitive development, or behavior measures. There might be a small reduction in the recurrence of acute otitis media, but there is little research in this area. Another study of tubes found no long-term (6 years to 9 years) benefit on development (N Engl J Med 2007;356:248-261). (LOE = 1a-)
Reference: *Steele DW, Adam GP, Di M, Halladay CW, Balk EM, Trikalinos TA. Effectiveness of tympanostomy tubes for otitis media: a meta-analysis. Pediatrics 2017;139(6):e20170125*

#19: Surface swimming all right with tympanostomy tubes

Clinical question: What precautions, if any, are required to decrease the incidence of otorrhea in children with tympanostomy tubes?
Study design: Non-randomized controlled trial **Setting:** Outpatient (any)
Synopsis: Five hundred thirty-three children who were undergoing placement of tympanostomy tubes were enrolled in the study. Of those enrolled, only 399 had comprehensive follow-up. Clinical examination occurred two weeks after the procedure and then every 3 months until the tubes were extruded. Parents were asked to recall the number of episodes of otorrhea for their children and the relationship of otorrhea to swimming, bathing, and upper respiratory infections (URIs). The authors report only the total percentage of subjects who developed otorrhea. A child who swam once and developed otorrhea was counted the same as a child who went swimming on multiple occasions and developed otorrhea once. It was not possible therefore to calculate the risk of otorrhea based on the amount of exposure. Parents self-selected one of four interventions for their children: 1) swimming allowed with no precautions, 2) swimming allowed with no precautions, but on days with water exposure three drops of a suspension of polymyxin B sulfate, neomycin sulfate, and hydrocortisone were instilled into each ear before bedtime, 3) swimming allowed only with custom-molded ear plugs, and 4) swimming not allowed. Diving or swimming more than 180 cm (approximately 6 feet) below the surface was discouraged for all subjects. The groups differed by age (mean age of 29, 31, 60, and 26 months for groups 1, 2, 3, and 4, respectively). No other comparisons between the groups were given such as gender or the performance of simultaneous tonsillectomy or adenoidectomy. No reason was given for subjects that were lost to follow-up (25%). There were no comparisons between those in the study and those lost to follow-up. No power calculations were performed so it is uncertain if there were sufficient subjects in each group to show a statistically significant difference between the groups, if one truly existed. Most episodes of otorrhea were related to URIs and not to swimming. There was no difference between the three swimming groups with respect to swimming-related, URIs-related or bathing-related otorrhea. Although not statistically significant, swimming children using ear molds were nearly twice as likely to report otorrhea compared with children using no precautions (20 percent vs. 11 percent). Nonswimmers had a lower overall incidence of otorrhea (59%) than the swimming groups (68%), but this difference was not statistically significant. The place of swimming (pool, ocean, lake, river) did not make a significant difference on the incidence of swimming-related otorrhea.
Bottom line: Preventing children from swimming during the hot summer months may cause considerable family strife and should not be mandated without clear evidence of harm. Allowing surface swimming without specific precautions for children with tubes is a reasonable approach until there is evidence to the contrary. (LOE = 3b)
Reference: *Salata JA, Derkay CS. Water precautions in children with tympanostomy tubes. Arch Otolaryngol Head Neck Surg 1996;122:276-80.*

#20: Antibiotic/steroid drops best treatment for otorrhea in afebrile kids with tympanostomy tubes

Clinical question: In children with tympanostomy tubes, what is the best treatment for acute otorrhea?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (any)
Synopsis: These researchers identified children with TT who had at least 7 days of otorrhea symptoms; excluded were any kids with temperature > 38.5 C, and any with recent TT placement, recent episode of otorrhea, recent antibiotics, or secondary cause such as immunodeficiency or craniofacial abnormality. Patients were recruited, and either immediately enrolled in the trial if currently symptomatic or the parents were asked to call in if the child became symptomatic. Of 1133 children who were registered for the study, 886 did not report an episode of otorrhea and 247 had home visits for otorrhea. After excluding those with fever, 230 children were randomized to 1 of 3 groups: (1) hydrocortisone-bacitracin-colistin eardrops -- 5 drops given 3 times daily for 7 days; (2) oral amoxicillin-clavulanate -- 30 mg/7.5 mg per kilogram divided into 3 daily doses for 7 days; or (3) observation only for 2 weeks. The patients' mean age was 4.5 years, 58% were male, and 17% had bilateral symptoms. Patients or parents kept a symptom diary for 6 months, and the children were examined in their home by a study physician at 2 weeks and at 6 months. Adherence to to the assigned treatment, or lack thereof, was best for eardrops (93%), then for oral antibiotics (88%), and least for observation (79%); analysis was by intention to treat. The primary outcome was persistent otorrhea at 2 weeks, and was much less common with the eardrops than with oral antibiotics or observation (5% vs 44% vs 55%; P < .05; number needed to treat = 2). The median duration of otorrhea was 4 days with eardrops, 5 days with antibiotics, and 12 days with observation. There was also a median of 1 fewer recurrence in the eardrop group than in the oral antibiotic group (P = 0.03). Gastrointestinal symptoms were fairly common in children receiving an oral antibiotic, and pain with eardrop administration was also common. No complications or serious adverse events were reported. Note that the specific antibiotic combination studied is only available in Europe. Also, the dose of amoxicillin used was lower than typically used in the United States (30 mg/kg divided 3 times a day instead of 80 to 90 mg/kg divided 3 times a day).
Bottom line: For nonfebrile children aged 1 year to 10 years with tympanostomy tubes (TT) and at least 1 week of otorrhea symptoms, a combination hypdrocortisone-bacitracin-colistin eardrop is the best initial therapy. (LOE = 1b)
Reference: *van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med 2014;370(8):723-733.*

Bottom Lines

1. Clinical signs and symptoms of serious infection can be unreliable in children; your "gut feeling" may be the most useful
2. There may be a limited role for CRP in diagnosing serious infection in children, but there are no high quality studies in primary care settings.
3. Well child exams should be evidence based; there is insufficient evidence for many interventions currently recommended by experts
4. Evidence to support tympanostomy tubes in children with otitis media with effusion is weak, but they may be indicated in children with effusion and 3 months of hearing loss.

Screening Update — Mark H. Ebell MD, MS

Objectives

1. Review new recommendations regarding co-testing for cervical cancer screening
2. Understand the (large) potential benefits and (modest) harms of colorectal cancer screening
3. Learn how lung cancer screening is doing in “the real world”.
4. Review the latest screening recommendations for kids

Cervical cancer

USPSTF draft is in progress. It now recommends screening with cervical cytology alone age 21 to 29 years, and from 30 to 65 with cytology every 3 years or HPV testing every 5 years. Do not screen women over age 65 with adequate previous screening, or who have had a hysterectomy for benign disease. The main proposed change has to do with co-testing, which is ordering both cytology and HPV simultaneously: “Both clinical trial evidence and modeling suggest that co-testing increases the number of follow-up tests by as much as twofold and does not lead to increased detection of CIN3+ (CIN3 and all invasive cancers) or cervical cancer compared with screening with high risk HPV testing alone. Therefore, the USPSTF did not include co-testing in this recommendation statement.”

So, no more co-testing.

Breast cancer

USPSTF guidelines: 40 to 49: shared decision-making; 50 to 74: every other year; 75+: insufficient evidence

ACS guidelines: 40 to 44: shared decision making; 45 to 54: every year; 55 to 74: every other year; 75+: until < 10 years to live.

Table 2. Recommendations for breast cancer screening with mammography, in order of overall healthcare spending

Country	Organization (Type)	Year	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
United States	US Preventive Services Task Force (A)	2016								
United States	American Cancer Society (B)	2015								*
United States[1]	American College of Obstetrics & Gynecology (C)	2017								*
United States	American College of Radiology (C)	2016								
Luxembourg	Ministry of Health (A)	NA								
Switzerland[2]	League Against Cancer (B)	2016								
Norway	Cancer Registry of Norway (B)	2010								
Netherlands[3]	NIPHE (A)	2017								
Germany	Federal Joint Committee (A)	2015								
Sweden[4]	National Board of Health and Welfare (A)	2013								
Ireland	National Screening Service (A)	NA								
Austria	Austrian Cancer Aid Society (B)	2014								
Denmark	National Board of Health (A)	2014								
Belgium	Foundation Against Cancer (B)	2017								
Canada[5]	CTFPHC (A)	2011								
Australia	Australian Government Department of Health (A)	2015								
France[6]	National Cancer Institute (A)	2015								
Japan[7]	National Cancer Center (A)	2016								
Iceland	Icelandic Cancer Society (B)	NA								
UK	UK National Screening Committee (A)	2012								
Finland	Cancer Society of Finland (B)	2010								
New Zealand	Ministry of Health (B)	2014								
Italy	National Screening Observatory (A)	2015								
Spain	Cancer Strategy of National Health System (A)	2009								

Recommend:		Recommend selectively:		Do not recommend		Insufficient evidence:	
Every 3 years:		Every 2 years:		Every 1 year:			

1. PubMed: Computer aid does not improve mammography accuracy

Clinical question: Does computer-aided detection improve the accuracy of digital screening mammography?

Study design: Cohort (prospective) **Setting:** Other
Synopsis: Data for this study were assembled from 5 mammography registries in different geographic areas of the United States, using the data from women between the ages of 40 years and 89 years who had digital screening mammography (N = 625,625) in the period of 2003-2009. This was not a controlled study; the 272 radiologists involved in the study each decided whether to use computer assistance. Readings were compared with a breast cancer diagnosis over the next 12 months (or until the next mammogram), including ductal carcinoma in situ. The prevalence of cancer was low, 0.3% in women ages 40-49 years and 0.44% in women 50-73 years of age (remember, this was screening). Since the use of CAD increased over time, the authors did various adjustments to account for differences across time, as well as among the different radiologists. CAD did not decrease the risk of either false positive or false negative results or improve the performance of individual radiologists. Mammography sensitivity was 85.3% (95% CI 83.6%-86.9%) with CAD and 87.3% (84.5%-89.7%) without CAD. Specificity was 91.6% (91.0%-92.2%) with CAD and 91.4% (90.6%-92.0%) without CAD. Among radiologists who only occasionally used CAD, diagnostic sensitivity decreased when they used CAD.
Bottom line: Computer-aided detection (CAD) does not improve the diagnostic accuracy of screening digital mammography. False positive and false negative rates are similar regardless of whther CAD is used. The use of CAD worsens the performance of radiologists who only use it occasionally.
Lehman CD, Wellman RD, Buist DS, et al, for the Breast Cancer Surveillance Consortium. Diagnostic accuracy of digital screening mammography with and without computer-aided detection. JAMA Intern Med 2015;175(11):1828-1837.

There has been more than 2x increase in the incidence of low-grade breast cancers since the 1980's, but only a small reduction in late stage cancers. Many of these low grade cancers are ductal carcinoma in situ (DCIS):

2. POEM: Limited evidence of benefit to treating low-grade DCIS

Clinical question: Does surgery increase the likelihood of survival among women with ductal carcinoma in situ of the breast?
Study design: Cohort (prospective) **Setting:** Outpatient (specialty)
Synopsis: DCIS is a noninvasive lesion that is normally treated with surgery (and often radiation). The incidence of DCIS has increased nearly 7-fold in the last 40 years, because of increased detection via screening mammography. The question is whether all of these lesions need immediate, aggressive treatment. In the absence of randomized trials, these authors turned to the SEER cancer registry and identified 56,053 women with DCIS who had surgery and 1169 who did not have surgery. The women who did not choose surgery were older and were more likely to have low-grade disease. Clearly, women who choose not to have surgery are likely to be quite different from those who opt for it. The authors used propensity score weighting to try and adjust for these differences, although one can only adjust for known, measured confounders and there is likely to be some degree of unmeasured confounding. Thus, these results are not the final word. Nevertheless, these authors found that for low-grade DCIS tumors, there was no survival difference after propensity weighting between women with and without surgery. There was, however, a difference for intermediate-grade and high-grade tumors.
Bottom line: This observational study highlights the lack of good evidence regarding the treatment of ductal carcinoma in situ (DCIS). Randomized trials are currently underway to compare watchful waiting ("active surveillance") with surgery and radiation.
Sagara Y, Mallory MA, Wong S, et al. Survival benefit of breast surgery for low-grade ductal carcinoma in situ: a population-based cohort study. JAMA Surg 2015 doi:10.1001/jamasurg.2015.0876. [Epub ahead of print]

Colorectal cancer

USPSTF: Screen using one of 7 methods between ages of 50 and 75 (A). From 76 to 85, individualize decision based on health (C). Family history in 1 (RR 2.2) or more (RR 4.0) first degree relatives, inflammatory bowel disease (RR 1.7), and relative with diagnosis < 45 years (RR 3.9) all increase risk.

3. Pubmed: Gastroenterology society guidelines for colorectal cancer screening

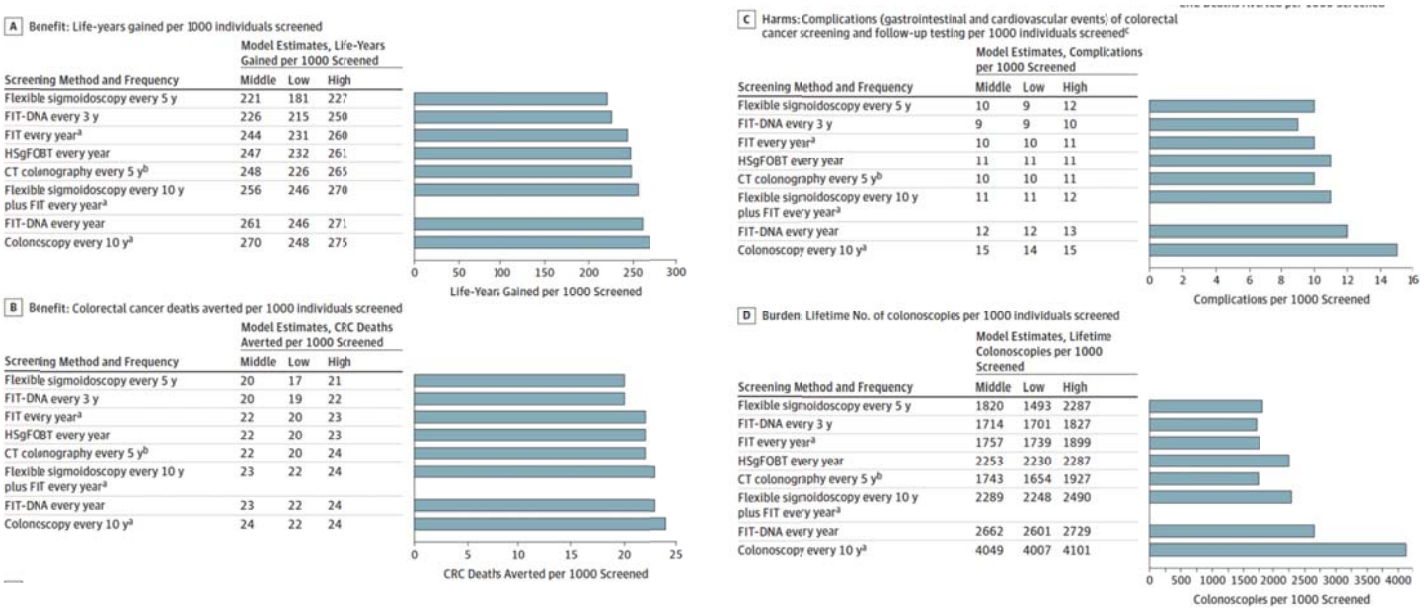
This document updates the colorectal cancer (CRC) screening recommendations of the U.S. Multi-Society Task Force of Colorectal Cancer (MSTF), which represents the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy. CRC screening tests are ranked in 3 tiers based on performance features, costs, and practical considerations. The fi st-tier tests are colonoscopy every 10 years and annual fecal immunochemical test (FIT). Colonoscopy and FIT are recommended s the cornerstones of screening regardless of how screening is offered. Thus, in a sequential approach based on colonoscopy offered first, FIT should be offered to patients who decline colonoscopy. Colonoscopy and FIT are recommended as tests of choice when multiple options are presented as alternatives. A risk-stratified approach is also appropriate, with FIT screening in populations with an estimated low prevalence of advanced neoplasia and colonoscopy screening in high prevalence populations. The second-tier tests include CT colonography every 5 years, the FIT-fecal DNA test every 3 years, and flexible sigmoidoscopy every 5 to 10 years. These tests are appropriate screening tests, but each has disadvantages relative to the tier 1 tests. Because of limited evidence and current obstacles to use, capsule colonoscopy every 5 years is a third-tier test. We suggest that the Septin9 serum assay (Epigenomics, Seattle, Wash) not be used for screening. Screening should begin at age 50 years in average-risk persons, except in African Americans in whom limited evidence supports screening at 45 years. CRC incidence is rising in persons under age 50, and thorough diagnostic evaluation of young persons with suspected colorectal bleeding is recommended. Discontinuation of screening should be considered when persons up to date with screening, who have prior negative screening (particularly colonoscopy), reach age 75 or have <10 years of life expectancy. Persons without prior screening should be considered for screening up to age 85, depending on age and comorbidities. Persons with a family history of CRC or a documented advanced adenoma in a fi rst-degree relative age <60 years or 2 first-degree relatives with these findings at any age are recommended to undergo screening by colonoscopy every 5 years, beginning 10 years before the age at diagnosis of the youngest affected relative or age 40, whichever is earlier. Persons with a single first-degree relative diagnosed at ≥60 years with CRC or an advanced adenoma can

be offered average-risk screening options beginning atage 40 years.
***Reference**: Rex D, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2017; 112: 1016-30.*

Table. Characteristics of Colorectal Cancer Screening Strategies[a]

Screening Method	Frequency[b]	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT[c]	Every year	Test characteristic studies: Improved accuracy compared with gFOBT Can be done with a single specimen	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 y[d]	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test Improved sensitivity compared with FIT per single screening test	There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test
Direct Visualization Tests			
Colonoscopy[c]	Every 10 y	Prospective cohort study with mortality end point	Requires less frequent screening Screening and diagnostic follow-up of positive findings can be performed during the same examination
CT colonography[e]	Every 5 y	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT[c]	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy

These tables summarize the benefits and harms. What you see on the left is that the benefit is substantial (mean 3 months/person on average, 20 to 24 fewer CRC deaths per 1000) but that harms vary, with more harm from colonoscopy based strategies (and cost).



Systematic review (*Am J Gastroenterol 2016;111):1092)* found that for every 100,000 colonoscopies, there were 50 perforations (1 in 2000), 260 bleeds (1 in 400) and 3 deaths (1 in 33,000).

Bottom-line: colorectal cancer screening is a home run, and getting our patients to do colonoscopy or FIT is an important priority. Screening rates could be better: 66% in AZ, 63% in IL, 68% in GA, 64% in ND, and 72% in MI. Do something! But: do not do as part of DRE in the office!

FIT testing is more acceptable than colonoscopy, is cheap, and requires no prep. So how accurate is it? 93% sensitive and 91% specific for cancer, but for advanced neoplasia 48% sensitive and 93% specific. So FIT will miss half of polyps on a single test – is that good enough if done every year? We'll see.

4. POEM: Fecal immunochemical testing accurate for colorectal cancer

Clinical question: How accurate is fecal immunochemical testing for the diagnosis of colorectal cancer in patients with personal or familial history?
Study design: Meta-analysis (other) **Setting:** Various (meta-analysis)
Synopsis: These authors identified 12 studies through a systematic search of 6 databases and study reference lists. The studies enrolled a total of 6204 asymptomatic adults with a family history of colorectal cancer (most studies limited to first-degree relatives) or a personal history of cancer or advanced adenoma and used colonoscopy as the reference standard. Two researchers independently selected the studies for inclusion and abstracted the data. Six of the studies had a high risk of bias. For colorectal cancer, the pooled sensitivity of the FIT was 93% (95% CI 53% - 99%), and specificity was 91% (89% - 92%). These translate into a positive likelihood ratio of 10.30 (7.7 - 13.9) and a negative likelihood ratio of 0.08 (0.01 - 0.75). For advanced neoplasia, the pooled sensitivity of the FIT was only 48% (39% - 57%); and the pooled specificity was 93% (91% - 94%), translating to a positive likelihood ratio of 6.55 (5.0 - 8.5) and a negative likelihood ratio of 0.57 (0.48 - 0.67).
Bottom line: As a screening tool for patients at increased risk of colorectal cancer, the fecal immunochemical test (FIT) is an accurate screening test in the same range as screening colonoscopy. However, the quality of the included studies isn't great and there is large variability among the studies.
Katsoula A, Paschos P, Haidich AB, Tsapas A, Giouleme O. Diagnostic accuracy of fecal immunochemical test in patients at increased risk for colorectal cancer. A meta-analysis. JAMA Intern Med 2017;177(8):1110-1118.

5. POEM: Colonoscopy more than 10 months after positive FIT increases risk of colorectal cancer and more advanced-stage disease

Clinical question: Does the time of follow-up colonoscopy after a positive fecal immunochemical test affect the risk of colon cancer and more advanced-stage disease?
Study design: Cohort (retrospective) **Setting:** Population-based
Synopsis: These invesigators retrospectively analyzed data obtained from a large health care system in California on adults, aged 50 to 75 years, with a positive screening FIT result and a subsequent referral for colonoscopy scheduling. Exclusion criteria included a history of colon cancer, less than a year of membership in the system and no record of a colonoscopy since enrollment, a colonoscopy within less than 10 years or sigmoidoscopy within less than 5 years, and colonoscopy or colorectal cancer diagnosis within 1 to 7 days after the positive FIT result. Of the eligible participants with a positive FIT result (N = 81,518), 86% received a follow-up colonoscopy. Of these 33.3% received a colonoscopy within 30 days, 63.6% within 2 months, 74.2% within 3 months, 80.6% within 6 months, and 83.2% within 12 months. No significant differences occurred in the risk of colorectal cancer with follow-up colonoscopy within 6 months compared with follow-up between 8 days and 30 days. For those patients with follow-up from 7 months to 9 months, the risk of stage II colorectal cancer was significantly increased compared with the patients with follow-up in less than 30 days (12 vs 9 cases per 1000 patients). For follow-up colonoscopy at 10 months to 12 months the risk of any colorectal cancer was significantly increased (49 cases per 1000 patients), as was advanced-stage disease (19 cases per 1000 patients) and stage IV colorectal cancer (7 cases per 1000 patients). Risks were even more significantly increased with follow-up examinations more than 12 months after initial FIT.
Bottom line: In adults with a positive fecal immunochemical test (FIT) result, there are no differences in colorectal cancer outcomes if the follow-up colon examination occurs within 6 months. Follow-up colon examination from 6 months to 10 months is associated with an increased risk of stage II colorectal cancer. Follow-up after 10 months is significantly associated with an increased risk of advanced-stage disease, including stage IV colorectal cancer.
Corley DA, Jensen CD, Quinn VP, et al. Association between time to colonoscopy after a positive fecal test result and risk of colorectal cancer and cancer stage at diagnosis. JAMA 2017;317(16):1631-1641.

Trials comparing FIT to colonoscopy for real clinical outcomes are ongoing. Preliminary results find much better uptake for FIT, better polyp detection for colonoscopy. Remember, we are comparing a **program of screening**, not a single test:

Ongoing Screening Colonoscopy Randomized Controlled Trials

RCT	Setting	Comparison	Primary Outcome
ColonPrev NCT00906997	Spain	Screening colonoscopy versus biennial FIT	10-year CRC and incidence
NordICC NCT00883792	Sweden, Norway, the Netherlands, Poland	Screening colonoscopy versus no screening	15-year CRC and incidence
CONFIRM (VA CSP 577) NCT01239082	United States VA system	Screening colonoscopy versus annual FIT	10-year CRC mortality
SREESCO NCT02078804	Sweden	Screening colonoscopy versus 2 FIT rounds versus no screening	15-year CRC mortality

CRC, colorectal cancer; *FIT*, fecal immunochemical test; *RCT*, randomized controlled trial.

6. POEM: Aspirin = screening to prevent colorectal cancer mortality

Clinical question: Is regular aspirin use as effective as screening to prevent colorectal cancer mortality?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The authors of this meta-analysis searched 3 databases including Cochrane CENTRAL, to identify randomized controlled trials of aspirin, FOBT, and flexible sigmoidoscopy/colonoscopy on colorectal mortality. The aspirin studies were designed to evaluate its effect on cardiovascular outcomes or on general prevention in general populations but also collected data on cancer incidence. There were no direct comparisons of these approaches so the authors conducted a network analysis, which allows for indirect comparisons when direct comparisons were not performed. Study quality was high. The effect of aspirin was similar to effects of FOBT and flexible sigmoidoscopy on colorectal cancer mortality. Aspirin was more effective than FOBT (relative risk [RR] .36; 95% predictive interval [PrI] .22 - .59) and flexible sigmoidoscopy (RR .37; 95% PrI .22 - .62) in preventing proximal colon cancer or death from it. Aspirin was equally effective as screening in reducing colorectal cancer incidence. Network meta-analysis is a relatively new technique and this study isn't the final answer.
Bottom line: As the authors of this study point out, using aspirin to prevent colorectal cancer, rather than using methods to screen for it, might be a game changer. This indirect meta-analysis found aspirin to have a similar effect to fecal occult blood testing (FOBT) and flexible sigmoidoscopy on colorectal cancer mortality. However, these results are based on comparisons using network meta-analysis. We need direct study, but these results suggest we might consider fewer screenings in patients who take aspirin regularly.
Emilsson L, Holme O, Bretthauer M, et al. Systematic review with meta-analysis: the comparative effectiveness of aspirin vs. screening for colorectal cancer prevention. Aliment Pharmacol Ther 2017;45(2):193-204.

Lung cancer screening

It's been several years now since the USPSTF recommendation for lung cancer screening. Trials are still underway in UK, targeting high risk current smokers (narrower indication for screening).

7. POEM: Lung cancer screening requires additional imaging in 40% of patients in real world

Clinical question: How often do adults who undergo lung cancer screening with low-dose CT require additional imaging?
Study design: Cohort (retrospective) **Setting:** Outpatient (primary care)
Synopsis: The USPSTF recently gave a "B" recommendation for annual lung cancer screening with low-dose computed tomography (LDCT) for adult current smokers and recent smokers who meet specific increased risk criteria. This recommendation is based mainly on the results of the National Lung Screening Trial, which included patients who are younger and with fewer co-morbidities than the general community-based population. These investigators retrospectively reviewed medical records for radiologic outcomes of all patients receiving LDCT screening in a community-based hospital. Eligible patients included those aged 55 to 79 years with a documented smoking history of equal to or greater than 30 pack-years and smoking within the previous 15 years. In the first year after publication of the USPSTF guidelines 149 patients received LDCT scans, of which 94 were ordered specifically as screening tests. Of these 94 screening tests, 22 (23.4%) did not meet the screening guideline criteria. Of the 72 cases that met recommended screening criteria, 29 (40.3%) required additional imaging on the basis of the initial scan results. The LDCT screening identified 2 patients with lung cancer and one with breast cancer.
Bottom line: In this community hospital-based real world study, more than 1 in 5 patients who underwent screening did not meet the specific criteria recommended by the United States Preventive Services Task Force (USPSTF). In addition, the initial screening examination prompted additional imaging in more than 40% of patients who met the recommended screening criteria. In contrast, many hospitals inform patients that only 5% to 10% of low-dose computed tomography scans may also detect things not related to lung cancer that might require additional imaging or testing.
Ledford CJ, Gawrys BL, Wall JL, Saas PD, Seehusen DA. Translating new lung cancer screening guidelines into practice. The experience of one community hospital. J Am Board Fam Med 2016(1);29:152-155.

8. POEM: High false-positive rate with lung cancer screening

Clinical question: What can patients expect when they undergo computed tomography to screen for lung cancer?
Study design: Cohort (prospective) **Setting:** Outpatient (primary care)
Synopsis: This study was conducted in 8 academic medical centers among 93,033 primary care patients. From this group (96.3% of whom were men), the researchers identified 4246 current or former (quit date less than 15 years ago) cigarette smokers who had smoked a minimum of 30 pack-years and invited them to be screened for lung cancer using low-dose CT. Of these, 2106 patients had the screening CT. Overall, 1257 screened patients (59.7%) had a positive finding, including 1184 patients (56.2%) who had 1 or more nodules that needed to be followed. A total of 73 patients (3.5% of all patients screened) had findings suspicious for possible lung cancer and 31 (1.5%) had that diagnosis confirmed within the following year. So, let's run the numbers: This means that for appropriately screened patients undergoing CT, more than half the patients will have a positive finding and 94% of these patients will need additional follow-up. One patient in 17 will be told they may have lung cancer but only 1 in 42 patients with a positive result will actually have lung cancer. Overall, 97.5% of patients with a positive CT scan will not have lung cancer.
Bottom line: If you are thinking about adding lung cancer screening to your delivery of preventive care, be sure to prepare patients. They are likely to receive a positive result, most of the positive results will not be lung cancer, and 1 in 4 patients will require additional tracking (ie, follow-up scans). In this study, more than half (59.7%) of the current or former smokers screened for lung cancer using low-dose computed tomography (CT) had a positive result of some sort. However, 97.5% of them were falsely positive, and half of the patients who screened positive were identified as needing to undergo additional monitoring.
Kinsinger LS, Anderson C, Kim J, et al. Implementation of lung cancer screening in the Veterans Health Administration. JAMA Intern Med 2017;177(3):399-406.

PAR LDCT Screening Measures
(Baseline Exam Date 7/28/2014 - 9/29/2017)

	Study Time Point			
	T0	T1	T2	Grand Total
No. of Screens	994	304	55	1,353
No. of Unique Patients	988	304	55	996
No. of Positive Screens	219	46	9	274
Rt of Positive Screens	0.220	0.151	0.164	0.203
Rt of False Positive Screens (Overall)	0.197	0.141	0.164	0.183
Rt of False Positive Screens (+ Only)	0.895	0.935	1.000	0.905
No. of Cancer Diagnoses	24	3	0	27
Rt of Cancer Diagnosis	0.024	0.010	0.000	0.020
No. Screens Resulting n Biopsy	13	4	0	17
Rt of Screens Resulting in Biopsy	0.013	0.013	0.000	0.013
No. of Screens Resulting in Biopsy w/o CA Diagnosis	4	1	0	5
No. of Deaths	3	1	0	4
No. of Cancer Related Deaths	1	0	0	1
Rt of cases >90 Days Late for Next Exam	0.279	0.151	0.000	0.237

On the positive side, the Italian trial, while smaller, found consistent results to NLST:

9. POEM: Italian lung cancer screening findings consistent with US National Lung Screening Trial results (ITALUNG)

Question: Does lung cancer screening reduce mortality and avoid overdiagnosis?
Design: Randomized controlled trial (nonblinded); LOE: 1b **Setting**: Outpatient (any)
Synopsis: Lung cancer screening is controversial because of concerns of the harms of follow-up scans, biopsies, and surgeries, and uncertainty regarding benefit. The ITALUNG trial randomized 3206 smokers to low-dose computed tomography screening annually or to usual care for 4 years. The patients' average age was 61 years and 64% were male, with a median of 39 pack years of smoking. This report provides 9.3-year follow-up results, 4 years of the screening intervention plus a median 5 year follow-up period. The study was much smaller than the NLST on which the US Preventive Services Task Force recommendations were based. These authors found strong trends regarding reductions in all-cause mortality (105 vs 127 deaths per 10,000 person years; rate ratio 0.83; 95% CI 0.67 - 1.03) and lung cancer–specific mortality (29.3 vs 42.1 deaths/10,000 person years; rate ratio 0.70; 0.47 - 1.03). These findings are similar in magnitude and direction to those of the NLST. During the median 9.3 year follow-up period, 67 lung cancers were diagnosed in the screened group and 71 in the control group. The number of lung cancers detected during the screening period was 55% higher in the screened group, which is to be expected, and was then 45% lower in the 5-year postscreening period, suggesting that overdiagnosis was not an important problem (if it was, one would have expected to see more lung cancer diagnosed in the screened group cumulatively).
Bottom line: The findings from the ITALUNG trial, while not statistically significant, are of the same magnitude and direction as those in the US National Lung Screening Trial (NLST), which found a reduction in disease-specific and all-cause mortality with lung cancer screening. Further, the findings suggest that overdiagnosis is not an important problem. Data from "real world" implementation of lung cancer screening is still forthcoming.
***Reference**: Paci E, Puliti D, Pegna AL, et al, for the ITALUNG Working Group. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 2017;72(9):825-831.*

Screening in kids

Guidelines for screening in children come from the USPSTF and AAP, with the latter having somewhat "looser" criteria for what is acceptable evidence (i.e. "it makes sense").

Condition	USPSTF	AAP
Depression	Screen adolescents using PHQ-A	Screen adolescents
Vision screening	Screen age 3 to 5 years	Screen beginning age 3 years
Obesity	Screen children and adolescents	Screen starting at age 2 years
HIV	Screen once between 15 and 18	Screen once between 15 and 18
Hyperlipidemia	Insufficient evidence	Screen once between 9 and 11, and once between 17 and 21
Autism	Insufficient evidence	Screen using M-CHAT
Hip dysplasia	No recommendation	Screen using physical exam

PHQ-A (9 questions, scored 0 to 3) here: http://www.uacap.org/uploads/3/2/5/0/3250432/phq-a.pdf

M-CHAT: https://m-chat.org/

10. American Academy of Pediatrics guidelines for hip dysplasia screening and treatment

Clinical question: How should infants be screened and treated for hip dysplasia?
Study design: Practice guideline **Setting:** Various (guideline)
Synopsis: These guidelines, largely in line with guidelines from the Canadian Task Force and other groups, recommend screening for developmental hip dysplasia through physical examination that includes leg length comparison, examination for asymmetric thigh/gluteal creases, the Ortolani maneuver around the time of birth, and observation for limited abduction after 3 months of age. Though they recommend against universal ultrasonography, they suggest that it be considered between the ages of 6 weeks and 6 months for "high-risk" infants without positive physical findings (though they go on to say that most hip dysplasia occurs in children without risk factors). Evaluation for possible hip dislocation should be performed by an orthopedist. The authors also suggest counseling parents to swaddle the infant in a way that does not restrict hip motion. The guideline developers acknowledge these guidelines are very conservative and err on the side of overdiagnosis; the US Preventive Services Task Force has concluded there is insufficient evidence to support screening. If you find a click or clunk on examination, remember that only 1 in 8 children with positive findings will have dysplasia (Arch Dis Child Fetal Neonatal Ed 2005;90:F25-30).
Bottom line: The American Academy of Pediatrics continues to recommend physical examination for the screening of newborns for developmental hip dysplasia, reserving ultrasound screening for infants at "high risk." A video showing an abnormal Barlow-Ortolani test result can be downloaded at www2.aap.org/sections/ortho/BarlowOrtolani.avi. The authors also suggest counseling parents to swaddle infants in a way that does not restrict hip motion.
Shaw BA, Segal LS, SECTION ON ORTHOPAEDICS. Evaluation and referral for developmental dysplasia of the hip in infants. Pediatrics 2016;138(6):e20163107.

11. USPSTF: Screen for depression only in children 12 to 18 years old

Clinical question: Should children be screened for depression?
Study design: Practice guideline **Setting:** Various (guideline)
Synopsis: Based on the incidence of depression in adolescents (~ 8% per year), evidence of fair to good accuracy of screening tools, and demonstration of the effectiveness of treatment, the U.S. Preventive Services Task Force continues to recommend screening for depression in adolescents aged 12 years to 18 years (B recommendation, moderate net benefit). They continue to conclude that the evidence for screening children below these ages is insufficient to weigh benefits and harms and so do not provide a recommendation. Pharmacotherapy, psychotherapy, collaborative care, psychosocial support interventions, and complementary and alternative medicine approaches are all now fair game as treatment, in contrast with the previous recommendations that focused on nondrug treatment.
Bottom line: The U.S. Preventive Services Task Force continues to recommend screening for depression in adolescents aged 12 years to 18 years, and still concludes that there is insufficient evidence to develop a recommendation for children younger than age 12. For teenagers, the authors suggest screening with the Patient Health Questionnaire for Adolescents (PHQ-A) or the primary care version of the Beck Depression Inventory. Missing from these updated recommendations is the previous advice to start with counseling instead of pharmacologic treatment.
Siu AL, on behalf of the U.S. Preventive Services Task Force. Screening for depression in children and adolescents: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016;164(5):360-366. Forman-Hoffman V, McClure E, McKeeman J, et al. Screening for major depressive disorder in children and adolescents: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164(5):342-349.

Miscellaneous

12. Two questions effective in identifying older adults who are not depressed

Clinical question: Can two questions screen for depression in older adults?
Study design: Meta-analysis (other) **Setting:** Various (meta-analysis)
Synopsis: These investigators used several databases to identify a total of 133 studies that evaluated 16 screening instruments for depression in older adults. The study was conducted according to PRISMA standards. Most (80%) of the studies were deemed to be at low risk of bias. Six studies evaluated the Two-Question Screen in 1670 patients (prevalence of depression = 14.3%). The combined sensitivity of Two-Question Screen was 91.8% (95% CI 85.2 - 95.6) and the specificity was 67.6% (58.1 - 76.0). There was moderate heterogeneity among the sensitivity results and substantial heterogeneity among specificity results. In other words, the 2 questions are good at ruling out depression in older patients but further questioning is needed to confirm depression. The performance of the Two-Question Screen is similar to other screening tests, though no studies have directly compared them.
Bottom line: The Two-Question Screen for depression is recommended by the United Kingdom's National Institute for Health and Care Excellence and consists of 2 written questions: (1) In the past month, have you been troubled by feeling down, depressed or hopeless? and (2) In the past month, have you experienced little interest or pleasure in doing things? If both answers are "no," these questions are good at quickly ruling out depression (sensitivity 92%), but if either answer is "yes," more patient questioning is needed to confirm the diagnosis (specificity 68%).
Tsoi KK, Chan JY, Hirai HW, Wong SY. Comparison of diagnostic performance of Two-Question Screen and 15 depression screening instruments for older adults: systematic review and meta-analysis. Br J Psychiatry 2017;210(4):255-260.

13. USPSTF: screening for latent tuberculosis infection (B statement)

Clinical question: Should clinicians screen for latent tuberculosis infection in asymptomatic adults at increased risk?
Study design: Practice guideline **Setting:** Outpatient (any)
Synopsis: In this evidence review the USPSTF found adequate evidence that accurate screening tests are available to detect latent tuberculosis infection. These tests include the Mantoux tuberculin skin test and interferon-gamma release assays. Although no studies

were found that directly compared the benefits of screening with no screening, the USPSTF found adequate evidence that the treatment of latent disease decreases progression to active tuberculosis. No direct evidence of harms of screening was detected, and the magnitude of the harms of treatment is small, with the primary risk being hepatotoxicity due to prophylactic medication. The range of numbers needed to treat to prevent 1 case of latent tuberculosis infection from progressing to active tuberculosis is 111 to 314, while the range of numbers needed to treat to harm to cause 1 case of hepatotoxicity from treatment is 279 to 2531. The USPSTF found no evidence regarding the optimal frequency of screening. This review did not focus on persons who are immunosuppressed or persons who have contact with individuals with active tuberculosis, including health care workers. The American Academy of Family Physicians, the Centers for Disease Control, the American Thoracic Society, and the Infectious Diseases Society of America all recommend screening for latent tuberculosis infection only among populations at increased risk.
Bottom line: The United States Preventive Services Task Force (USPSTF) concludes there is adequate evidence that the benefits outweigh the risks of screening for latent tuberculosis infection in adults, 18 years and older, who are at increased risk for infection (B statement). At-risk populations include persons who were born in, or are former residents of, countries with increased tuberculosis prevalence, and persons who live in, or have lived in, high-risk settings (eg, homeless shelters and correctional facilities). This recommendation is essentially unchanged from the previous USPSTF recommendation on latent tuberculosis infection screening from 1996.
Bibbins-Domingo K; US Preventive Services Task Force. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. JAMA 2016;316(9):962-969.

14. Older patients do not like discussions involving choices based on "limited life expectancy"

Clinical question: How do older patients react to the idea of stopping cancer screening toward the end of life?
Study design: Cohort (prospective) **Setting:** Outpatient (any)
Synopsis: Many guidelines, such as those from the Choosing Wisely campaign, suggest stopping screening for cancer at an age when early identification is not likely to produce a net benefit. This study enrolled 40 patients, with an average age of 75.7 years, to collect their thoughts about how the topic of stopping screening should be broached. Individuals were interviewed after they were given a brief overview of the benefits and harms of cancer screening, using common cancers as examples. They were also told that someone who will not live for 10 more years might not benefit and might be harmed by screening. Patients were then asked what factors they would consider to stop getting regular screening, and what their reactions would be if a clinician suggested stopping screening. Patients were interviewed by an investigator not known to them and the interviews were recorded, transcribed, and open-coded to identify themes. Transcripts were coded independently by 2 investigators. Three themes emerged: (1) participants were amenable to stopping cancer screening, especially if suggested by a trusted clinician; (2) they objected to the concept that a clinician could accurately predict life expectancy; and (3) they preferred that a clinician explain a recommendation to stop screening by incorporating individual health status, but were divided as to whether life expectancy should be brought into the discussion.
Bottom line: It seems that we don't want to be reminded that we are approaching what Harlan Ellison calls "the downhill side" of life. When bringing up the idea that cancer screening may no longer be beneficial given a patient's limited life expectancy, using direct language such as "You may not live long enough to benefit from this test" is perceived by many patients as overly harsh. Instead, statements such as "This test will not help you live longer" may be better received. Although not studied, this same approach may be helpful for de-prescribing efforts.
Schoenborn NL, Lee K Pollack CE, et al. Older adults' views and communication preferences about cancer screening cessation. JAMA Intern Med 2017;177(8):1121-1128.

Things not to do

USPSTF recommends against:

- Screening for COPE in asymptomatic adults
- Screening for thyroid cancer
- Screening for ovarian cancer

Also, USPSTF, AAFP and ACP all recommend against screening low-risk adults for cardiac disease

15. POEM: ACP: Do not screen low-risk adults for cardiac disease

Clinical question: When should adults be screened for cardiac diseases?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This statement from the ACP is based on a systematic review and recommendations from the United States Preventive Services Task Force and on guidelines and standards developed by the American College of Cardiology. The guidelines apply to screening (ie, testing for disease in asymptomatic individuals) in patients with a 10-year heart disease risk of less than either 7.5% or 10% (the cutoff is under debate). Risk can be calculated using the Framingham calculator in Essential Evidence Plus or at: http://cvdrisk.nhlbi.nih.gov/calculator.asp). In these patients, there is no evidence showing that screening improves clinical outcomes. Given the low prevalence of heart disease in these patients, this screening will produce many false-positive results and expose patients to risks of additional testing. Both true positives and false positives may also result in labeling and denial of insurance. Also, the out-of-pocket cost for an uninsured patient is an estimated $500USD to $3000USD for a simple ECG, which is outrageous for a service that is typically reimbursed at approximately $35USD by insurance companies in the United States.
Bottom line: Citing low yield, ineffectiveness in preventing patient outcomes, and high cost, the American College of Physicians (ACP) recommends against resting electrocardiography (ECG) or stress ECG, stress echocardiography, or stress myocardial perfusion

imaging for asymptomatic, low-risk adults. In these patients, the risks of labeling and downstream harm outweigh the benefits.
Chou R, for the High Value Care Task Force of the American College of Physicians. Cardiac screening with electrocardiography, stress echocardiography, or myocardial perfusion imaging: advice for high-value care from the American College of Physicians. Ann Intern Med 2015;162(6):438-447.

Take home points

1. Co-testing (ordering both cytology and HPV) is no longer recommended based on draft USPSTF guidelines for cervical cancer screening
2. The potential benefits of screening for colorectal cancer are large (2 fewer deaths per 100 persons screened) and the harms are modest. Harms are greatest for colonoscopy based strategies vs FIT based on modeling; RCTs are pending.
3. The benefits and harms of lung cancer screening is doing in “the real world” do not always match those of the NLST (but sometimes they do). How we do it matters.
4. Screen adolescents for depression, children 3 to 5 years for vision problems, children and adolescents for obesity, and adolescents for HIV.
5. Don’t screen for thyroid cancer, ovarian cancer, and COPD in asymptomatic average risk adults.

Objectives

1. Know the findings of recent studies regarding potential benefits and harms of screening for and treating prostate cancer

2. Know the findings of recent studies regarding understand the potential benefits and harms of testosterone therapy

Prostate Cancer

The landscape of prostate cancer screening and treatment has changed greatly during the past 5 years. Because most prostate cancer is relatively indolent, active surveillance of low grade (Gleason 6) prostate cancer has expanded dramatically, with about half of US men choosing active surveillance. This has caused the USPSTF to reconsider the D recommendation for PSA screening and reclassify as a C recommendation for men 55 to 69.

"The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)–based screening for prostate cancer. The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older." (Draft 2017 recommendations.)

Here is some of the recently published evidence.

1. Prostate cancer screening: no mortality benefit after 15 years of follow-up (PLCO)

Clinical question: Does screening of asymptomatic men for prostate cancer improve mortality?
Study design: Randomized controlled trial (single-blinded)
Setting: Population-based
Synopsis: We have previously reported data from the original PLCO study (http://www.essentialevidenceplus.com/content/poem/110501) and its 13-year follow-up (http://www.essentialevidenceplus.com/content/poem/140343). In the original trial, more than 76,000 men between the ages of 55 years and 74 years at 10 centers were randomized to receive prostate cancer screening (annual prostate-specific antigen for 6 years plus digital rectal examination for 4 years) or no scheduled screening. This study reports additional follow-up (up to 19 years; median 15 years). The cumulative prostate cancer mortality rates were virtually identical (4.8 and 4.6 per 10,000 person-years, respectively). Additionally, there was no difference in all-cause mortality between the groups (173 and 177 per 10,000 person-years).
Bottom line: After nearly 2 decades of follow-up from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, there appears to be no mortality benefit to screening asymptomatic men for prostate cancer.
Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123(4):592-599.

2. Active surveillance for localized prostate CA: no increased mortality, but higher rates of clinical progression (ProtecT)

Clinical question: What is the best approach to the management of localized prostate cancer?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (specialty)
Synopsis: Clinically localized prostate cancer is defined as stage T1c or T2, and is confined to the prostate gland. In this study, 82,429 British men aged 50 to 69 years had a prostate-specific antigen (PSA) test. Of those, 2664 had grade T1c or T2 cancer, and 1643 agreed to be randomized to 1 of 3 groups: radical prostatectomy, radiotherapy, or a program of AS. AS consisted of frequent PSA tests (every 3 months in the first year and every 6 to 12 months after that), with a rise of 50% or more triggering an evaluation for possible biopsy, and treatment, if indicated. Approximately 80% of men assigned to surgery or radiotherapy received the assigned treatment during the first year following randomization. In the AS group, there was a steady increase in the percentage of men who received radiotherapy, prostatectomy, or another treatment with curative intent, from 20% at year 2, to 40% at year 5, to slightly more than 50% at year 10. There was no difference between groups in mortality due to prostate cancer, in prostate cancer–specific survival at 5 or 10 years, or in all-cause mortality. However, there was a greater likelihood of developing metastatic disease in the AS group, with approximately 3 more metastatic cancers detected per 1000 person-years than in the surgery or radiotherapy groups (P = .004). Clinical progression (defined as progression to T3 or T4 disease, urinary or rectal complications, or the use of androgen deprivation therapy) was also more common in the AS group, with approximately 13 additional patients progressing per 1000 person-years. Stratification of patients by age, PSA result, Gleason score, or stage at diagnosis did not affect the results.
Bottom line: This landmark study compared active surveillance (AS) with radical prostatectomy or radiation therapy for patients with T1c or T2 prostate cancer. The benefits of AS include avoiding radical therapy in half the patients, with no effect on disease-specific

survival or all-cause survival. The potential harms include a greater risk of metastatic disease (3 additional cases per 1000 person years, corresponding to 3 additional cases for 100 men followed up for 10 years) and a greater likelihood of clinical progression. An accompanying study (N Engl J Med 2016; 2016;375(15):1425-1437) discusses the effects on quality of life and complications of treatment.
Hamdy FC, Donovan JL, Lane JA, et al, for the ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375(15):1415-1424.

3. Prostatectomy for local prostate cancer does not significantly reduce mortality in up to 20 years of follow-up

Clinical question: For men with localized prostate cancer, does surgery improve long-term health outcomes?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: This is a long-term follow-up of patients in the PIVOT trial, which compared radical prostatectomy with observation. Patients in each group saw a physician to assess progression of symptoms every 6 months and had bone scans every 5 years, although "active surveillance" was not practiced. All patients had localized (T1-G2NxM0) prostate cancer with a PSA level of less than 50 ng/mL, were younger than 75 years, and were expected to live at least 10 years. See our original review of the PIVOT trial for more details: http://www.essentialevidenceplus.com/content/poem/140901. In the current study, the authors report mortality data through 2014 (range: 12 years to 19.4 years), and provide additional details regarding disease progression and other health outcomes during the original study period (through 2010). Analyses were by intention to treat, and groups were balanced at the start of the study. There was a 5.5% absolute reduction in all-cause mortality and a 4% absolute reduction in prostate cancer–specific mortality at the end of follow-up. These differences were not statistically significant (P = .06 in both cases), but are potentially clinically significant. The absolute risk reductions were greater in patients younger than 65 years (12.2% vs 2.6%) and in those with an initial PSA level greater than 10 ng/mL, though these differences were not statistically significant due in part to small sample size for these subgroups. There was a statistically significant increase in all-cause mortality for patients in the intermediate-risk group based on the D'Amici risk score (in Essential Evidence at http://www.essentialevidenceplus.com/content/rules/304), but not in the low-risk or high-risk groups. The likelihood of disease progression was lower in the surgery group (33.0% vs 59.7%; P < .05; number needed to treat [NNT] = 4), although this was largely due to a greater likelihood of biochemical or local progression. Systemic progression (ie, metastasis) occurred less often in the radical surgery group (4.7% vs 8.7%; P < .05; NNT = 25), similar to the findings of the UK ProtecT trial (http://www.essentialevidenceplus.com/content/poem/181203). However, erectile dysfunction (14.6% vs 5.4%; P < .05; NNTH = 11) and incontinence (17.3% vs 4.4%, NNTH = 8) were also more common in the surgery group.
Bottom line: Radical prostatectomy has benefits and harms. There was a strong and consistent trend toward greater mortality in the PIVOT trial, which obtained a prostate-specific antigen (PSA) test every 6 months but left the subsequent follow-up to the individual physicians. But it is important to view this study in the context of the recent UK ProtecT trial, which used a more aggressive and structured active surveillance protocol. The UK study had higher rates of eventual treatment in the active surveillance arm than the PIVOT trial, and found no difference in mortality. Both studies found similar but small increases in rates of progression to metastatic disease, and much higher rates of erectile dysfunction and incontinence in the surgery group. The reduction in mortality was greatest in younger patients and in those with a PSA level greater than 10 ng/mL (though the reduction was not statistically significant because of the small numbers in these subgroups).
Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377(2):132-142.

Testosterone Replacement Therapy

Because of several well done studies published in the past several years, we are getting closer to understanding potential benefits and harms of testosterone replacement therapy. Positive treatment effects appear relatively small. There does not appear to be risk of prostate cancer, but there is cardiovascular risk, at least for high risk men. In low risk men, benefits may outweigh potential cardiovascular harms.

4. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

OBJECTIVE: To review and quantify the association between endogenous and exogenous testosterone and prostate-specific antigen (PSA) and prostate cancer.
METHODS: Literature searches were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Prospective cohort studies that reported data on the associations between endogenous testosterone and prostate cancer, and placebo-controlled randomized trials of testosterone replacement therapy (TRT) that reported data on PSA and/or prostate cancer cases were retained. Meta-analyses were performed using random-effects models, with tests for publication bias and heterogeneity.
RESULTS: Twenty estimates were included in a meta-analysis, which produced a summary relative risk (SRR) of prostate cancer for an increase of 5 nmol/L of testosterone of 0.99 (95% confidence interval [CI] 0.96, 1.02) without heterogeneity (I^2 = 0%). Based on 26 trials, the overall difference in PSA levels after onset of use of TRT was 0.10 ng/mL (-0.28, 0.48). Results were similar when conducting heterogeneity analyses by mode of administration, region, age at baseline, baseline testosterone, trial duration, type of patients and type of TRT. The SRR of prostate cancer as an adverse effect from 11 TRT trials was 0.87 (95% CI 0.30; 2.50). Results were consistent across studies.

CONCLUSIONS: Prostate cancer appears to be unrelated to endogenous testosterone levels. TRT for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of prostate cancer development. The current data are reassuring, although some caution is essential until multiple studies with longer follow-up are available.
Boyle P, Koechlin A, Bota M, d'Onofrio A, Zaridze DG, Perrin P, Fitzpatrick J, Burnett AL, Boniol M. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. BJU Int. 2016 Nov;118(5):731-741.

5. Testosterone gel has little, if any, symptom benefit for older men with hypogonadism

Clinical question: Is testosterone replacement therapy safe and effective for older men with hypogonadism?
Study design: Randomized controlled trial (double-blinded)
Setting: Population-based
Synopsis: These researchers used mass mailings to recruit participants from the community, a strength of this particular study. Included patients were 65 years or older and had a mean serum testosterone level of less than 275 ng/dL. Three groups of men were recruited: (1) those with decreased libido on a standardized instrument and a partner willing to have sex at least twice a month, (2) those with difficulty climbing stairs or a speed of 1.2 m/sec on a 6-minute walk test, and (3) those with self-reported low vitality and fatigue. The authors used standardized, validated instruments to measure libido, physical function, and vitality/fatigue. Anyone with prostate cancer, depression, uncontrolled hypertension, cardiovascular disease, or symptoms of prostate enlargement was excluded. A total of 51,085 men were screened, of whom 1490 had 2 testosterone measurements with a mean value below the cutoff. Of those 1490 men, 790 met all of the other study criteria and were enrolled. They were randomized to receive testosterone gel 1% in an initial dose of 5 g daily (with the dose titrated to achieve a final value in the midpoint of the normal range for young men) or matching placebo. The mean age of participants was 72 years, 89% were white, 76% were married or living with a partner, and 52% were college graduates. Groups were balanced at baseline and analysis was by intention to treat, although how the allocation into groups was concealed is not reported. A total of 705 men completed the 12-month follow-up period. The only benefit with the testosterone was a small increase (0.58) in the Psychosexual Daily Questionnaire score compared with placebo. This is a 12-point scale, and patients in both groups had a baseline score of 1.4, so this is unlikely to be clinically significant. Another score measuring sexual desire showed a somewhat more impressive gain in the treatment group than in the control group: approximately 3 points higher than a baseline of about 12 points. However, both of these differences narrowed at 12 months. There was no significant difference in walking speed among the group of men specifically enrolled for that reason, but there was a small benefit (number needed to treat = 12 for one more man to walk 50 additional meters in 6 minutes) when you included all 790 patients. There was no difference between groups regarding measures of vitality or fatigue. There was no difference in harms, but the exclusion criteria were extensive and included anyone with or at risk for cardiovascular disease. Although the study was funded by the National Institutes of Health, the investigators report extensive conflicts of interest relevant to the study.
Bottom line: It's difficult to get too excited about these results. There are small, probably clinically insignificant changes on some measures of sexual desire, but the patient-oriented outcomes (more frequent and more satisfactory sex) were not reported. The change in physical function was small, there was no effect on mood or fatigue, and the study was too small to evaluate harms.
Snyder PJ, Bhasin S, Cunningham GR, et al, for the Testosterone Trials Investigators. Effects of testosterone treatment in older men. N Engl J Med 2016;374(7):611-624.

Testosterone and Cardiovascular Risk

Cardiovascular risk for testosterone therapy is real, but the degree of danger varies depending on baseline risk. For example, the first large study of testosterone replacement in older men was terminated early because of excessive cardiovascular events. On the other hand, some studies have shown no excess risk in younger, healthy men.

6. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels

BACKGROUND: Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.
OBJECTIVES: To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.
DESIGN, SETTING, AND PATIENTS: A retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011.
MAIN OUTCOMES AND MEASURES: Primary outcome was a composite of all-cause mortality, MI, and ischemic stroke.
RESULTS: Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography. Of the 1710 outcome events, 748 men died, 443 had MIs, and 519 had strokes. Of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with events were 19.9%in the no testosterone therapy group vs 25.7%in the testosterone therapy group, with an absolute risk difference of 5.8%(95%CI, -1.4%to 13.1%) [corrected].The Kaplan-Meier estimated cumulative percentages with events among the no testosterone therapy group vs testosterone therapy group at 1 year after coronary angiography were 10.1% vs 11.3%; at 2 years, 15.4% vs 18.5%; and at 3 years, 19.9% vs 25.7 [corrected].There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, P = .41).
CONCLUSIONS AND RELEVANCE: Among a cohort of men in the VA health care system who underwent coronary angiography and

had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.
Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013 Nov 6;310(17):1829-36.

7. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

AIMS: There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke. The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.
METHODS AND RESULTS: We retrospectively examined 83 010 male veterans with documented low TT levels. The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels), (Gp2: TRT without normalization of TT levels) and (Gp3: Did not receive TRT). By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42-0.46], risk of MI (HR: 0.76, CI 0.63-0.93), and stroke (HR: 0.64, CI 0.43-0.96) were significantly lower in Gp1 (n = 43 931, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 (n = 13 378, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort. Similarly, the all-cause mortality (HR: 0.53, CI 0.50-0.55), risk of MI (HR: 0.82, CI 0.71-0.95), and stroke (HR: 0.70, CI 0.51-0.96) were significantly lower in Gp1 vs. Gp2 (n = 25 701, median age = 66 years, mean follow-up = 4.6 years). There was no difference in MI or stroke risk between Gp2 and Gp3.
CONCLUSION: In this large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.
Sharma R, Oni OA, Gupta K, Chen G, Sharma M, Dawn B, Sharma R, Parashara D, Savin VJ, Ambrose JA, Barua RS. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J. 2015 Oct 21;36(40):2706-15.

8. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men with Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial

IMPORTANCE: Testosterone use in older men is increasing, but its long-term effects on progression of atherosclerosis are unknown.
OBJECTIVE: To determine the effect of testosterone administration on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels.
DESIGN, SETTING, AND PARTICIPANTS: Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) was a placebo-controlled, double-blind, parallel-group randomized trial involving 308 men 60 years or older with low or low-normal testosterone levels (100-400 ng/dL; free testosterone <50 pg/mL), recruited at 3 US centers. Recruitment took place between September 2004 and February 2009; the last participant completed the study in May 2012.
INTERVENTIONS: One hundred fifty-six participants were randomized to receive 7.5 g of 1% testosterone and 152 were randomized to receive placebo gel packets daily for 3 years. The dose was adjusted to achieve testosterone levels between 500 and 900 ng/dL.
MAIN OUTCOMES AND MEASURES: Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium; secondary outcomes included sexual function and health-related quality of life.
RESULTS: Baseline characteristics were similar between groups: patients were a mean age of 67.6 years; 42% had hypertension; 15%, diabetes; 15%, cardiovascular disease; and 27%, obesity. The rate of change in intima-media thickness was 0.010 mm/year in the placebo group and 0.012 mm/year in the testosterone group (mean difference adjusted for age and trial site, 0.0002 mm/year; 95% CI, -0.003 to 0.003, P = .89). The rate of change in the coronary artery calcium score was 41.4 Agatston units/year in the placebo group and 31.4 Agatston units/year in the testosterone group (adjusted mean difference, -10.8 Agatston units/year; 95% CI, -45.7 to 24.2; P = .54). Changes in intima-media thickness or calcium scores were not associated with change in testosterone levels among individuals assigned to receive testosterone. Sexual desire, erectile function, overall sexual function scores, partner intimacy, and health-related quality of life did not differ significantly between groups. Hematocrit and prostate-specific antigen levels increased more in testosterone group.
CONCLUSIONS AND RELEVANCE: Among older men with low or low-normal testosterone levels, testosterone administration for 3 years vs placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium nor did it improve overall sexual function or health-related quality of life. Because this trial was only powered to evaluate atherosclerosis progression, these findings should not be interpreted as establishing cardiovascular safety of testosterone use in older men.
Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, Pencina KM, Vita J, Dzekov C, Mazer NA, Coviello AD, Knapp PE, Hally K, Pinjic E, Yan M, Storer TW, Bhasin S. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. JAMA. 2015 Aug 11;314(6):570-81.

9. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone

IMPORTANCE: Recent studies have yielded conflicting results as to whether testosterone treatment increases cardiovascular risk.
OBJECTIVE: To test the hypothesis that testosterone treatment of older men with low testosterone slows progression of noncalcified coronary artery plaque volume.
DESIGN, SETTING, AND PARTICIPANTS: Double-blinded, placebo-controlled trial at 9 academic medical centers in the United States. The participants were 170 of 788 men aged 65 years or older with an average of 2 serum testosterone levels lower than 275 ng/dL (82 men assigned to placebo, 88 to testosterone) and symptoms suggestive of hypogonadism who were enrolled in

the Testosterone Trials between June 24, 2010, and June 9, 2014.
INTERVENTION: Testosterone gel, with the dose adjusted to maintain the testosterone level in the normal range for young men, or placebo gel for 12 months.
MAIN OUTCOMES AND MEASURES: The primary outcome was noncalcified coronary artery plaque volume, as determined by coronary computed tomographic angiography. Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score (range of 0 to >400 Agatston units, with higher values indicating more severe atherosclerosis).
RESULTS: Of 170 men who were enrolled, 138 (73 receiving testosterone treatment and 65 receiving placebo) completed the study and were available for the primary analysis. Among the 138 men, the mean (SD) age was 71.2 (5.7) years, and 81% were white. At baseline, 70 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units, reflecting severe atherosclerosis. For the primary outcome, testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months (from median values of 204 mm3 to 232 mm3 vs 317 mm3 to 325 mm3, respectively; estimated difference, 41 mm3; 95% CI, 14 to 67 mm3; P = .003). For the secondary outcomes, the median total plaque volume increased from baseline to 12 months from 272 mm3 to 318 mm3 in the testosterone group vs from 499 mm3 to 541 mm3 in the placebo group (estimated difference, 47 mm3; 95% CI, 13 to 80 mm3; P = .006), and the median coronary artery calcification score changed from 255 to 244 Agatston units in the testosteronegroup vs 494 to 503 Agatston units in the placebo group (estimated difference, -27 Agatston units; 95% CI, -80 to 26 Agatston units). No major adverse cardiovascular events occurred in either group.
CONCLUSIONS AND RELEVANCE: Among older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary computed tomographic angiography. Larger studies are needed to understand the clinical implications of this finding.
Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER 3rd, Wenger NK, Bhasin S, Barrett-Connor E, et. al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA. 2017 Feb 21;317(7):708-716.

10. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews

Given the conflicting evidence regarding the association between exogenous testosterone and cardiovascular events, we systematically assessed published systematic reviews for evidence of the association between exogenous testosterone and cardiovascular events. We searched PubMed, MEDLINE, Embase, Cochrane Collaboration Clinical Trials, ClinicalTrials.gov, and the US Food and Drug Administration website for systematic reviews of randomised controlled trials published up to July 19, 2016. Two independent reviewers screened 954 full texts from 29 335 abstracts to identify systematic reviews of randomised controlled trials in which the cardiovascular effects of exogenous testosterone on men aged 18 years or older were examined. We extracted data for study characteristics, analytic methods, and key findings, and applied the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist to assess methodological quality of each review. Our primary outcome measure was the direction and magnitude of association between exogenous testosterone and cardiovascular events. We identified seven reviews and meta-analyses, which had substantial clinical heterogeneity, differing statistical methods, and variable methodological quality and quality of data abstraction. AMSTAR scores ranged from 3 to 9 out of 11. Six systematic reviews that each included a meta-analysis showed no significant association between exogenous testosterone and cardiovascular events, with summary estimates ranging from 1·07 to 1·82 and imprecise confidence intervals. Two of these six meta-analyses showed increased risk in subgroup analyses of oral testosterone and men aged 65 years or older during their first treatment year. One meta-analysis showed a significant association between exogenous testosterone and cardiovascular events, in men aged 18 years or older generally, with a summary estimate of 1·54 (95% CI 1·09-2·18). Our optimal information size analysis showed that any randomised controlled trial aiming to detect a true difference in cardiovascular risk between treatment groups receiving exogenous testosterone and their controls (with a two-sided p value of 0·05 and a power of 80%) would require at least 17 664 participants in each trial group. Therefore, given the challenge of adequately powering clinical trials for rare outcomes, rigorous observational studies are needed to clarify the association between testosterone-replacement therapy and major adverse cardiovascular outcomes.
Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. Lancet Diabetes Endocrinol. 2016 Nov;4(11):943-956.

Testosterone Replacement Therapy and Sexual Function

Although it is entirely reasonable to think that testosterone replacement would improve sexual function, it appears to have only a small effect on libido and no improvement in performance.

11. Low serum testosterone levels are poor predictors of sexual dysfunction

OBJECTIVE: To identify predictors of sexual dysfunction using baseline data from the reduction by dutasteride of prostate cancer events (REDUCE) study.
PATIENTS AND METHODS: REDUCE was a 4-year randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of once-daily dutasteride 0.5 mg in over 8000 men aged 50-75 years with a prostate-specific antigen (PSA) level of 2.5-10 ng/mL (50-60 years) or 3.0-10 ng/mL (>60 years) and a negative prostate biopsy within 6 months of enrolment. • Baseline values (mean serum testosterone, age, International Prostate Symptom Score [IPSS], total prostate volume [TPV], body mass index [BMI], and presence of diabetes/glucose intolerance) were compared in subjects with and without sexual dysfunction (sexual inactivity, impotence, decreased libido or a Problem Assessment Scale of the Sexual Function Index [PAS-SFI] score <9).
RESULTS: Multivariate logistic regression showed that baseline age and IPSS were significant predictors of all four sexual function criteria examined (P < 0.0001). • BMI was a significant predictor of decreased libido, impotence and a PAS-SFI score <9, while diabetes/glucose intolerance was a significant predictor of sexual inactivity, impotence and a PAS-SFI score <9. • Testosterone and TPV were not significant predictors of any sexual function criterion examined.

CONCLUSIONS: Age, IPSS, BMI and diabetes/glucose intolerance, but not serum testosterone or TPV, were significant independent predictors of sexual dysfunction in the REDUCE study population. • The lack of association between sexual dysfunction and serum testosterone questions the value of modestly reduced or low normal testosterone levels as criteria for choosing testosterone replacement in older men with sexual dysfunction.
Marberger M, Wilson TH, Rittmaster RS. Low serum testosterone levels are poor predictors of sexual dysfunction. BJU Int. 2011 Jul;108(2):256-62.

12. Testosterone Treatment and Sexual Function in Older Men with Low Testosterone Levels

CONTEXT: The Testosterone Trials are a coordinated set of seven trials to determine the efficacy of T in symptomatic men ≥65 years old with unequivocally low T levels. Initial results of the Sexual Function Trial showed that T improved sexual activity, sexual desire, and erectile function.
OBJECTIVE: To assess the responsiveness of specific sexual activities to T treatment; to relate hormone changes to changes in sexual function; and to determine predictive baseline characteristics and T threshold for sexual outcomes.
DESIGN: A placebo-controlled trial.
SETTING: Twelve academic medical centers in the United States.
PARTICIPANTS: A total of 470 men ≥65 years of age with low libido, average T <275 ng/dL, and a partner willing to have sexual intercourse at least twice a month.
METHODS: Men were assigned to take T gel or placebo for 1 year. Sexual function was assessed by three questionnaires every 3 months: the Psychosexual Daily Questionnaire, the Derogatis Interview for Sexual Function, and the International Index of Erectile Function.
RESULTS: Compared with placebo, T administration significantly improved 10 of 12 measures of sexual activity. Incremental increases in total and free T and estradiol levels were associated with improvements in sexual activity and desire, but not erectile function. No threshold T level was observed for any outcome, and none of the 27 baseline characteristics predicted responsiveness to T.
CONCLUSIONS: In older men with low libido and low T levels, improvements in sexual desire and activity in response to T treatment were related to the magnitude of increases in T and estradiol levels, but there was no clear evidence of a threshold effect.
Cunningham GR, Stephens-Shields AJ, Rosen RC, Wang C, Bhasin S, et. al. Testosterone Treatment and Sexual Function in Older Men With Low Testosterone Levels. J Clin Endocrinol Metab. 2016 Aug;101(8):3096-104.

Testosterone Replacement Therapy and Diabetes Mellitus

13. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes: RCT

OBJECTIVE: The objective of the study was to assess the effect of T treatment on constitutional and sexual symptoms in men with type 2 diabetes (T2D).
DESIGN: This was a randomized double-blind, parallel, placebo-controlled trial.
SETTING: The study was conducted at a tertiary referral center.
PATIENTS: Men aged 35-70 years with T2D, a hemoglobin A1c less than 8.5%, and a total T level less than 12.0 nmol/L (346 ng/dL) with mild to moderate aging male symptoms and erectile dysfunction.
INTERVENTION: Eighty-eight participants were randomly assigned to 40 weeks of im T undecanoate (n = 45) or matching placebo (n = 43).
MAIN OUTCOME MEASURES: Constitutional symptoms using the aging male symptoms (AMS) score, sexual desire (question 17 AMS score), and erectile function (International Index of Erectile Function-5).
RESULTS: T treatment did not substantially improve aging male symptoms [mean adjusted difference (MAD) in change over 40 weeks across the T and placebo groups in AMS total score, -0.9 (95% confidence interval [CI] -4.1, 2.2), P = .67] or sexual desire [MAD in question 17 AMS, -0.3 (95% CI -0.8, 0.2), P = .17]. Although compared with placebo, erectile function in men assigned to T was reduced [MAD in International Index of Erectile Function abridged version 5, -2.0 (95% CI -3.4, -0.6), P < .02], there was no significant difference between baseline and 40-week International Index of Erectile Function abridged version 5 scores if both groups were analyzed separately. At baseline, symptoms were worse in men with depression and microvascular complications but did not correlate with T levels.
CONCLUSIONS: In this trial, T treatment did not substantially improve constitutional or sexual symptoms in obese, aging men with T2D with mild to moderate symptoms and modest reduction in T levels typical for the vast majority of such men.
Gianatti EJ, Dupuis P, Hoermann R, Zajac JD, Grossmann M. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2014 Oct;99(10):3821-8.

14. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study

INTRODUCTION: The association between testosterone deficiency and insulin resistance in men with type 2 diabetes is well established and current endocrine society guidelines recommend the measurement of testosterone levels in all men with type 2 diabetes or erectile dysfunction.
AIM: We report the first double-blind, placebo-controlled study conducted exclusively in a male type 2 diabetes population to assess metabolic changes with long-acting testosterone undecanoate (TU).
METHODS: The type 2 diabetes registers of seven general practices identified 211 patients for a 30-week double-blind, placebo-controlled study of long-acting TU 1,000 mg followed by 52 weeks of open-label use. Because of the established impact of age, obesity, and depression on sexual function, these variables were also assessed for influence on metabolic parameters.
MAIN OUTCOME MEASURE: Changes in glycated hemoglobin (HbA1c) and the level of testosterone at which response are achieved.

RESULTS: Treatment with TU produced a statistically significant reduction in HbA1c at 6 and 18 weeks and after a further 52 weeks of open-label medication most marked in poorly controlled patients with baseline HbA1c greater than 7.5 where the reduction was 0.41% within 6 weeks, and a further 0.46% after 52 weeks of open-label use. There was significant reduction in waist circumference, weight, and body mass index in men without depression, and improvements were related to achieving adequate serum levels of testosterone. There were no significant safety issues.
CONCLUSIONS: Testosterone replacement therapy significantly improved HbA1c, total cholesterol, and waist circumference in men with type 2 diabetes. Improvements were less marked in men with depression at baseline, and therapeutic responses were related to achieving adequate serum testosterone levels. Current advice on 3- to 6-month trials of therapy may be insufficient to achieve maximal response. Patients reported significant improvements in general health.
Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P; BLAST Study Group. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med. 2014 Mar;11(3):840-56.

Other Effects of Testosterone Replacement Therapy

15. Association of Testosterone Levels with Anemia in Older Men: A Controlled Clinical Trial

IMPORTANCE: In one-third of older men with anemia, no recognized cause can be found.
OBJECTIVE: To determine if testosterone treatment of men 65 years or older with unequivocally low testosterone levels and unexplained anemia would increase their hemoglobin concentration.
DESIGN, SETTING, AND PARTICIPANTS: A double-blinded, placebo-controlled trial with treatment allocation by minimization using 788 men 65 years or older who have average testosterone levels of less than 275 ng/dL. Of 788 participants, 126 were anemic (hemoglobin ≤12.7 g/dL), 62 of whom had no known cause. The trial was conducted in 12 academic medical centers in the United States from June 2010 to June 2014.
INTERVENTIONS: Testosterone gel, the dose adjusted to maintain the testosterone levels normal for young men, or placebo gel for 12 months.
MAIN OUTCOMES AND MEASURES: The percent of men with unexplained anemia whose hemoglobin levels increased by 1.0 g/dL or more in response to testosterone compared with placebo. The statistical analysis was intent-to-treat by a logistic mixed effects model adjusted for balancing factors.
RESULTS: The men had a mean age of 74.8 years and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 30.7; 84.9% were white. Testosterone treatment resulted in a greater percentage of men with unexplained anemia whose month 12 hemoglobin levels had increased by 1.0 g/dL or more over baseline (54%) than did placebo (15%) (adjusted OR, 31.5; 95% CI, 3.7-277.8; P = .002) and a greater percentage of men who at month 12 were no longer anemic (58.3%) compared with placebo (22.2%) (adjusted OR, 17.0; 95% CI, 2.8-104.0; P = .002). Testosterone treatment also resulted in a greater percentage of men with anemia of known cause whose month 12 hemoglobin levels had increased by 1.0 g/dL or more (52%) than did placebo (19%) (adjusted OR, 8.2; 95% CI, 2.1-31.9; P = .003). Testosterone treatment resulted in a hemoglobin concentration of more than 17.5 g/dL in 6 men who had not been anemic at baseline.
CONCLUSIONS AND RELEVANCE: Among older men with low testosterone levels, testosterone treatment significantly increased the hemoglobin levels of those with unexplained anemia as well as those with anemia from known causes. These increases may be of clinical value, as suggested by the magnitude of the changes and the correction of anemia in most men, but the overall health benefits remain to be established. Measurement of testosterone levels might be considered in men 65 years or older who have unexplained anemia and symptoms of low testosterone levels.
Roy CN, Snyder PJ, Stephens-Shields AJ, Artz AS, Bhasin S, Cohen HJ, Farrar JT, et. al. Association of Testosterone Levels With Anemia in Older Men: A Controlled Clinical Trial. Intern Med. 2017 Apr 1;177(4):480-490. doi: 10.1001/jamainternmed.2016.9540.

16. Effects of Testosterone Supplementation for 3 Years on Muscle Performance and Physical Function in Older Men

Context: Findings of studies of testosterone's effects on muscle strength and physical function in older men have been inconsistent; its effects on muscle power and fatigability have not been studied.
Objective: To determine the effects of testosterone administration for 3 years in older men on muscle strength, power, fatigability, and physical function.
Design, Setting, and Participants: This was a double-blind, placebo-controlled, randomized trial of healthy men ≥60 years old with total testosterone levels of 100 to 400 ng/dL or free testosterone levels <50 pg/mL.
Interventions: Random assignment to 7.5 g of 1% testosterone or placebo gel daily for 3 years.
Outcome Measures: Loaded and unloaded stair-climbing power, muscle strength, power, and fatigability in leg press and chest press exercises, and lean mass at baseline, 6, 18, and 36 months.
Results: The groups were similar at baseline. Testosterone administration for 3 years was associated with significantly greater performance in unloaded and loaded stair-climbing power than placebo (mean estimated between-group difference, 10.7 W [95% confidence interval (CI), -4.0 to 25.5], P = 0.026; and 22.4 W [95% CI, 4.6 to 40.3], P = 0.027), respectively. Changes in chest-press strength (estimated mean difference, 16.3 N; 95% CI, 5.5 to 27.1; P < 0.001) and power (mean difference 22.5 W; 95% CI, 7.5 to 37.5; P < 0.001), and leg-press power were significantly greater in men randomized to testosterone than in those randomized to placebo. Lean body mass significantly increased more in the testosterone group.
Conclusion: Compared with placebo, testosterone replacement in older men for 3 years was associated with modest but significantly greater improvements in stair-climbing power, muscle mass, and power. Clinical meaningfulness of these treatment effects and their impact on disability in older adults with functional limitations remains to be studied.
Storer TW, Basaria S, Traustadottir T, Harman SM, Pencina K, Li Z, et. al. Effects of Testosterone Supplementation for 3 Years on

Muscle Performance and Physical Function in Older Men. J Clin Endocrinol Metab. 2017 Feb 1;102(2):583-593. doi: 10.1210/jc.2016-2771.

17. Testosterone does not improve cognition in memory-impaired older men with low testosterone levels

Clinical question: Does supplemental testosterone improve cognitive function in memory-impaired older men with low testosterone levels?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: These investigators recruited adult men, 65 years or older, with a mean of 2 morning serum testosterone concentrations of less than 275 ng/dL (9.54 nmol/L). Exclusion criteria included significant cognitive impairment (Mini-Mental State Examination score < 24) and severe depression. Age-associated memory impairment was classified as subjective memory complaints and relative memory impairment (defined as more than 1 standard deviation below the performance scores for men aged 20 years to 24 years, but not greater than 2 standard deviations below the scores of age-matched men) on a standard scoring tool. A total of 493 men randomly received (concealed allocation assignment) testosterone gel 1% concentration at an initial dose of 5 g daily or matched placebo. The dose of testosterone was adjusted by an unmasked study investigator to achieve a level within the mid-normal range for young men (500-800 ng/dL; 17.4-27.8 nmol/L). To maintain participant and treating-clinician masking, the dose of placebo gel was also adjusted simultaneously. Individuals masked to treatment group assignment assessed outcomes. Complete follow-up occurred for 97.3% of participants at 12 months. Using intention-to-treat analyses, there were no significant improvements between the testosterone and control group on measurements of delayed paragraph recall scores, visual memory, executive function, or spatial ability.
Bottom line: Testosterone supplementation for men 65 years or older with both age-associated memory impairment and a low baseline testosterone level was not associated with significant improvements in memory or other cognitive functions.
Resnick SM, Matsumoto AM, Stephens-Shields AJ, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017;317(7):717-727.

18. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations

BACKGROUND: The effects of testosterone on cognitive function in older men are incompletely understood. We aimed to establish the effects of long-term testosterone administration on multiple domains of cognitive function in older men with low or low-to-normal testosterone concentrations.
METHODS: We did the randomised, double-blind, placebo-controlled, parallel-group TEAAM trial at three medical centres in Boston, Phoenix, and Los Angeles, USA. Men aged 60 years and older with low or low-to-normal testosterone concentrations (3·47-13·9 nmol/L, or free testosterone <173 pmol/L) were randomly assigned (1:1), via computer-generated randomisation, to receive either 7·5 g of 1% testosterone gel or placebo gel daily for 3 years. Randomisation was stratified by age (60-75 years vs >75 years) and study site. The testosterone dose was adjusted to achieve concentrations of 17·3-31·2 nmol/L. Participants and all study personnel were masked to treatment allocation. Multiple domains of cognitive function were assessed as prespecified secondary outcomes by use of standardised tests at baseline and months 6, 18, and 36. We did analyses by intention to treat (in men who had baseline assessments of cognitive function) and per protocol (restricted to participants who completed the study drug and had both baseline and 36 month assessments of cognitive function). The TEAAM trial is registered with ClinicalTrials.gov, number NCT00287586.
FINDINGS: Between Sept 1, 2004, and Feb 12, 2009, we randomly assigned 308 participants to receive either testosterone (n=156) or placebo (n=152). 280 men had baseline cognitive assessments (n=140 per group). Mean follow-up time was 29·0 months (SD 11·5) in the testosterone group and 31·1 months (9·5) in the placebo group. The last participant completed the study on May 11, 2012. In the testosterone group, mean concentrations of serum total testosterone increased from 10·6 nmol/L (SD 2·2) to 19·7 nmol/L (9·2) and free testosterone concentrations increased from 222 pmol/L (62) to 364 pmol/L (222). In the placebo group, mean concentrations of serum total testosterone were 10·7 nmol/L (SD 2·3) at baseline and 11·1 nmol/L (3·2) post-intervention and free testosterone concentrations were 210 pmol/L (61) and 172 pmol/L (49), respectively. We recorded no between-group differences in changes in visuospatial ability (mean difference: Complex Figure Test -0·51, 95% CI -2·0 to 1·0), phonemic or category verbal fluency (phonemic fluency test 0·90, -1·3 to 3·1; categorical fluency test 1·1, -0·3 to 2·6), verbal memory (paragraph recall test 0·29, -1·2 to 1·8), manual dexterity (Grooved Pegboard Test 4·2, -1·3 to 9·7), and attention or executive function (Stroop Interference Test -2·6, -7·4 to 2·3) after adjustment for age, education, and baseline cognitive function. In both the intention-to-treat and per-protocol (n=86 per group) populations, changes in cognitive function scores were not related significantly to changes in total or free testosterone, or oestradiol concentrations.
INTERPRETATION: Testosterone administration for 36 months in older men with low or low-to-normal testosterone concentrations did not improve cognitive function. Future long-term trials are needed to investigate the efficacy of testosterone replacement in patients with impaired cognition, such as people with Alzheimer's disease.
Huang G, Wharton W, Bhasin S, Harman SM, Pencina KM, Tsitouras P, Li Z, Hally KA, Asthana S, Storer TW, Basaria S. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations: a prespecified secondary analysis of data from the randomised, double-blind, placebo-controlled TEAAM trial. Lancet Diabetes Endocrinol. 2016 Aug;4(8):657-65.

Meta-analyses of Testosterone Replacement Therapy

19. Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-controlled trials

Abstract: The purpose of the present meta-analysis was to evaluate the efficacy and safety of testosterone replacement therapy in men with hypogonadism. A search was conducted for appropriate randomized controlled trials and the data from 16 trials were pooled. The intended primary outcome of the present study was to determine the efficacy and safety of testosterone replacement therapy. The current data demonstrated that scores for Aging Male Symptoms (AMS) were significantly reduced following testosterone replacement therapy, with a mean decrease in AMS score of 1.52 [95% confidence interval (CI), 0.72 to 2.32; P=0.0002]. Testosterone replacement therapy increased lean body mass [mean difference (MD), 1.22; 95% CI, 0.33 to 2.11; P=0.007], reduced fat mass in a non-significantly manner (MD, -0.85; 95% CI, -1.74 to 0.04; P=0.06) and significantly reduced total cholesterol (MD, -0.16; 95% CI, -0.29 to -0.03; P=0.01). No significant differences were identified in body weight (MD, 0.09; 95% CI, -1.13 to 1.31; P=0.89), body mass index (MD, 0.10; 95% CI, -0.62 to 0.82; P=0.78) or bone mineral density (MD, -0.01; 95% CI, -0.03 to 0.02; P=0.60). Average prostate volume increased (MD, 1.58; 95% CI, 0.6 to 2.56; P=0.002) following testosterone replacement therapy, but the levels of prostate-specific antigen (PSA) (MD, 0.10; 95% CI, -0.03 to 0.22; P=0.14) and the International Prostate Symptom Scores (MD, 0.01; 95% CI, -0.37 to 0.39; P=0.96) did not change. In conclusion, testosterone replacement therapy improves quality of life, increases lean body mass, significantly decreases total cholesterol, and is well-tolerated and safe for men with hypogonadism who are exhibiting PSA levels of <4 ng/ml.
Guo C, Gu W, Liu M, Peng BO, Yao X, Yang B, Zheng J. Efficacy and safety of testosterone replacement therapy in men with hypogonadism: A meta-analysis study of placebo-controlled trials. Exp Ther Med. 2016 Mar;11(3):853-863.

20. Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials

Abstract: Although testosterone replacement therapy can restore serum testosterone concentrations to normal level in late-onset hypogonadism patients, whether it can improve patients' quality of life remains uncertain. Therefore, we perform a meta-analysis of randomized controlled trials on this issue. Five randomized controlled trials total 1,212 patients were included. Fixed-effect model was used to calculate the weighted mean difference of score of Aging Males' Symptom rating scale. Our result reveals that testosterone replacement therapy improves patients' health-related quality of life in terms of the decrease in the AMS total score [WMD = -2.96 (-4.21, -1.71), p < .00001] and the psychological [WMD = -0.89 (-1.41, -0.37), p = .0008], somatic [WMD = -0.89 (-1.41, -0.37), p = .0008] and sexual [WMD = -1.29 (-1.75, -0.83), p < .00001] subscale score.
Nian Y, Ding M, Hu S, He H, Cheng S, Yi L, Li Y, Wang Y. Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials. Andrologia. 2017 May;49(4).

21. Treatment of Men for "Low Testosterone": A Systematic Review

Testosterone products are recommended by some prescribers in response to a diagnosis or presumption of "low testosterone" (low-T) for cardiovascular health, sexual function, muscle weakness or wasting, mood and behavior, and cognition. We performed a systematic review of 156 eligible randomized controlled trials in which testosterone was compared to placebo for one or more of these conditions. We included studies in bibliographic databases between January 1, 1950 and April 9, 2016, and excluded studies involving bodybuilding, contraceptive effectiveness, or treatment of any condition in women or children. Studies with multiple relevant endpoints were included in all relevant tables. Testosterone supplementation did not show consistent benefit for cardiovascular risk, sexual function, mood and behavior, or cognition. Studies that examined clinical cardiovascular endpoints have not favored testosterone therapy over placebo. Testosterone is ineffective in treating erectile dysfunction and controlled trials did not show a consistent effect on libido. Testosterone supplementation consistently increased muscle strength but did not have beneficial effects on physical function. Most studies on mood-related endpoints found no beneficial effect of testosterone treatment on personality, psychological well-being, or mood. The prescription of testosterone supplementation for low-T for cardiovascular health, sexual function, physical function, mood, or cognitive function is without support from randomized clinical trials.
Huo S, Scialli AR, McGarvey S, Hill E, Tügertimur B, Hogenmiller A, Hirsch AI, Fugh-Berman A. Treatment of Men for "Low Testosterone": A Systematic Review. PLoS One. 2016 Sep 21;11(9):e0162480.

22. 2016 Update on Medical Overuse: A Systematic Review

I**mportance:** Overuse of medical care is an increasingly recognized problem in clinical medicine.
Objective: To identify and highlight original research articles published in 2015 that are most likely to reduce overuse of medical care, organized into 3 categories: overuse of testing, overtreatment, and questionable use of services. The articles were reviewed and interpreted for their importance to clinical medicine.
Evidence Review: A structured review of English-language articles on PubMed published in 2015 and review of tables of contents of relevant journals to identify potential articles that related to medical overuse in adults.
Findings: Between January 1, 2015, and December 31, 2015, we reviewed 1445 articles, of which 821 addressed overuse of medical care. Of these, 112 were deemed most relevant based on their originality, methodologic quality, and number of patients potentially affected. The 10 most influential articles were selected by consensus using the same criteria. Findings included a doubling of specialty referrals and advanced imaging for simple headache (from 6.7% in 2000 to 13.9% in 2010); unnecessary hospital admission for low-risk syncope, often leading to adverse events; and overly frequent colonoscopy screening for 34% of patients. Overtreatment was common in the following areas: 1 in 4 patients with atrial fibrillation at low risk for thromboembolism received anticoagulation; **94% of testosterone replacement therapy was administered off guideline recommendations;** 91% of patients resumed taking opioids after overdose; and 61% of patients with diabetes were treated to potentially harmfully low hemoglobin A1c levels (<7%). Findings also identified medical practices to question, including questionable use of treatment of acute low-back pain with cyclobenzaprine and oxycodone/acetaminophen; of testing for Clostridium difficile with molecular assays; and serial follow-up of benign thyroid nodules.
Conclusions and Relevance: The number of articles on overuse of medical care nearly doubled from 2014 to 2015. The present review promotes reflection on the top 10 articles and may lead to questioning other non-evidence-based practices.
Morgan DJ, Dhruva SS, Wright SM, Korenstein S. 2016 Update on Medical Overuse: A Systematic Review. JAMA Intern Med. 2016 Nov 1;176(11):1687-1692.

Bottom Lines

1. Many more men with low grade prostate cancer are choosing active surveillance over surgery or radiation therapy, and the outcomes of active surveillance appear nearly as good with fewer side effects.

2. Since many men are choosing active surveillance, it is reasonable to screen for prostate cancer with PSA testing with shared decision making. The optimal screening protocol for prostate cancer screening with PSA is not known.

3. Testosterone replacement therapy has some small positive effects in some men, such as increased muscle strength and sense of well-being.

4. There is likely cardiovascular risk with TRT in patients at high risk of CAD. Cardiovascular risk in low risk men is uncertain.

5. TRT is not helpful for ED. It does increase desire in some men.

6. TRT raises the hemoglobin level about 1.0. The therapeutic benefit is uncertain.

Editor's Choice

1. Cost-effectiveness of confirmatory testing before treatment of onychomycosis

Clinical question: Is confirmatory diagnostic testing cost-effective for the management of clinically suspected onychomycosis?
Bottom line: The most cost-effective approach to the patient with clinically suspected onychomycosis is empiric therapy with oral terbinafine. The chance of liver injury is estimated to be only 1 in 50,000 to 1 in 120,000, so testing to confirm the diagnosis would cost tens of millions of dollars per case of liver injury avoided. If you plan to prescribe the much more expensive topical solution efinaconazole 10% (Jublia), then confirmatory testing with periodic acid-Schiff (PAS) reduces costs (LOE = 2a)
Study design: Decision analysis **Funding source:** Unknown/not stated
Setting: Outpatient (any)
Synopsis: An annoyance of clinical practice is the requirement by many insurance companies to perform confirmatory diagnostic testing prior to initiating treatment for patients with clinically suspected onychomycosis. This was based on analyses done 15 years ago, when terbinafine was significantly more expensive. Terbinafine is now affordable (approximately $10 for a full 12-week course), but the topical solution efinaconazole 10% provides a new, more expensive option (more than $500 for each 4-mL bottle in the United States). These authors performed a decision analysis that compared 3 strategies: (1) treat all patients empirically; (2) if in-office potassium hydroxide testing result is positive, treat; if negative, order PAS stain and treat if positive; or (3) order PAS stain on all patients and treat only if positive. They assumed, on the basis of previous studies, that between 65% and 95% of patients presenting with clinical nail dystrophy have a fungal infection, and that the cost of a course of treatment was $2307 for efinaconazole and $53 for terbinafine (including monitoring liver function). They concluded that if you are going to prescribe terbinafine, empiric therapy without confirmatory testing is the preferred strategy (and the least expensive overall) with a very low risk of serious adverse effects. If you are going to prescribe efinaconazole, then confirmatory testing with PAS is preferred. However, this is a much more expensive treatment option.
Mikailov A, Cohen J, Joyce C, Mostaghimi A. Cost-effectiveness of confirmatory testing before treatment of onychomycosis. JAMA Dermatol 2016;152(3):276-281.

2. AAN Guideline on managing patients with restless leg syndrome

Clinical question: How should clinicians manage restless leg syndrome?
Bottom line: The American Academy of Neurology recommends using dopamine agonists to treat patients with moderate to severe restless leg syndrome (RLS). Second-line treatments include long-acting opioid/naltrexone combinations or iron supplements (in patients with a ferritin level < 75 mcg/L). For patients who prefer nonpharmaceutical treatment, pneumatic compression appears to be the most studied alternative. (LOE = 5)
Study design: Practice guideline **Funding source:** Foundation
Setting: Outpatient (any)
Synopsis: This committee of the American Academy of Neurology, staffed by members who had multiple ties to industry, systematically assessed multiple studies to develop guidance on managing patients with RLS. Before reviewing the studies, the committee decided to use a change of 3 points on the International Restless Legs Syndrome Study Group rating scale (IRLS) as clinically meaningful. Additionally, the authors established criteria for meaningful findings on polysomnography (periodic leg movement index, total sleep time, sleep efficiency, sleep latency, wake after sleep onset), as well as measures of sleep outcomes. Finally, when making their treatment recommendations, the committee suggested that establishing qualifying criteria is not necessary before treating patients with moderate to severe RLS. Many of the agents in question are also used in treating Parkinson's disease, yet the number of high-quality studies on treating patients with RLS are limited. Most studies are of short duration (approximately 12 weeks), rarely evaluate individual agents head-to-head, and I suspect from my experience in reviewing studies that they also tend to underreport the harms of treatment. Most of the existing data are on the use of dopamine agonists: ropinorole (Requip), pramipexole (Mirapex), rotigotine (Neupro), cabergoline (Cabaser, Dostinex), and levodopa. Each appears effective in managing various symptoms, though cabergoline has not been rigorously studied in RLS and the data on levodopa are mixed. Additionally, dopamine agonists have the potential problem of augmentation—gradual worsening of symptoms after treatment that often requires changing medication or adding a new agent. Gabapentin (Neurontin) and pregabalin (Lyrica) also improve the IRLS score but less clearly decrease periodic limb movements. Iron, oral and parenteral, also improves the IRLS score. Long-acting opioid/naltrexone combinations improve the IRLS score and improve sleep quality in patients with poor response to other agents. Very limited data suggest that the following clinical interventions are also likely to be effective: near-infrared spectroscopy, pneumatic compression, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and vibrating pads.
Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2016;87(24):2585-2593.

3. Meta-analysis: alpha blockers effective for kidney stones

Clinical question: In patients with kidney stones (ureteric calculi), is treatment with an alpha blocker effective in improving passage rate and decreasing pain?
Bottom line: Although a recent large study found no benefit to alpha blocker treatment (Lancet 2015;386:341-49), this meta-analysis of 55 studies found a benefit to using alpha blockers to increase the likelihood of stone passage, decrease surgical intervention, and decrease episodes of pain. These findings support European and US guidelines that recommend their use. Patients with larger (at least 5 mm) stones are more likely to benefit. (LOE = 1a-)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Self-funded or unfunded
Allocation: Concealed **Setting:** Population-based

Synopsis: To conduct this study, the authors searched 5 databases (including Cochrane CENTRAL), a previous systematic review, reference lists of other reviews, and clinical trial registries. Two researchers independently selected randomized controlled trials that compared alpha blockers with placebo or no treatment in patients with ureteric stones. Two researchers independently extracted the data from 55 studies enrolling a total of 5990 patients. Stone passage, which occurs in approximately half of patients without intervention, is 50% greater with treatment (number needed to treat [NNT] = 3.74) and will occur an average 9.5 days after presentation as compared with 13.3 days without treatment. Episodes of pain will also be decreased. The need for surgery will decrease by approximately half (NNT = 6.17) and hospital admissions will decrease approximately 60% (NNT = 10.6) Patients with larger stones (at least 5 mm) are more likely to benefit. There was some evidence of publication bias; for some outcomes, results were calculated only using data from the larger studies. There was significant heterogeneity among the studies regarding stone passage rate.
Hollingsworth JM, Canales BK, Rogers MA, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ 2016;355:i6112.

4. Better outcomes for hospitalized patients treated by female physicians

Clinical question: Are there differences in outcomes for hospitalized patients who are treated by female physicians versus male physicians?
Bottom line: Patients hospitalized for medical conditions who are treated by female physicians are less likely to die or be readmitted within 30 days than those treated by male physicians. Although the effects shown in this study were modest, at less than a percentage point reduction for both outcomes, the difference may be clinically meaningful when applied to more than 10 million annual Medicare hospitalizations. (LOE = 2b)
Study design: Cross-sectional
Funding source: Government
Allocation: Uncertain
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: These authors analyzed a 20% sample of Medicare patients who had a nonelective hospitalization for a medical condition between 2011 and 2014. The main physician caring for the patient during the hospitalization was identified as the physician who garnered the highest amount of Medicare Part B spending, which includes professional fees as well as other fees determined by the physician. The analysis was restricted only to those hospitalizations in which the main physician was identified as a general internist. More than 1.5 million hospitalizations treated by almost 58,000 physicians were included in the sample. The characteristics of patients treated by female physicians and those treated by male physicians were well-balanced, with a mean age of 81 years and similar comorbidities across the 2 groups. The overall 30-day mortality rate and 30-day readmission rates were 11.32% and 15.42%, respectively. After adjusting for patient, hospital, and physician factors, patients treated by female physicians had a lower 30-day mortality than those treated by male physicians (11.07% vs 11.49%; P < .001; number needed to treat [NNT] = 233). Similarly, 30-day readmission rates were lower in the group treated by female physicians (15.02% vs 15.57%; P < .001; NNT = 182). When the sample was restricted to patients treated by hospitalists only, the findings remained the same with lower mortality and readmission rates for patients treated by female hospitalists. Furthermore, the results were consistent when analyzed across specific medical conditions and different categories of severity of illness.
Tsugawa Y, Jena AB, Figueroa JF, Orav EJ, Blumenthal DM, Jha AK. Comparison of hospital mortality and readmission rates for Medicare patients treated by male vs. female physicians. JAMA Intern Med 2017;177(2):206-213.

5. Type 2 diabetes: metformin first, other treatments second

Clinical question: What should we use as the primary treatment of type 2 diabetes mellitus?
Bottom line: The American College of Physicians recommends treating patients with type 2 diabetes with metformin first, then adding a second oral treatment (a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor) if needed for glycemic control. The group saves advice about when to initiate treatment, treatment goals, use of insulin, and when to add the second treatment for another guideline. (LOE = 5)
Study design: Practice guideline
Funding source: Foundation
Setting: Various (guideline)
Synopsis: These guidelines, developed by the American College of Physicians, were based on a systematic review (doi:10.7326/M15-2650). The committee represented a single primary care specialty and members had no reported financial conflicts of interest. The recommendations focus on improving patient-oriented outcomes and are based on graded evidence, but they are a bit fuzzy. The authors recommend prescribing metformin "when pharmacologic therapy is needed to improve glycemic control" (strong recommendation, moderate-quality evidence), implying that there should be a specific goal for glycemic control but not stating what it should be. Metformin remains the cornerstone of treatment on the basis of its effectiveness in reducing cardiovascular mortality as compared with sulfonylurea treatment, its effectiveness in reducing glycemic levels, its association with weight loss, low risk of hypoglycemic, and cost. When additional glycemic control is needed (again, no guidance regarding when that would be), the authors suggest using either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor in addition to metformin (weak recommendation, moderate-quality evidence). The authors focused only on oral therapy here and did not give recommendations regarding insulin.
Qaseem A, Barry M, Humphrey LL, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166(4):279-290.

6. No added benefit with higher doses of ketorolac for treatment of acute pain in the ED

Clinical question: Are lower doses of ketorolac as effective as standard doses for acute pain control in patients presenting to the emergency department?

Bottom line: A 10-mg dose of ketorolac is as effective as higher doses for the short-term treatment of acute pain for emergency department (ED) patients. (LOE = 1b)
Study design: Randomized controlled trial (double-blinded) **Funding source:** Government
Allocation: Concealed **Setting:** Emergency department
Synopsis: Ketorolac is a nonsteroidal anti-inflammatory drug available in parenteral form for the treatment of acute pain. Although higher doses are often used, ketorolac may have a therapeutic ceiling of 10 mg. To investigate the efficacy of lower doses of ketorolac, these investigators used a convenience sample of patients presenting to the ED on weekdays between 8 AM and 8 PM to enroll patients with acute flank, abdominal, musculoskeletal, or headache pain rated at least 5 on a 0 to 10 numeric rating scale. The authors excluded patients with unstable vitals, active peptic ulcer disease or gastrointestinal bleeding, history of liver or renal disease, and those who were pregnant or breastfeeding. Using concealed allocation, investigators randomized 240 patients to receive either a 10-mg, 15-mg, or 30-mg dose of ketorolac. Patients who still required pain medication after 30 minutes of administration of the study drug received intravenous morphine at a dose of 0.1 mg per kg. The 3 groups were similar at baseline: They all had a mean age of approximately 40 years, two-thirds were female, and the baseline pain score was between 7 and 8. Analysis was by intention to treat. The primary outcome was a reduction of pain scores at 30 minutes after administration of the study drug. In all 3 groups, there was a significant decrease in pain scores from baseline to 30 minutes by at least 2 points. However, there were no significant differences in reduction of pain scores across the 3 groups at 30 minutes, or at subsequent time points of 60, 90, and 120 minutes. Further, there were no differences in the use of rescue morphine analgesia between the 3 groups. The most common adverse effects reported were dizziness, nausea, and headache, and again, were similar in all 3 groups.
Motov S, Yasavolian M, Likourezos A et al. Comparison of intravenous ketorolac *at three single-dose regimens for treating acute pain in the emergency department. 2016 Dec 16 [Epub ahead of print].*

7. Two-year outcomes better with endovascular stroke treatment in selected patients (MR CLEAN follow-up)

Clinical question: Does mechanical thrombectomy using a stent retriever improve long-term outcomes in patients with acute stroke?
Bottom line: Mechanical thrombectomy using a stent retriever appears to have some functional benefits, with a greater likelihood that patients have no more than slight disability (number needed to treat [NNT] = 7). There was a trend toward reduced all-cause mortality, but this was not significant, and the loss of more than 20% of patients to follow-up is concerning. (LOE = 1b-)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Industry + govt
Allocation: Concealed **Setting:** Inpatient (any location) with outpatient follow-up
Synopsis: This is a follow-up study to the original MR CLEAN trial, which compared usual care with mechanical thrombectomy using a stent retriever in patients within 6 hours of the onset of acute stroke. The original trial, funded by industry and a foundation, found that the intervention improved 90-day outcomes. This follow-up study was funded by the Dutch government. Of the original 500 patients enrolled in the study, 391 were included in the follow-up study of function and quality of life. The authors evaluated function using a modified Rankin Scale (0 to 6 points, where lower scores are better) every 6 months for up to 2 years following the original intervention. The patients' quality of life was also evaluated, and the vital status was assessed even for patients not giving consent. A modified Rankin score of 0, 1, or 2 was more likely in the intervention group (37% vs 24%, NNT = 7 over 2 years), and the quality of life score was also significantly but modestly better in the intervention group (effect size 0.1). However, all-cause mortality was not significantly different (26% vs 31%; P = .46; adjusted hazard ratio 0.9; 95% CI 0.6 - 1.2). Patients in the follow-up study were more likely to have been in the intervention group, and they had a lower incidence of atrial fibrillation and a shorter time from stroke to randomization.
van den Berg LA, Dijkgraaf MG, Berkhemer OA, et al, for the MR CLEAN Investigators. Two-year outcome after endovascular treatment for acute ischemic stroke. N Engl J Med 2017;376(14):1341-1349.

8. Children with appendicitis do fairly well with antibiotic treatment!

Clinical question: Do children with appendicitis treated with antibiotics do as well as those treated with surgery?
Bottom line: The existing data are limited to a few small studies. While surgery is clearly better at improving short term and long-term outcomes, it is expensive and patients need to recover. Most children treated with antibiotics will do well, but about 1 in 4 will undergo surgery within a year. This is the perfect place for shared decision-making. (LOE = 2a)
Study design: Meta-analysis (randomized controlled trials)
Funding source: Unknown/not stated
Setting: Various (meta-analysis)
Synopsis: These authors searched multiple databases and a trial registry to identify trials comparing antibiotics and surgery in children with acute uncomplicated appendicitis. Two authors independently evaluated each potential paper for inclusion and assessed each included paper's risk of bias. They included five small studies with 404 children; 168 were treated with antibiotics and 236 were treated surgically. Only one of the trials was randomized. Three studies reported one year follow up and one followed the children for 4.3 years. One planned one year of follow up but only reported a median of 4.7 months. The range of patients not available after one year ranged from 0% to 23% and was similar among those treated surgically or with antibiotics. The included studies also used different diagnostic approaches. In the children treated with antibiotics, 9.5% failed initial treatment - resolution of symptoms without needing surgery within 48 hours or recurrence of appendicitis 1 month after antibiotics while all 236 of those treated surgically had confirmed appendicitis and only one needed reoperation. In other words, about 90% of children treated with antibiotics will do well initially. Forty-five of the antibiotic-treated children (26.8%), however, underwent appendectomy within the following year, 8 of whom had normal appendices on histopathology. Children treated with antibiotics had 8 days of disability compared with 21 in those treated surgically. Four studies reported data on children with an appendicolith, three of which reported that its presence was associated with a 50% rate of antibiotic failure.
Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis in Children: A Meta-analysis. JAMA Pediatr. 2017;171(5):426-434.

9. Medication reminder gizmos don't help adherence

Clinical question: Do medication reminder devices improve adherence to chronic disease medication?
Bottom line: William Osler believed that "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals." Well, perhaps we like the idea more than the practice. None of 3 different devices improved adherence to chronic disease medication as measured by prescription refill rates. I'm waiting for the study in which they give the participants Apple Watches to improve adherence; I'd sign up for that one. (LOE = 1b)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Industry
Allocation: Uncertain **Setting:** Population-based
Synopsis: These researchers enrolled 53,480 participants with an average age of 45 years who were identified through a pharmacy benefits manager. The patients took 1 to 3 chronic medications but did not take them regularly. The researchers randomized patients (allocation concealment unknown) to receive 1 of 3 reminder systems: (1) a strip to be attached to a prescription bottle with toggles to keep track of dosing; (2) a digital timer cap that displays the elapsed time since the previous dose, or (3) a standard pillbox. A fourth group did not receive any device. Over 12 months, only approximately 15% of the patients in each of the 4 groups took at least 80% of their chronic medicine, according to prescription records. Similar results were found in patients who were prescribed antidepressants. Analysis was by intention to treat. The researchers simply mailed the devices to patients. Perhaps direct delivery of the device by prescribers or pharmacists would result in better results; the added aspect of "I'm watching you" might have benefit. Reminders delivered via text have been shown to be effective in studies of mixed adherers and nonadherers (JAMA Intern Med 2016;176(3):340-349).
Choudhry NK, Krumme AA, Ercole PM, et al. Effect of reminder devices on medication adherence: The REMIND randomized clinical trial. JAMA Intern Med 2017;177(5):624-631.

10. Umbrellas alone do not provide adequate sun protection

Clinical question: Which provides better sun protection, sunscreen or a beach umbrella?
Bottom line: This study had a number of important limitations: industry sponsorship, small size, uncertain clinical significance of "sunburn scores," and a somewhat contrived set of study conditions (who doesn't get in the water when you're at the beach on a hot day?). Nevertheless, I think the authors are correct in concluding that an umbrella alone does not provide complete protection from the reflected and diffused ultraviolet (UV) rays that reach the shaded person. This makes some sense since it isn't pitch black under an umbrella. So, slather on that sunscreen, even if you plan to stay under an umbrella. (LOE = 2b)
Study design: Randomized controlled trial (single-blinded) **Funding source:** Industry
Allocation: Uncertain **Setting:** Population-based
Synopsis: These researchers recruited 81 patients, all of whom spent 3.5 hours at a beach in Texas. The participants are not described at all, an important deficiency in the study, other than that all but one had Fitzpatrick skin type II or III (moderately pale, either European Scandinavian or southern/central European). Half were randomized to receive a standard-sized beach umbrella (just over 6 feet in diameter) and half received an application of sunscreen with a sun protection factor of 100. Participants in the sunscreen group reapplied it an average of twice during the study period. Those under the umbrella were told to stay there, and could only leave it for a total of 30 minutes and only after covering up. Neither group was allowed to enter the water, which seems cruel. The investigators evaluated the exposed areas 24 hours later for the presence of redness or sunburn using a 4-point sunburn score, where 0 indicated no sunburn, 2 indicated defined redness clearly caused by UV rays, and 4 meant edema and/or blisters. The global sunburn score was more likely to increase (worsen) in the umbrella group, and there were more sunburned body sites in the umbrella group than in the sunscreen group (142 vs 17). This study was sponsored and conducted by Johnson & Johnson, the manufacturer of Neutrogena sunscreens and skin care products.
Ou-Yang H, Jiang LI, Meyer K, Wang SQ, Farberg AS, Rigel DS. Sun protection by beach umbrella vs sunscreen with a high sun protection factor: a randomized controlled trial. JAMA Dermatol 2017;153(3):304-308.

11. Treatment of subclinical hypothyroidism ineffective in older adults

Clinical question: Is there a clinical benefit to treating subclinical hypothyroidism in older adults?
Bottom line: Treatment of patients with a minimally elevated thyrotropin (thyroid-stimulating hormone) level did not result in any improvement in symptoms. If patients present with a thyrotropin level between 4.6 mIU and 10 mIU per liter, repeat the test as the levels often normalize (this occurred in 60% of the patients initially referred for the study). Only consider treatment if levels increase to above 10.0 mIU/L. (LOE = 1b)
Study design: Randomized controlled trial (double-blinded) **Funding source:** Government
Allocation: Concealed **Setting:** Outpatient (any)
Synopsis: Whether to treat patients with subclinical hypothyroidism (slightly elevated thyrotropin, normal T4, and no or minimal symptoms) remains controversial. The authors of this study recruited 737 such adults, 65 years and older, and randomized them to receive thyroid replacement or matching placebo. The mean baseline thyrotropin level was 6.4 mIU/L (normal range: 0.4 to 4.59 mIU/L), and few had a value greater than 10.0 mIU/L. The groups were balanced, allocation was appropriately concealed, and analysis was by intention to treat. Patients were followed up for 1 year, and the primary outcomes were the 4-item ThyPRO thyroid symptom score and a 7-item Tiredness Score. The treatment dose of levothyroxine was started at 50 mcg daily for most patients, and gradually increased until the thyrotropin was in the normal range (the placebo group had sham titration of their "dose"). The final achieved average thyrotropin level was just over 3.0, which is a bit higher than the target 2.5 mIU/L recommended by some guidelines (Eur Thyroid J 2013;2:215-28). At the end of the study period, there was no difference in any clinical outcomes. A subset of slightly more than half the patients in each group had extended follow-up for a median of 2 years, and at that time there was a slightly greater improvement in the Tiredness Score in the levothyroxine group, but this was of marginal clinical and statistical significance. There was no difference in harms, including cardiovascular events, although the study was not powered to detect a difference if there was one.

Stott DJ, Rodondi N, Kearney PM, et al, for the TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 2017;376(26):2534-2544.

12. "Bendopnea"—dyspnea in heart failure patients when bending forward—predicts adverse outcomes

Clinical question: What is bendopnea and what does it tell us?
Bottom line: Unlike '"Twas brillig, and the slithy toves did gyre and gimble in the wabe," bendopnea is not a nonsense word but a neologism used to describe the shortness of breath experienced by some patients with heart failure. Bendopnea is defined as becoming dyspneic within 20 seconds of leaning forward while seated in a chair as if to tie a shoelace. It seems to be predictive of a worse prognosis; at the very least it's another marker for worsening symptoms. Patients experiencing bendopnea were more likely to have New York Heart Association (NYHA) class IV heart failure, were more likely to have a subsequent hospitalization within 3 months, and might have a worse long-term prognosis. We'll need to wait for research that compares patients with similar heart failure symptoms to determine how much additional prognosis value this has. (LOE = 1b)
Study design: Cohort (prospective)
Funding source: Self-funded or unfunded
Setting: Outpatient (specialty)
Synopsis: Don't know about bendopnea? It is a recently described observation that occurs in approximately 20% of patients with heart failure and associated with higher ventricular filling pressures, especially in patients with a low cardiac index. For this study, the researchers enrolled a convenience sample (ie, not randomized) of 179 patients in a heart failure clinic. The patients were an average 57 years old, there were slightly more men than women, and approximately 60% were white. Patients with bendopnea were more likely to have NYHA class IV heart failure. Higher body mass index was not associated with bendopnea, and other studies have not shown an association with abdominal circumference and bendopnea. The patients were followed up for 1 year. Those with bendopnea were at increased risk of experiencing death, admission for heart failure, inotrope use, left ventricular assist device implantation, and cardiac transplantation—though none of these outcomes was individually significantly more likely. Patients were more likely to be admitted for heart failure treatment within 3 months.
Thibodeau JT, Jenny BE, Maduka JO, et al. Bendopnea and risk of adverse clinical outcomes in ambulatory patients with systolic heart failure. Am Heart J 2017;183:102-107.

13. No mortality benefit and higher costs with early goal-directed therapy for septic shock

Clinical question: Does early goal-directed therapy improve outcomes when treating septic shock?
Bottom line: Early goal-directed therapy (EGDT)—a 6-hour resuscitation protocol using central venous monitoring to administer fluids, vasopressors, inotropes, and as-needed transfusions for early treatment of septic shock—does not improve mortality and can lead to longer intensive care unit stays and higher hospitalization costs. Even patients at the highest risk of mortality did not benefit from EGDT in this analysis. Notably, another study in the same journal of the timing of more basic care for septic shock in the emergency department, including drawing blood cultures, measuring lactate levels, and administering antibiotics within 3 hours, showed that longer times were associated with higher in-hospital mortality. (LOE = 1a)
Study design: Meta-analysis (randomized controlled trials)
Allocation: Concealed
Funding source: Government
Setting: Inpatient (any location)
Synopsis: The ProCESS, ARISE, and ProMISe trials were multi-center randomized controlled trials that compared EGDT with usual care for the management of septic shock. Each trial revealed a lack of mortality benefit with the use of EGDT. The investigators planned a prospective meta-analysis prior to the enrollment of the first patient into the first trial with the goal of pooling patient-level data from all 3 trials (N = 3723). Patients in the EGDT group and the usual care group were balanced at baseline. For the primary outcome of 90-day mortality, the 2 groups had similar mortality rates (24.9% in the EGDT group vs 25.4% in the usual care group). Additionally, the EGDT group had longer intensive care unit stays, higher costs, and required more cardiovascular support. Subgroup analyses showed no benefit of EGDT in patients with greater severity of illness or those with a higher intensity of underlying care. A separate restrospective study looked at New York's mandated emergency care for the treatment of severe sepsis and septic shock. In this study, a delay in timing of the delivery of a 3-hour bundle, consisting of obtaining blood cultures prior to starting antibiotics, measuring serum lactate, and administering broad-spectrum antibiotics, was associated with higher in-hospital mortality with each incremental hour until the completion of the 3-hour bundle (odds ratio of death until completion of 3-hour bundle: 1.04 per hour; 95% CI 1.02 - 1.05).
The PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. N Engl J Med 2017;376(23):2223-2234. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376(23):2235-2244.

14. Pathologists disagree with each other and themselves on melanoma diagnoses

Clinical question: How accurate are pathologists' evaluations of skin lesions for melanoma?
Bottom line: Pathologists use a wide variety of descriptors to report biopsy results. Even so, a diagnosis of normal (nevus or mild atypia) can be trusted most of the time. But pathologists often disagree with one another (and themselves): They disagree with one another on moderate atypia (only 25% agreement), severe atypia (40% agreement), and early melanoma (43% agreement). Approximately 8% of all cases will be overinterpreted and 9% will be underinterpreted. (LOE = 1c)
Study design: Diagnostic test evaluation
Funding source: Government
Setting: Other
Synopsis: These investigators enrolled 187 US pathologists who interpret melanocytic lesions for this study. To test the pathologists' interpretive skills, the investigators assembled slides from 240 shave, punch, and excisional specimens. The cases represented more atypia than is commonly encountered, with approximately 75% of cases representing from severe atypia to invasive melanoma (class III

- class V). Each pathologist randomly received 1 of 5 sets of 48 cases and were asked to evaluate them and provide recommendations. Eight or more months later they received the same slides again. Given the slippery nature of identification, the researchers used 3 reference standards: (1) a panel of 3 dermatopathologists, (2) the most common diagnosis by the board-certified and/or fellowship–trained participants in the study, and (3) the most frequent diagnosis by all participants. Participants were given case information but were unaware of the reference diagnosis or the prevalence distribution of the cases. In the first phase, an average of 10 different diagnostic terms were applied to each case. The pathologists agreed with one another at either extreme: 92% of the time for class I (nevus or mild atypia) and 72% of the time for class V (T1b invasive melanoma or higher). However, they only agreed with one another 25% of the time for class II (moderate atypia), 40% for class III (severe atypia or melanoma in situ); and 43% for class IV (early invasive melanoma). These numbers translate into 8.0% overinterpreted and 9% underinterpreted. When asked to re-read the same slides, the pathologists agreed with themselves most of the time for class I (76.7%) and class V (82.6%); agreement was lower for class II (35.2%), III (59.5%), and IV (63.2%). Pathologists in this study are aware of the problem, with 96% describing interpretation of melanocytic lesions as challenging.
Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. BMJ 2017;357:j2813.

15. Treating sleep apnea with positive airway pressure does not reduce adverse CV outcomes or mortality

Clinical question: Does positive airway pressure for adults with sleep apnea reduce cardiovascular disease morbidity and mortality?
Bottom line: The use of positive airway pressure (PAP) for adults with sleep apnea does not reduce adverse cardiovascular events or mortality. Patients who experience daytime fatigue at baseline benefit from reduced sleepiness and improved physical and mental well-being. Order sleep testing only in patients with signs or symptoms of sleep apnea who also experience clinically significant symptoms of daytime fatigue. No one else will benefit. (LOE = 1a)
Study design: Meta-analysis (randomized controlled trials)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, and the Cochrane Library, as well as reference lists from clinical trials, review articles, conference abstracts, and the clinicaltrials.gov website. Eligible studies included randomized clinical trials that assessed the use of PAP compared with standard care or sham PAP among adults, 18 years or older, with either obstructive sleep apnea (OSA) or central sleep apnea (CSA). No language restrictions were applied. Two individuals independently assessed studies for inclusion criteria and for methodologic quality using a standard risk of bias assessment tool. Disagreements were resolved by consensus. A total of 10 studies that assessed the use of PAP in adults (N = 7266) with OSA and CSA met the inclusion criteria—9 evaluated continuous positive airway pressure and 1 evaluated adaptive servo-ventilation. The overall risk of bias was low to medium; all studies concealed allocation assignment and masked outcomes assessment. No significant associations occurred between the use of PAP and major adverse cardiovascular events, cardiovascular mortality, or all-cause mortality in patients with both OSA and CSA. In addition, there was no significant association with length of follow-up, adherence with using PAP, and baseline apnea-hypopnea index. The use of PAP was significantly associated with improvements in sleepiness and quality of life. A formal analysis found no evidence of publication bias and minimal heterogeneity of assessed outcomes.
Yu J, Zhou Z, McEvoy D, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea. A systematic review and meta-analysis. JAMA 2017;318(2):156-166.

16. Personal sound amplification works as well as a hearing aid for understanding speech at 20% of the cost

Clinical question: Are personal sound amplification devices useful for improving speech understanding in noisy environments?
Bottom line: The mean cost of a pair of hearing aids ($4700) is out of reach for most adults and not currently covered by Medicare. This study found that 3 of 5 commercially available personal sound amplification products (PSAPs) improved speech understanding in noisy environments as well as hearing aids. The most expensive of these is still less than one-fifth the cost of a conventional hearing aid. Hmmm… this sounds like useful information for our Medicare patients. (LOE = 2b)
Study design: Cohort (prospective)
Funding source: Foundation
Setting: Outpatient (specialty)
Synopsis: Understanding what a friend is saying from across the table in a noisy restaurant can be a frustrating experience, especially as one ages (as I know from personal experience). For most adults, the price of 2 hearing aids (mean cost $4700) is way out of their budget. These investigators identified 42 adults, aged 60 to 85 years, with mild to moderate hearing loss (20 - 55 dB HL) with no history of prior amplification use or cognitive impairment. Participants completed a standard sentence-in-noise hearing test used to measure speech understanding and functional hearing in the presence of background noise under 7 conditions: unaided, with a standard hearing aid, and with each of 5 commercially available PSAPs. The primary outcome was speech accuracy, defined as the percentage of words repeated correctly. The mean unaided accuracy was 76.5%. Hearing aids improved speech understanding accuracy to 88.4% (absolute improvement 11.9%; 95% CI 9.8 - 14.0%). Three PSAPs improved accuracy by a similar absolute improvement amount: Sound World Solutions C550+ (11%; 8.8% - 13.1%), Soundhawk (10.2%; 8.0% - 12.3%), and Etymotic BEAN (7.7%; 5.5% - 9.8%). The Tweak Focus improved hearing but to a lesser degree than the other 3 (4.9%; 2.8% - 7.0%). One PSAP resulted in significantly worse speech accuracy (MSA 30X, accuracy 65%; absolute difference -11.2%; -15.2 to -7.3%). Among this sample, performance correlated with price: The 2 best are $350 and the worst is $30.
Reed NS, Betz J, Kendig N, Korczak M, Lin FR. Personal sound amplification products vs a conventional hearing aid for speech understanding in noise. JAMA 2017;318(1):89-90.

17. Price transparency doesn't change clinicians' ordering of inpatient lab tests (PRICE)

Clinical question: Does displaying the prices for inpatient laboratory tests in the electronic health record influence clinician ordering?
Bottom line: Displaying fees at the point of order entry did not affect the number of inpatient laboratory tests ordered. The fees displayed in this study were Medicare reimbursement rates rather than actual costs to patients. (LOE = 1b)
Study design: Randomized controlled trial (nonblinded) **Funding source:** Other
Allocation: Concealed **Setting:** Inpatient (any location)
Synopsis: To evaluate the effect of price transparency on clinical ordering, these investigators randomly assigned 60 groups of inpatient laboratory tests to either display the Medicare allowable fees in the electronic health record (intervention) or to not display the fees (control). The laboratory test groups were composed of tests that could be ordered both individually or within a panel. For example, the basic metabolic panel and all its individual components were in the same group. Randomization was stratified with attention to high-volume tests and more expensive tests so that there was an equal representation in the tests that displayed fees and those that did not. Any clinician who was able to place orders in the electronic health record was able to see the prices of the intervention tests at the time of order entry during the intervention period. The primary outcome was number of tests ordered per patient-day. An adjusted analysis, which took into account patient demographics and comorbidities, showed no significant change in the number of tests ordered from either the intervention group or the control group from a 1-year pre-intervention period to a 1-year postintervention period. Additionally, there were no changes in associated laboratory fees per patient-day over time. These findings suggest that displaying prices did not alter clinician behavior when ordering tests. Alert fatigue or one-time ordering of repeat daily labs (which would eliminate the daily price reminder) may have contributed to the lack of effect.
Sedrak MS, Myers JS, Small DS, et al. Effect of a price transparency intervention in the electronic health record on clinician ordering of inpatient laboratory tests: The PRICE randomized clinical trial. JAMA Intern Med 2017;177(7):939-945.

18. Guideline on managing adults with primary Sjogren's syndrome

Clinical question: How should clinicians manage the symptoms of adults with primary Sjogren's syndrome?
Bottom line: Primary care physicians can manage the bulk of symptoms experienced by patients with Sjogren's syndrome by using simple measures to improve local dryness: lubricants, sugar-free gum, and pilocarpine. (LOE = 5)
Study design: Practice guideline
Funding source: Other
Setting: Various (guideline)
Synopsis: The National Institute for Health and Care Excellence accredited the process used by the British Society for Rheumatology for this study. Although the society reported they received no funding to support the guideline, several authors had ties to industry. The authors searched several databases for studies published since 1990 and then used a formal Delphi process to develop this guideline; its target audience includes rheumatologists, primary care clinicians, and other specialists. The guideline covers management of the eye and mouth manifestations, xerosis, and systemic disease. Virtually all of the recommendations are based on expert opinion and other lower-quality evidence. Sicca syndrome is among the most bothersome of Sjogren's manifestations and all patients should be offered symptomatic treatment. Patients with mild eye symptoms can be managed with lubricants; those with moderately severe symptoms should also receive topical steroids or antibiotics (if blepharitis is present). Additionally, patients with moderate to severe symptoms benefit from punctal plugs or secretagogues such as pilocarpine. Patients with more severe eye problems should be referred to an ophthalmologist. You should not be surprised that the focus on xerostomia similarly focuses on moisture: room air humidification; the avoidance of medications that cause dry mouth; and the use of sugar-free chewing gum, anhydrous crystalline maltose, and pilocarpine. Additionally, the guideline recommends fastidious dental hygiene, the use of fluoride, and so forth because of the higher rate of dental caries associated with xerostomia. Additionally, since these patients often experience oral candida and cheilitis, the panel recommends topical antifungals when these occur. In patients who experience parotid enlargement, the panel recommends ultrasound to assess for stones, the use of massage, and treatment with systemic corticosteroids when inflamed. Systemic dryness, manifested as chronic cough and vaginal dryness, should be treated with local products, and with pilocarpine when the symptoms are more severe. The panel recommends immunomodulating agents (methotrexate, azathioprine, hydroxychloroquine, mycophenolate, biologics, and the like) and corticosteroids in patients with systemic disease. Mucosal lymphoma (salivary and gastrointestinal) occurs more frequently in patients with Sjogren's syndrome, especially those with lymphadenopathy, parotid enlargement, palpable purpura, low serum C4 levels, and cryoglobulins. The panel recommends the use of ultrasound and biopsy to evaluate patients with firm, palpable parotid swelling given the increased risk of lymphoma. Lymphoma can also be present in the orbits, thyroid, airways, and gastrointestinal tract, so symptoms in those areas may necessitate further evaluation.
Price EJ, Rauz S, Tappuni AR, et al, for the British Society for Rheumatology Standards, Guideline and Audit Working Group. The British Society for Rheumatology guideline for the management of adults with primary Sjogren's syndrome. Rheumatology (Oxford). 2017;56(10):e24-e48.

19. Patent foramen ovale closure in cryptogenic stroke reduces recurrence rate compared with antiplatelet agents

Clinical question: In patients with a patent foramen ovale and a history of cryptogenic stroke, does closure followed by antiplatelet therapy improve outcomes compared with antiplatelet therapy alone?
Bottom line: After closure, patients with a patent foramen ovale (PFO) and a cryptogenic stroke and had a reduced risk of recurrent stroke over a 5.4-year mean follow-up period (number needed to treat [NNT] = 16), though atrial fibrillation was a common complication, occurring in 4.6%. A second study in the same journal compared PFO closure followed by at least 6 months of antiplatelet therapy with anticoagulation or antiplatelet therapy alone in 980 patients, and found that PFO closure was more effective than antiplatelet therapy, especially for patients with a large shunt or an atrial septal aneurysm. However, that study did not find a benefit when compared with anticoagulation. Finally, a third study that randomized 664 patients to PFO closure plus antiplatelet therapy versus antiplatelet therapy alone found similar results to this study by Mas and colleagues. (LOE = 1b)

Study design: Randomized controlled trial (nonblinded) **Funding source:** Government
Allocation: Concealed **Setting:** Outpatient (specialty)
Synopsis: Previous studies (http://www.essentialevidenceplus.com/content/poem/140501, http://www.essentialevidenceplus.com/content/poem/150507) have not found a benefit to PFO closure in patients with a cryptogenic stroke (that is, a stroke in patients with no clear underlying cause such as atrial fibrillation or coronary artery disease). However, these studies showed trends in favor of intervention, and they may have been underpowered. The current study identified patients aged 16 to 60 years who had suffered an acute ischemic stroke in the past 6 months, had at least 30 microbubbles in the left atrium within 3 cardiac cycles on a bubble test, and had no alternative cause of stroke based on a standardized set of tests. This study was larger than previous trials and also included patients with lower vascular risk, making a recurrent stroke due to other vascular causes less likely. The mean age of patients was 44 years and they had few cardiovascular risk factors (10% hypertension, 3% diabetes mellitus, and 14% hyperlipidemia). In the primary comparison, 524 patients were randomized to receive either PFO closure plus antiplatelet therapy (aspirin plus clopidogrel for 3 months, followed by one of the drugs from then on), to antiplatelet therapy alone, or to anticoagulation alone. Patients with a contraindication to PFO closure (n = 10) were randomized to receive antiplatelet therapy or anticoagulation, and those with a contraindication to oral anticoagulants (n= 129) were randomized to PFO closure plus antiplatelet therapy or antiplatelet therapy alone. For the comparison of PFO closure plus antiplatelet therapy versus antiplatelet therapy alone, at 4.4 years of follow-up the likelihood of recurrent stroke was 0.0% in the former and 6.0% in the latter (hazard ratio [HR] 0.02; 95% CI 0.0 - 0.26; NNT = 16). The risk of the composite of stroke, transient ischemic stroke, or thromboembolic event was also lower in the PFO group (3.4% vs 8.9%; P = .01; NNT = 18). The risk of major or fatal complications (largely atrial fibrillation or flutter, supraventricular tachycardia, air embolism, or hypothermia) in the PFO group was 5.9%. For the comparison of anticoagulation with antiplatelet therapy, there was a nonsignificant trend favoring anticoagulation (HR 0.44; 0.11 - 1.48) for the outcome of recurrent stroke. There was only 1 death in the study (in a patient assigned to anticoagulation). Disabling strokes were rare, with no more than 1 occurring in each treatment group.
Mas JL, Derumeaux G, Guillon B, et al, for the CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med 2017;377(11):1011-1021.

20. Care by general internists who trained outside of US superior to that of US trained physicians

Objective To determine whether patient outcomes differ between general internists who graduated from a medical school outside the United States and those who graduated from a US medical school.
Design Observational study.
Setting Medicare, USA.
Participants 20% national sample of data for Medicare fee-for-service beneficiaries aged 65 years or older admitted to hospital with a medical condition in 2011-14 and treated by international or US medical graduates who were general internists. The study sample for mortality analysis included 1 215 490 admissions to the hospital treated by 44 227 general internists.
Main outcome measures Patients' 30 day mortality and readmission rates, and costs of care per hospital admission, with adjustment for patient and physician characteristics and hospital fixed effects (effectively comparing physicians within the same hospital). As a sensitivity analysis, we focused on physicians who specialize in the care of patients admitted to hospital ("hospitalists"), who typically work in shifts and whose patients are plausibly quasi-randomized based on the physicians' work schedules.
Results Compared with patients treated by US graduates, patients treated by international graduates had slightly more chronic conditions. After adjustment for patient and physician characteristics and hospital fixed effects, patients treated by international graduates had lower mortality (adjusted mortality 11.2% *v* 11.6%; adjusted odds ratio 0.95, 95% confidence interval 0.93 to 0.96; P<0.001) and slightly higher costs of care per admission (adjusted costs $1145 (£950; €1080) *v* $1098; adjusted difference $47, 95% confidence interval $39 to $55, P<0.001). Readmission rates did not differ between the two types of graduates. Similar differences in patient outcomes were observed among hospitalists. Differences in patient mortality were not explained by differences in length of stay, spending level, or discharge location.
Conclusions Data on older Medicare patients admitted to hospital in the US showed that patients treated by international graduates had lower mortality than patients cared for by US graduates.
Tsugawa Y, Jena AB, Orav EJ, Jha AK. Quality of care delivered by general internists in US hospitals who graduated from foreign versus US medical schools: observational study. BMJ 2017; 356 doi: https://doi.org/10.1136/bmj.j273 (Published 03 February 2017)Cite this as: BMJ 2017;356:j273

21. Scribes improve physician satisfaction and charting accuracy and efficiency: RCT

PURPOSE: Scribes are increasingly being used in clinical practice despite a lack of high-quality evidence regarding their effects. Our objective was to evaluate the effect of medical scribes on physician satisfaction, patient satisfaction, and charting efficiency.
METHODS: We conducted a randomized controlled trial in which physicians in an academic family medicine clinic were randomized to 1 week with a scribe then 1 week without a scribe for the course of 1 year. Scribes drafted all relevant documentation, which was reviewed by the physician before attestation and signing. In encounters without a scribe, the physician performed all charting duties. Our outcomes were physician satisfaction, measured by a 5-item instrument that included physicians' perceptions of chart quality and chart accuracy; patient satisfaction, measured by a 6-item instrument; and charting efficiency, measured by time to chart close.
RESULTS: Scribes improved all aspects of physician satisfaction, including overall satisfaction with clinic (OR = 10.75), having enough face time with patients (OR = 3.71), time spent charting (OR = 86.09), chart quality (OR = 7.25), and chart accuracy (OR = 4.61) (all *P* values <.001). Scribes had no effect on patient satisfaction. Scribes increased the proportion of charts that were closed within 48 hours (OR =1.18, *P*=.028).
CONCLUSIONS: To our knowledge, we have conducted the first randomized controlled trial of scribes. We found that scribes produced significant improvements in overall physician satisfaction, satisfaction with chart quality and accuracy, and charting efficiency without detracting from patient satisfaction. Scribes appear to be a promising strategy to improve health care efficiency and reduce physician burnout.
Gidwani R, Nguyen C, Kofoed A, Carragee C, Rydel T, Nelligan I, Sattler A, Mahoney M, Lin S. Impact of Scribes on Physician

Satisfaction, Patient Satisfaction, and Charting Efficiency: A Randomized Controlled Trial. Ann Fam Med. 2017 Sep;15(5):427-433.

22. Maybe I should give them that antibiotic for their cold after all!

IMPORTANCE: Prior studies suggesting clinician fulfillment or denial of requests affects patient satisfaction included limited adjustment for patient confounders. The studies also did not examine distinct request types, yet patient expectations and clinician fulfillment or denial might vary among request types.
OBJECTIVE: To examine how patient satisfaction with the clinician is associated with clinician denial of distinct types of patient requests, adjusting for patient characteristics.
DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional observational study of 1319 outpatient visits to family physicians (n = 56) by 1141 adults at one Northern California academic health center.
MAIN OUTCOMES AND MEASURES: We used 6 Consumer Assessment of Healthcare Providers and Systems Clinician and Group Adult Visit Survey items to measure patient satisfaction with the visit physician. Standardized items were averaged to form the satisfaction score (Cronbach α = 0.80), which was then percentile-transformed. Seven separate linear mixed-effects models examined the adjusted mean differences in patient satisfaction percentile associated with denial of each of the following requests (if present)-referral, pain medication, antibiotic, other new medication, laboratory test, radiology test, or other test-compared with fulfillment of the respective requests. The models adjusted for patient sociodemographics, weight, health status, personality, worry over health, prior visit with clinician, and the other 6 request categories and their dispositions.
RESULTS: The mean (SD) age of the 1141 patients was 45.6 (16.1) years, and 902 (68.4%) were female. Among 1319 visits, 897 (68.0%) included at least 1 request; 1441 (85.2%) were fulfilled. Requests by category were referral, 294 (21.1%); pain medication, 271 (20.5%); antibiotic, 107 (8.1%); other new medication, 271 (20.5%); laboratory test, 448 (34.0%); radiology test, 153 (11.6%); and other tests, 147 (11.1%). Compared with fulfillment of the respective request type, clinician denials of requests for referral, pain medication, other new medication, and laboratory test were associated with worse satisfaction (adjusted mean percentile differences, -19.75 [95% CI, -30.75 to -8.74], -10.72 [95% CI, -19.66 to -1.78], -20.36 [95% CI, -29.54 to -11.18], and -9.19 [95% CI, -17.50 to -0.87]), respectively.
CONCLUSIONS AND RELEVANCE: Clinician denial of some types of requests was associated with worse patient satisfaction with the clinician, but not for others, when compared with fulfillment of the requests. In an era of patient satisfaction-driven compensation, the findings suggest the need to train clinicians to deal effectively with requests, potentially enhancing patient and clinician experiences.
REFERENCE: Jerant A, Fenton JJ, Kravitz RL, Tancredi DJ, Magnan E, Bertakis KD, Franks P. Association of Clinician Denial of Patient Requests With Patient Satisfaction. JAMA Intern Med. 2018 Jan 1;178(1):85-91. doi: 10.1001/jamainternmed.2017.6611.

23. Even one cigarette per day raises CV risk significantly

OBJECTIVE: To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).
DESIGN: Systematic review and meta-analysis.
DATA SOURCES: Medline 1946 to May 2015, with manual searches of references.
ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Prospective cohort studies with at least 50 events, reporting hazard ratios or relative risks (both hereafter referred to as relative risk) compared with never smokers or age specific incidence in relation to risk of coronary heart disease or stroke.
DATA EXTRACTION/SYNTHESIS: MOOSE guidelines were followed. For each study, the relative risk was estimated for smoking one, five, or 20 cigarettes per day by using regression modelling between risk and cigarette consumption. Relative risks were adjusted for at least age and often additional confounders. The main measure was the excess relative risk for smoking one cigarette per day (RR1_per_day-1) expressed as a proportion of that for smoking 20 cigarettes per day (RR20_per_day-1), expected to be about 5% assuming a linear relation between risk and consumption (as seen with lung cancer). The relative risks for one, five, and 20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate analyses were done for each combination of sex and disorder.
RESULTS: The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one and 20 cigarettes per day (or 2.19 and 3.95 using relative risks adjusted for multiple factors). Men who smoked one cigarette per day had 46% of the excess relative risk for smoking 20 cigarettes per day (53% using relative risks adjusted for multiple factors), and women had 31% of the excess risk (38% using relative risks adjusted for multiple factors). For stroke, the pooled relative risks for men were 1.25 and 1.64 for smoking one or 20 cigarettes per day (1.30 and 1.56 using relative risks adjusted for multiple factors). In women, the pooled relative risks were 1.31 and 2.16 for smoking one or 20 cigarettes per day (1.46 and 2.42 using relative risks adjusted for multiple factors). The excess risk for stroke associated with one cigarette per day (in relation to 20 cigarettes per day) was 41% for men and 34% for women (or 64% and 36% using relative risks adjusted for multiple factors). Relative risks were generally higher among women than men.
CONCLUSIONS: Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.
***REFERENCE**: Hackshaw A1, Morris JK2, Boniface S3, Tang JL4, Milenković D5. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018 Jan 24;360:j5855. doi: 10.1136/bmj.j5855.*

24. PubMed: 21% of patients with HFrEF fulfilled inclusion criteria for PARADIGM-HF

AIMS: The PARADIGM-HF trial showed that sacubitril-valsartan, an ARB-neprilysin inhibitor, is more effective than enalapril for some patients with heart failure (HF). It is uncertain what proportion of patients with HF would be eligible for sacubitril-valsartan in clinical practice.
METHODS AND RESULTS: Between 2001 and 2014, 6131 patients consecutively referred to a community HF clinic with suspected HF were assessed. The criteria required to enter the randomized phase of PARADIGM-HF, including symptoms, NT-proBNP, and current treatment with or without target doses of ACE inhibitors or ARBs, were applied to identify the proportion of patients eligible for sacubitril-valsartan. Recognizing the diversity of clinical opinion and guideline recommendations concerning this issue, entry criteria were applied singly and in combination. Of 1396 patients with reduced left ventricular ejection fraction (≤40%, HFrEF) and contemporary measurement of NT-proBNP, 379 were on target doses of an ACE inhibitor or ARB at their initial visit and, of these, 172 (45%) fulfilled the key entry criteria for the PARADIGM-HF trial. Lack of symptoms (32%) and NT-proBNP <600 ng/L (49%) were common reasons for failure to fulfil criteria. A further 122 patients became eligible during follow-up (n = 294, 21%). However, if background medication and doses were ignored, then 701 (50%) were eligible initially and a further 137 became eligible during follow-up.
CONCLUSIONS: Of patients with HFrEF referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomization criteria, on which the ESC Guidelines are based; this proportion rises to 60% if background medication is ignored.
REFERENCE: Pellicori P et al. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? Eur J Heart Fail. 2017 Jun;19(6):768-778.

25. PubMed: NT-proBNP guided treatment adds nothing to usual care

Importance: The natriuretic peptides are biochemical markers of heart failure (HF) severity and predictors of adverse outcomes. Smaller studies have evaluated adjusting HF therapy based on natriuretic peptide levels ("guided therapy") with inconsistent results.
Objective: To determine whether an amino-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided treatment strategy improves clinical outcomes vs usual care in high-risk patients with HF and reduced ejection fraction (HFrEF).
Design, Settings, and Participants: The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study was a randomized multicenter clinical trial conducted between January 16, 2013, and September 20, 2016, at 45 clinical sites in the United States and Canada. This study planned to randomize 1100 patients with HFrEF (ejection fraction ≤40%), elevated natriuretic peptide levels within the prior 30 days, and a history of a prior HF event (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care.
Interventions: Patients were randomized to either an NT-proBNP-guided strategy or usual care. Patients randomized to the guided strategy (n = 446) had HF therapy titrated with the goal of achieving a target NT-proBNP of less than 1000 pg/mL. Patients randomized to usual care (n = 448) had HF care in accordance with published guidelines, with emphasis on titration of proven neurohormonal therapies for HF. Serial measurement of NT-proBNP testing was discouraged in the usual care group.
Main Outcomes and Measures: The primary end point was the composite of time-to-first HF hospitalization or cardiovascular mortality. Prespecified secondary end points included all-cause mortality, total hospitalizations for HF, days alive and not hospitalized for cardiovascular reasons, the individual components on the primary end point, and adverse events.
Results: The data and safety monitoring board recommended stopping the study for futility when 894 (median age, 63 years; 286 [32%] women) of the planned 1100 patients had been enrolled with follow-up for a median of 15 months. The primary end point occurred in 164 patients (37%) in the biomarker-guided group and 164patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% CI,0.79-1.22; P = .88). Cardiovascular mortality was 12% (n = 53) in the biomarker-guided group and 13% (n = 57) in the usual care group (HR, 0.94; 95% CI; 0.65-1.37; P = .75). None of the secondary end points nor the decreases in the NT-proBNP levels achieved differed significantly between groups.
Conclusions and Relevance: In high-risk patients with HFrEF, a strategy of NT-proBNP-guided therapy was not more effective than a usual care strategy in improving outcomes.
REFERENCE: Felker GM, et al. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial.JAMA. 2017 Aug 22;318(8):713-720.

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