NIH ACTIV THERAPEUTICS CLINICAL TRIALS

I. Overview and Updates

II. Host Tissue-Directed Therapeutics

NIH Advisory Council to the Director
Briefing

December 9, 2021

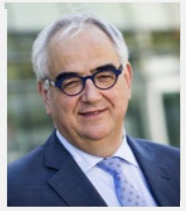
Rising to the Public Health Challenges of COVID-19 and Beyond: Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

- Unparalleled public-private partnership
- Collaborative forum to identify most promising interventions and accelerate clinical testing
  - Launch and open sharing of master protocols for evaluating candidates
  - Improve clinical trial capacity/effectiveness by leveraging infrastructure and expertise from across NIH and non-NIH networks and CROs
- Accelerate evaluation of vaccine candidates to enable rapid authorization or approval
- Identify emerging variants and coordinate data sharing (TRACE WG)
- Unprecedented data sharing between academia and industry

VISIONARY LEADERSHIP

Providing partnership, dedication, and support to ACTIV Therapeutic Clinical Enterprise

Francis Collins, M.D., Ph.D.



Paul Stoffels, M.D.

ACTIV enterprise provides pathway and model for future preparedness efforts

NIH ACTIV THERAPEUTICS CLINICAL TRIALS: AT-A-GLANCE

ENROLLMENTS & ACTIVATION

13,813 Patients enrolled into ACTIV trials
700+ Sites in partnership with **multiple networks** including ACTG, CONNECTS, DCRI, INSIGHT, PETAL, CTSN, PCORnet, CTSA, IDeA Sites, ACTT, and others

PUBLICATIONS

17 Scientific Publications on ACTIV Trials released in **7 Medical Journals**

These publications have been **cited 478 times** (*Google Scholar*)

AGENT REVIEWS & AUTHORIZATIONS

800+ Total agents reviewed by ACTIV Tx-Clinical and CONNECTS WGs Agent Review Panels

15 Agents fully enrolled and completed testing through the ACTIV Master Protocols

4 Agents proven efficacious against COVID-19 in analysis of data from ACTIV Trials.
Other priority agents being tested

- **EUA ACHIEVEMENTS:**
  - Lilly monoclonal approval
  - Brii Bio rolling submission
  - AZ applying for EUA intending to have ACTIV outpatient data noted in the submission package
- Both the **Merck and Pfizer compounds** being assessed for EUA were originally selected for testing in ACTIV trials
- ACTIV-4 work on heparin and other anticoagulants **changed clinical practice**

NIH ACTIV THERAPEUTICS MASTER PROTOCOL DESCRIPTIONS

Master Protocol	Protocol Description	Current Trial Status
ACTIV-1	• Inpatient, RCT, Double-blind Phase III Master Protocol • Host-targeted Immune Modulators • NCATS TIN + DCRI + TRI + CRO • Target Sample Size (Patients per Arm): 540	***Trial launched on October 16, 2020*** • Agent(s) being tested: Abatacept, Cenicriviroc, Infliximab
ACTIV-2	• Outpatient, RCT, Double-blind Phase II/III Master Protocol • Neutralizing Monoclonal Antibodies (nMABs) and Oral Antivirals • NIAID ACTG + CRO • Target Sample Size (Patients per Arm): 110 [Phase II] & 600 [Phase III]	***Trial launched on August 3, 2020*** • Agent(s) being tested: nMABs (Lilly, Brii Bio, RU-BMS), IFN-beta (Synairgen), camostat (Sagent), nPAB (SAB)
ACTIV-3	• Inpatient, RCT, Double-blind Phase III Master Protocol • Neutralizing Monoclonal Antibodies and other (e.g., protease inhibitor) • NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO • Target Sample Size (Patients per Arm): 500	***Trial launched on August 4, 2020*** • Agent(s) being tested: nMABs (Lilly, Brii, GSK-Vir, AZ), DARPin (Molecular Partners), protease inh. (Pfizer)
ACTIV-3B	• Inpatient, RCT, Double-blind Phase III Master Protocol • Host-targeted Immune Modulators • NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO • Target Sample Size (Patients per Arm): 310	***Trial launched on April 21, 2021*** • Agent(s) being tested: Aviptadil (VIP) (NeuroRX) • Agents in the Pipeline: Immune Modulators for ARDS

NIH ACTIV THERAPEUTICS MASTER PROTOCOL DESCRIPTIONS

Master Protocol	Protocol Description	Current Trial Status
ACTIV-4A	• Inpatient, Pragmatic, Randomized, Open Label Phase III Master Protocol • Host-tissue Directed Therapeutics including Anticoagulants, Anti-platelet, other Anti-thrombotics • NHLBI CONNECTS Network • Target Sample Size (Patients per Arm): 1000	***Trial launched on September 17, 2020*** • Agent(s) being tested: LMWH, UFH, P2Y12 Inhibitors (Anti-platelet Agents);
ACTIV-4B	• Outpatient, Randomized, Double-blind Phase III Master Protocol • Host-tissue Directed Therapeutics: Anticoagulants, Anti-platelet, other Antithrombotics • NHLBI CONNECTS Network • Target Sample Size (Patients per Arm): 1750	***Trial launched on September 17,2020*** • Agent(s) being tested: Low-dose Aspirin, Prophylactic-dose Apixaban, Therapeutic-dose Apixaban
ACTIV-4C	• Outpatient, Convalescent, RCT, Double-blind Phase III Master Protocol • Host-tissue Directed Therapeutics: Anticoagulants, Anti-platelet, other Antithrombotics • NHLBI CONNECTS Network • Target Sample Size (Patients per Arm): 2660	***Trial launched on February 9, 2021*** • Agent(s) being tested: Apixaban
ACTIV-4HT	• Inpatient, Pragmatic, Randomized, Open Label Phase II/III Master Protocol • Host-tissue Targeted Therapies (Most focusing on RAAS Pathway Regulation) • NHLBI CONNECTS Network • Target Sample Size (Patients per Arm): 300+	***Trial launched on July 2021*** • Agent(s) being tested: TXA127, TRV027, Fostamatinib

NIH ACTIV THERAPEUTICS MASTER PROTOCOL DESCRIPTIONS

Master Protocol	Protocol Description	Current Trial Status
ACTIV-5	• Inpatient, Randomized, Double-blind Phase II Master Protocol • Proof of Concept Study to Identify Promising Immuno Modulators • NIAID + CRO • Target Sample Size (Patients per Arm): 500	***Trial launched on October 9, 2020*** • Agent(s) being tested: Risankizumab, Lenzilumab, Danicopan
ACTIV-6	• Outpatient, RCT, Double-blind Phase III Master Protocol • Existing Prescription and Over-the-counter Medications • NCATS + DCRI + PCORnet + SignalPath + CRO • Target Sample Size (Patients per Arm): 300	***Trial launch on July 1, 2021*** • Agent(s) being tested: Ivermectin, fluvoxamine, fluticasone

Status Summary of ACTIV Agents: Completed and Currently Under Study

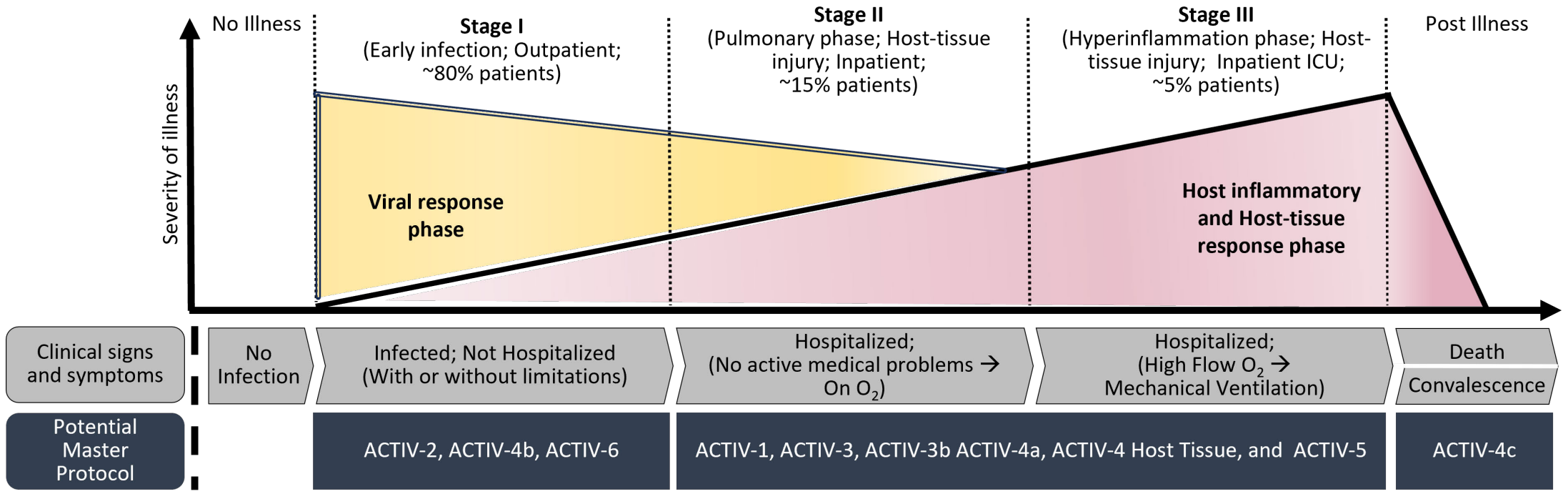
	Enrolling But Not Yet Reviewed for Efficacy / Futility	Ceased Enrollment (due to futility / low clinical value)	Continuing Enrollment (i.e., passed interim futility assessment)	Completed Enrollment
ACTIV-1		• Cenicriviroc[1]	• Infliximab • Abatacept	
ACTIV-2/2B		• AZD7442 (IM)* • AZD7442 (IV)* • Camostat Mesylate[1] • BMS-986414/BMS-986413[1]	• SAB-185 • SNG001 IFN-beta	• Brii-196/Brii-198[2] • LY-CoV-555[2]
ACTIV-3/3B	• Aviptadil and/or Remdesivir • Pfizer PF-07304814	• LY-CoV-555[1] • Brii-196/Brii-198[1] • VIR-7831[1] • DARPin MP0420[1]		• AZD7442 (IV) *(awaiting topline data)*
ACTIV-4A		• Therapeutic Heparin and P2Y12 Inhibitors in Moderately-ill Pts[1]	• Prophylactic Heparin and P2Y12 Inhibitors in Critically-ill Pts	• Un-fractionated and Low Molecular Weight Heparin[2]
ACTIV-4B		• Aspirin[1] • Apixaban[1]		
ACTIV-4C			• Apixaban	
ACTIV-4HT	• TXA127 • TRV027 • Fostamatinib			
ACTIV-5	• Danicopan		• Lenzilumab	• Risankizumab *(awaiting topline data)*
ACTIV-6	• Fluvoxamine • Fluticasone		• Ivermectin	

**Enrollment ceased at company's request*

[1]***Denotes*** *agent lack of efficacy*

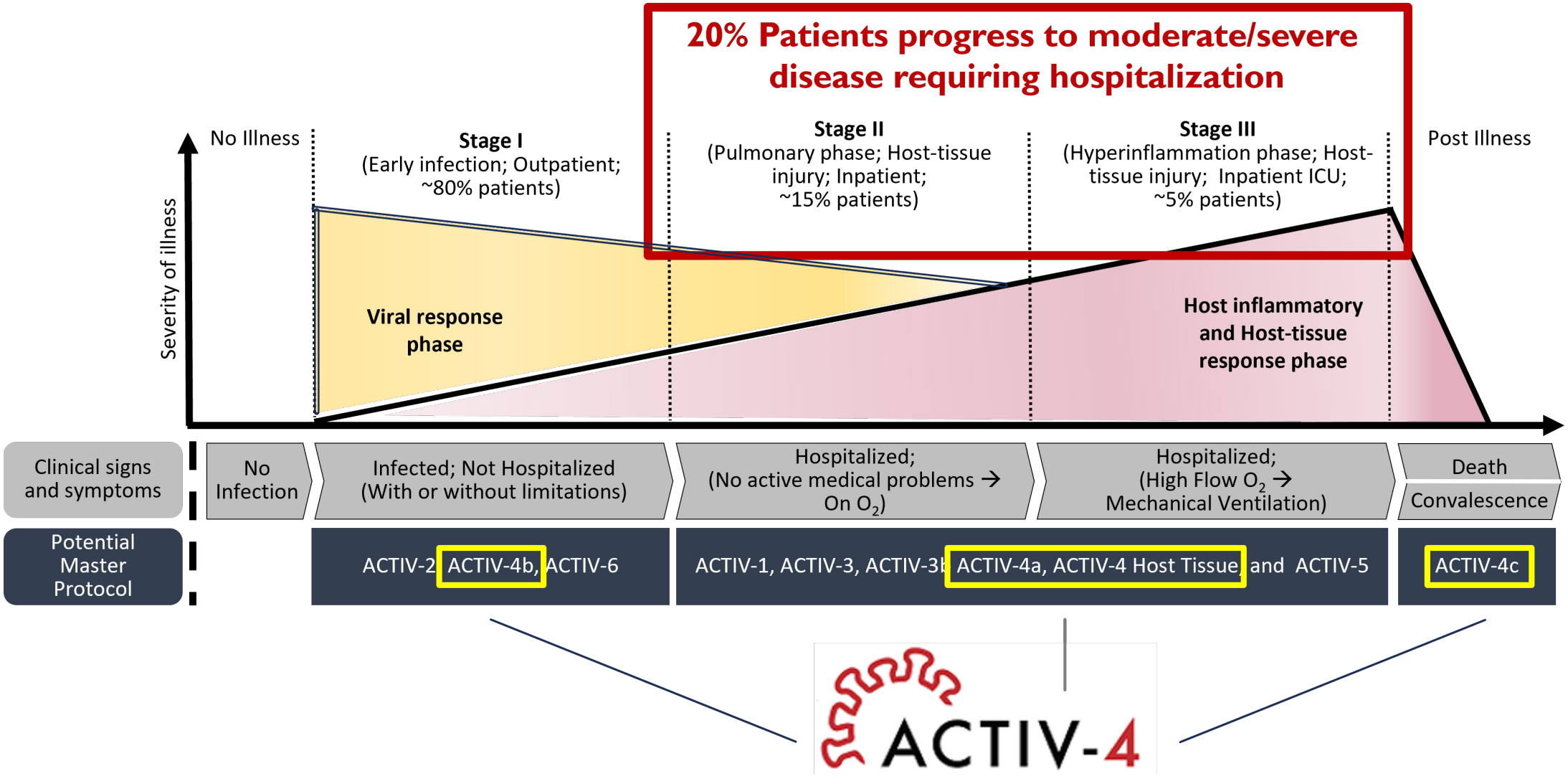
[2]***Denotes*** *proven agent efficacy*

NIH ACTIV CLINICAL TRIALS TARGETING STAGES OF DISEASE



Iterative learning process: Determining which therapeutic strategies work/don't work in which clinical setting/stage of disease/patient group

NIH ACTIV CLINICAL TRIALS TARGETING STAGES OF DISEASE

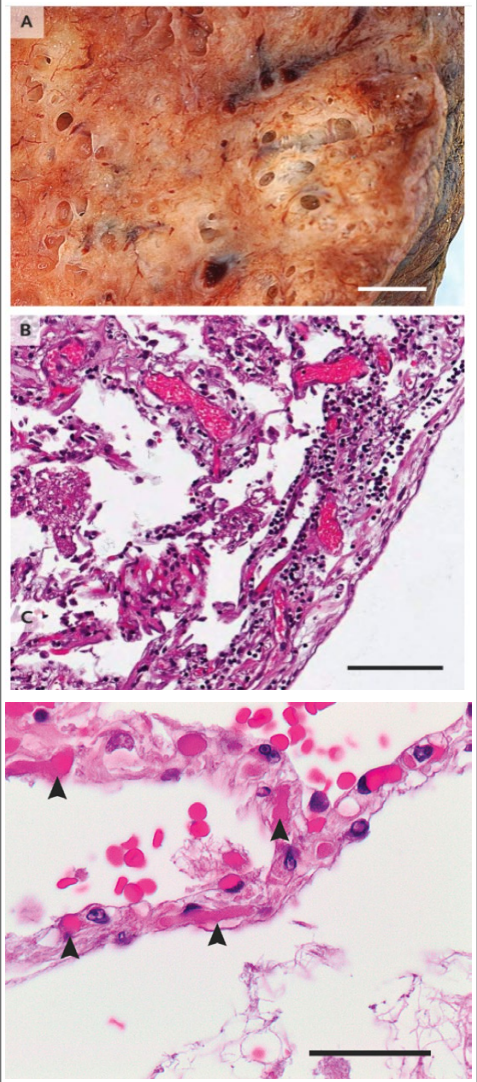


Host Tissue-Directed Therapeutics: A Critical Component of COVID-19 and Pandemic Preparedness Armamentarium

- **Majority (~80%) of SARS-CoV-2 infected patients experience mild to moderate symptoms** resolving w/in 6–10 days
- **~20% of patients develop severe illness** w/ typical interstitial bilateral pneumonia and ARDS; associated w/high fatality rate
- **Progression to more severe disease due to multi-tissue/organ dysfunction**
  - Endothelial dysfunction, systemic coagulopathy and complement-induced thrombosis with development of systemic microangiopathy and thromboembolism
- **Host tissue and organ targets:** lung epithelium, vascular endothelium, brain, kidney, gut, heart, and eye (among others)
- **Therapeutic interventions targeting host-tissue responses are a critical** complement to direct anti-virals and passive immune strategies

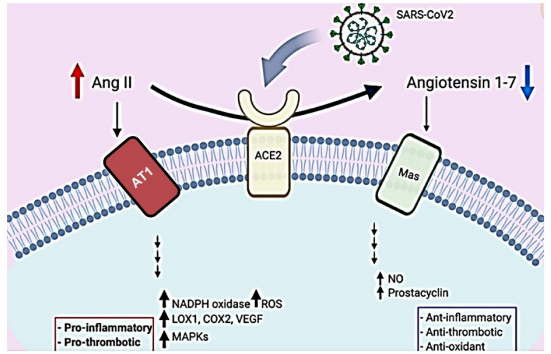
Illustrations credit: Anna & Elena Balbusso https://magazine.ucsf.edu/we-thought-it-was-just-respiratory-virus

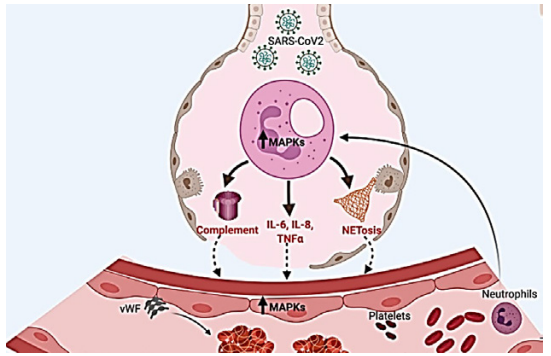
COVID-19 MULTI-TISSUE/MULTI-ORGAN INJURY: PATHOGENIC PATHWAYS

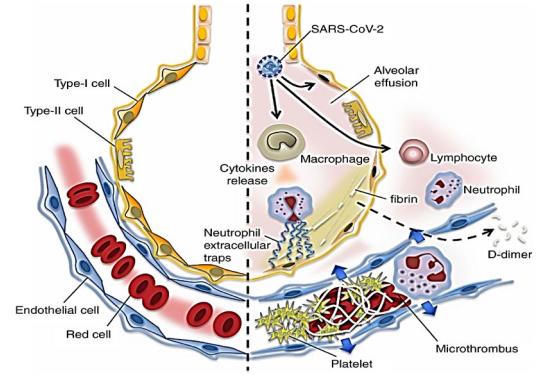


Host-tissue example: Lung

- Progressive COVID-19 characterized by severe inflammatory response, hypoxia, multi-tissue/organ injury due to direct and indirect viral mediated effects; high endothelial cell expression of ACE2
  - Vascular endotheliopathy and prothrombotic/coagulant state with high rates of thrombotic complications
- Poor prognosis consistently associated with dysregulation of:
  - **Renin-angiotensin-aldosterone system (RAAS)** leading to oxidative stress, vasoconstriction, endothelial dysfunction, release of P-selectin, and vWF activation
  - **Immune response** activating complement, neutrophil extracellular traps, and mitogen activated protein kinase pathways
  - **Coagulation cascade, thrombosis, and fibrinolysis** throughout macro- and microvasculature







Histology: N Engl J Med 2020; 383:120-128

Trends Cardiovasc Med. 2021 Apr; 31(3):143-160
Published online 2020 Dec 16. doi: 10.1016/j.tcm.2020.12.004

International Journal of Laboratory Hematology, Volume: 43, Issue: S1, Pages: 29-35, First published: 20 July 2021, DOI: (10.1111/ijlh.13500)

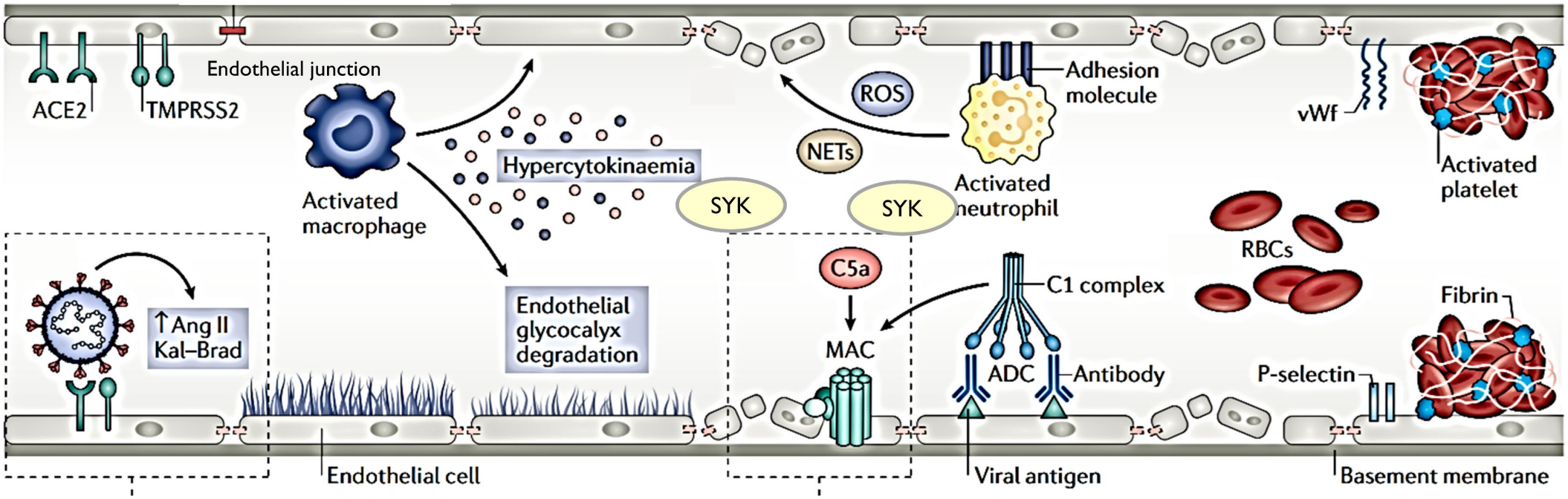
ACTIV-4 Host Tissue-Directed Therapeutics

Targeting Host-tissue Dysfunction Following SARS-CoV-2 Infection

Target:

RAAS Dysregulation | **Vascular Immuno-Thrombo-Inflammation Response** | **Hyper-Coagulation**

Inflammation | Hypoxia | Fibrosis | Capillary Leak | Pro-coagulant state | Hypo-fibrinolysis

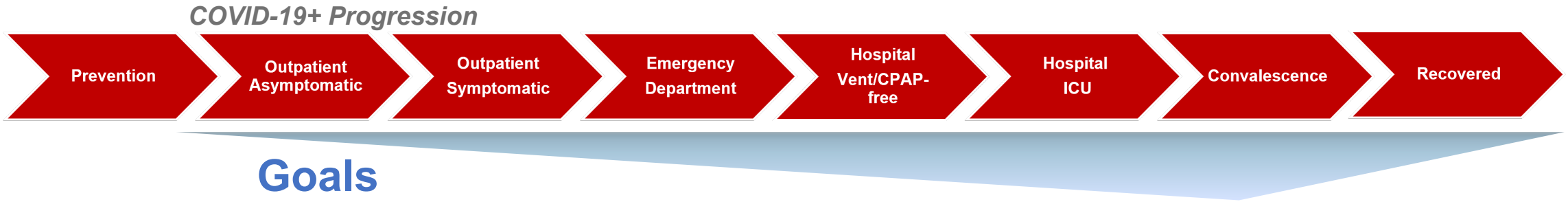


RAAS Agents (TXA127, TRV027)

Fostamatinib

Heparin, DOAC, ASA, P2Y12 inhibitors

NHLBI COVID-19 Clinical Research Framework



Goals

Reduce case severity/fatality, speed recovery	→ Host-Directed Therapeutics Clinical Trials
Identify biomarkers and therapeutic targets	Integrated pathobiology/mechanistic studies
Enable risk stratification, precision interventions	→ Screening, Referral and Registries
Understand short- and long-term trajectory	Cohort of Cohorts for Long-Term Follow up
Target populations most severely affected	→ Community-Engaged Research Consortium

CONNECTS

"Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies"

Goal: Leverage and expand NHLBI's national clinical research networks to rapidly and nimbly respond to emerging research and clinical needs for COVID-19

- **Part of NIH ACTIV**
- **Collaboration with NINDS, other ICs**
- **Leveraging existing assets**, data and studies and **forging new partnerships**
- Comprehensive, **expandable platform** linking trial network, registries, mechanistic studies, and cohorts
- Facilitating case finding, **clinical trial accrual**, **longitudinal studies, and community engagement**

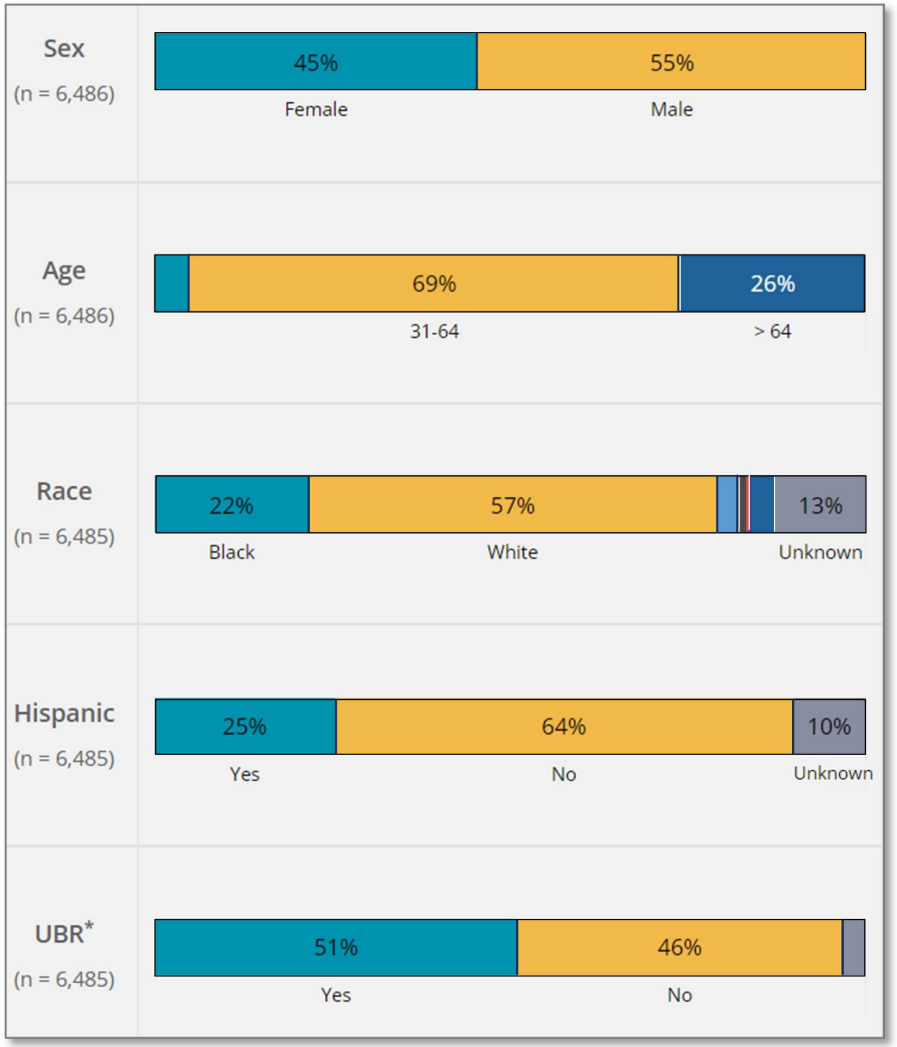
~300+ sites, ~ 6,500 ppts in clinical trials,
~58,000 ppts in longitudinal studies

ENGAGEMENT AND PARTICIPATION OF DIVERSE POPULATIONS

Enriching enrollment of disproportionately affected communities by leveraging community-engagement, multi-disciplinary partnerships across the NIH, and collaboration with patient groups

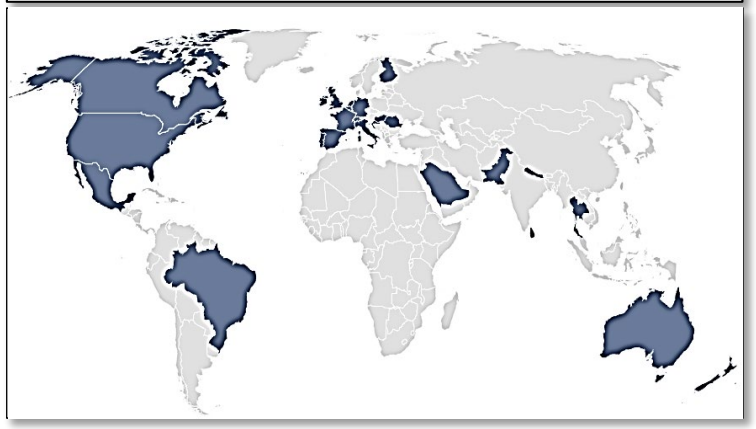
	% U.S. Population[1]	% U.S. COVID Cases[2]	% Ppts in CONNECTS Clinical Trials
Hispanic / Latinx	18.5	27.3	25
Black	13.4	16.4	22
Asian	5.9	2.4	3
Native Hawaiian & Pacific Islander	0.2	0.5	0
American Indian / Alaska Native	1.3	1.4	1

[1]United States Census Bureau (2019) [2]Hollis et al. (2021)

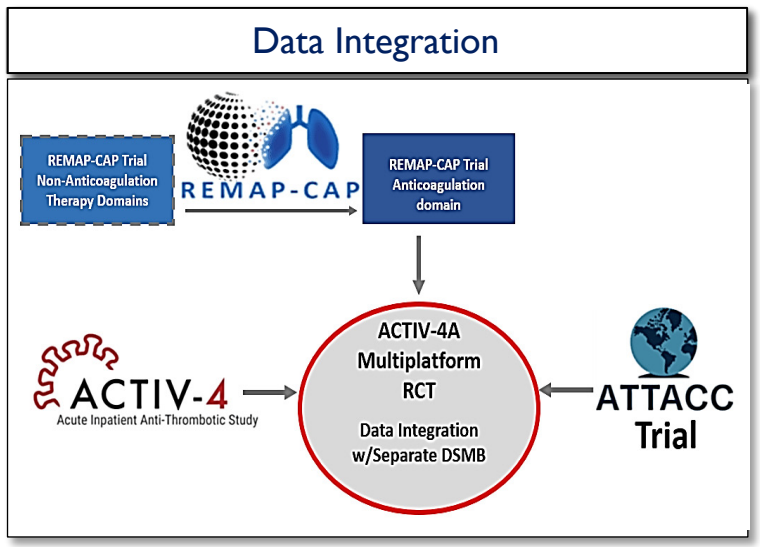


HOST TISSUE-DIRECTED CLINICAL TRIAL PLATFORM STRATEGY

International Collaboration

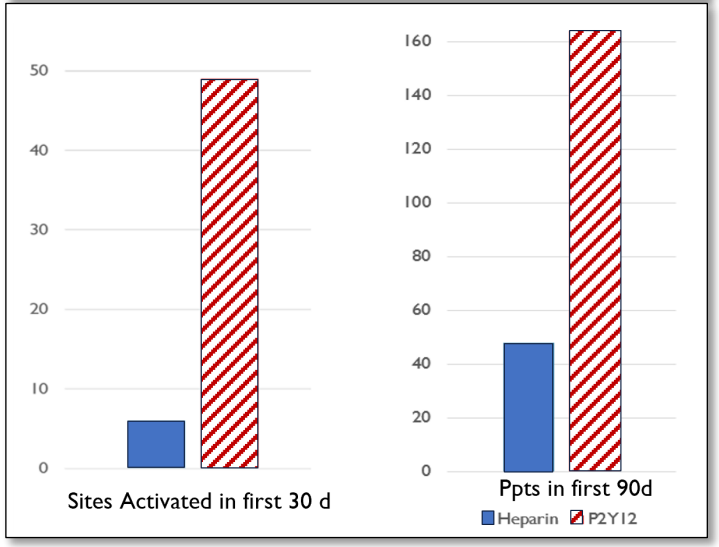


Data Integration

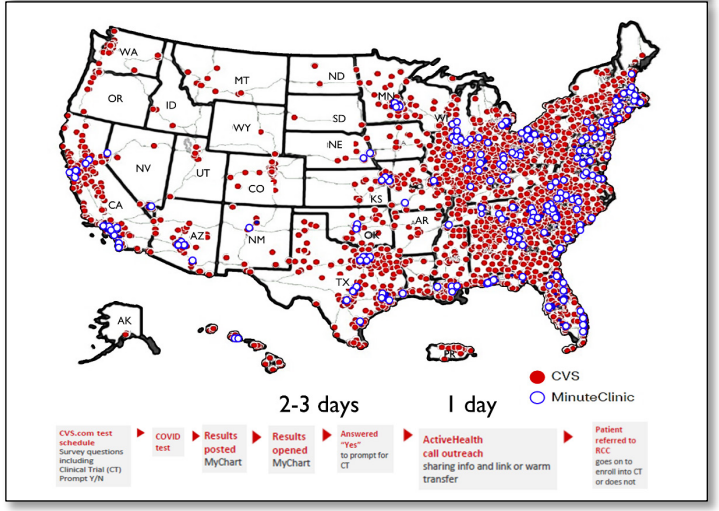


- **Collaborating with and leveraging international studies** examining same classes of agents:
  - Data integration
  - DSMB collaboration
- **Learning system: e.g., strategies to enhance trial start up and completion:**
  - 10-fold increase # sites activated and 4-fold increase # participants
  - Reaching more patients throughnew partners: Outreach through local pharmacies (e.g., CVS)

Accelerating Start-up and Enrollment



Reaching More Patients with New Partners



ACTIV-4A: A Phase III Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19

Prevention → Outpatient Asymptomatic → Outpatient Symptomatic → Emergency Department → **Hospital Vent/CPAP-free** → **Hospital ICU** → Convalescence → Recovered

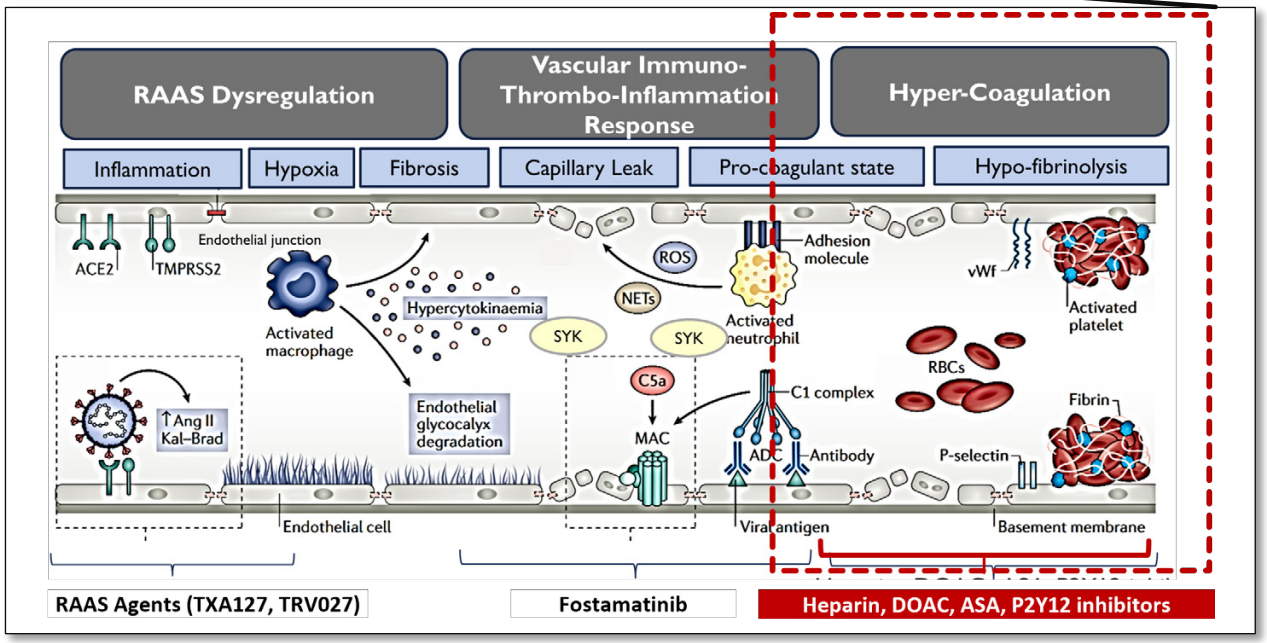
Patient Population: Moderately and severely ill hospitalized patients (+/- ventilatory support)

Interventions/Agents: Heparin, P2Y12 Inhibitors; (Planned: P-Selectin inhibitor (Crizanlizumab,) SGLT2 Inhibitor)

Primary Endpoint: Organ Support Free Days (OSFD)

Secondary Endpoints:

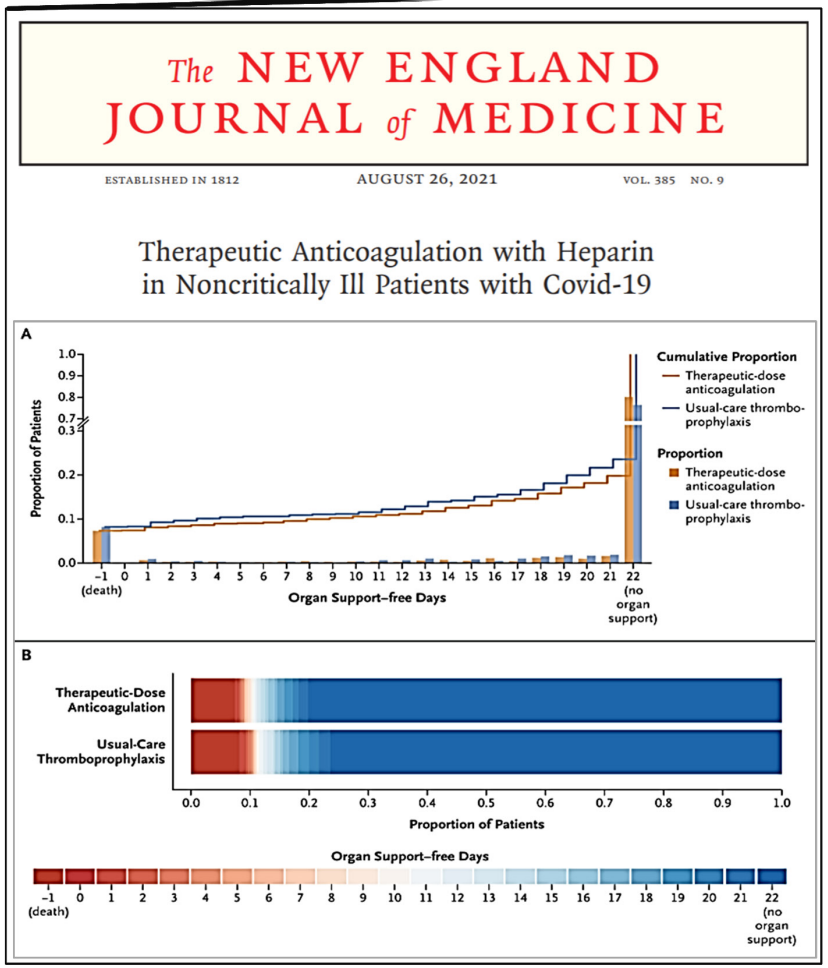
- Death, respiratory support, cardiovascular support, renal replacement therapy
- Composite endpoint (discharge or 28 days, whichever occurs first):
  - Death, PE, systemic arterial thromboembolism, MI, ischemic stroke
- Other Secondary Endpoints:
  - Acute kidney injury, 1˚ & 2˚endpoint components, death during hospitalization, WHO clinical scale, 90-day mortality

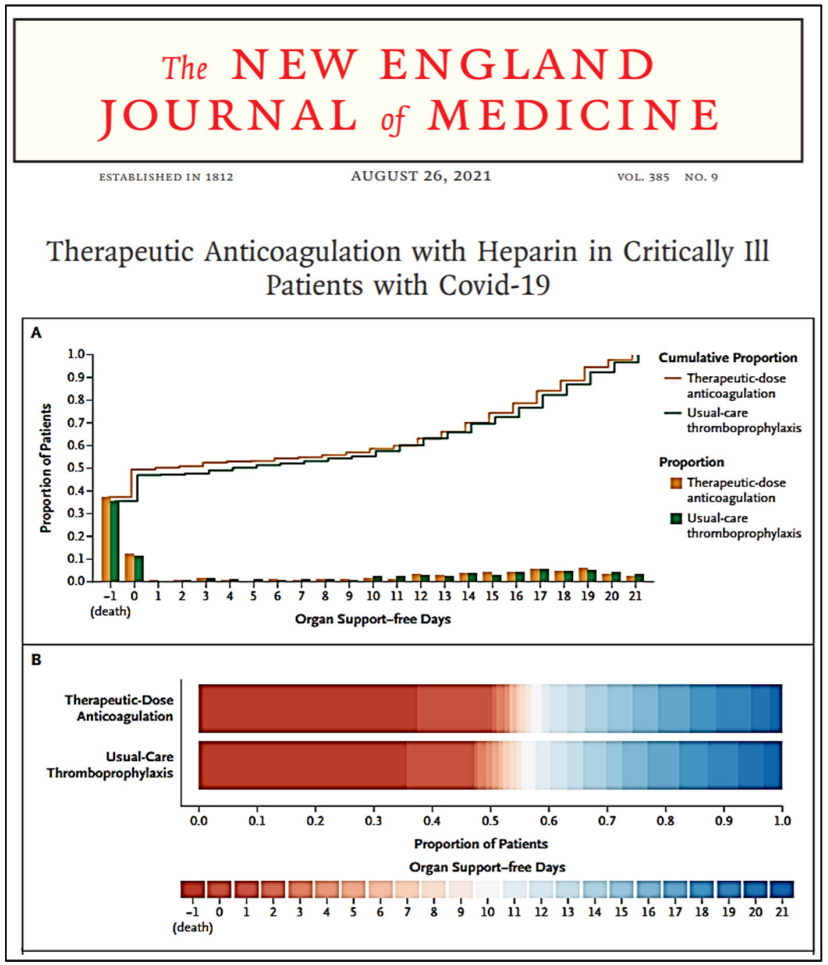


Does targeting the pro-thrombotic/pro-coagulant state and endotheliopathy of COVID-19 improve clinical outcomes for hospitalized patients?

ACTIV-4A: A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19

Prevention → Outpatient Asymptomatic → Outpatient Symptomatic → Emergency Department → **Hospital Vent/CPAP-free** → **Hospital ICU** → Convalescence → Recovered





Intervention: Prophylactic or therapeutic dose Heparin

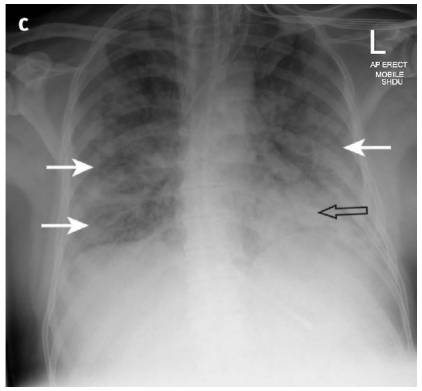
Therapeutic-dose anti-coagulation improved survival without need for organ support in moderately ill (non-critical) hospitalized patients but not in critically ill patients

https://www.nejm.org/doi/full/10.1056/NEJMoa2105911; https://www.nejm.org/doi/full/10.1056/NEJMoa2103417

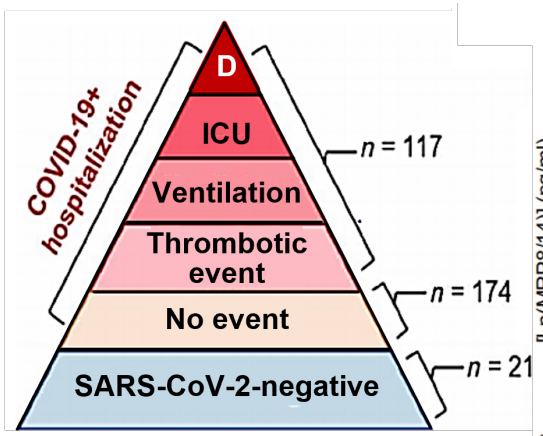
Science Advances | AAAS
SIGNIFICANT RESEARCH, GLOBAL IMPACT
Barrett et al., Sci. Adv. 2021; 7

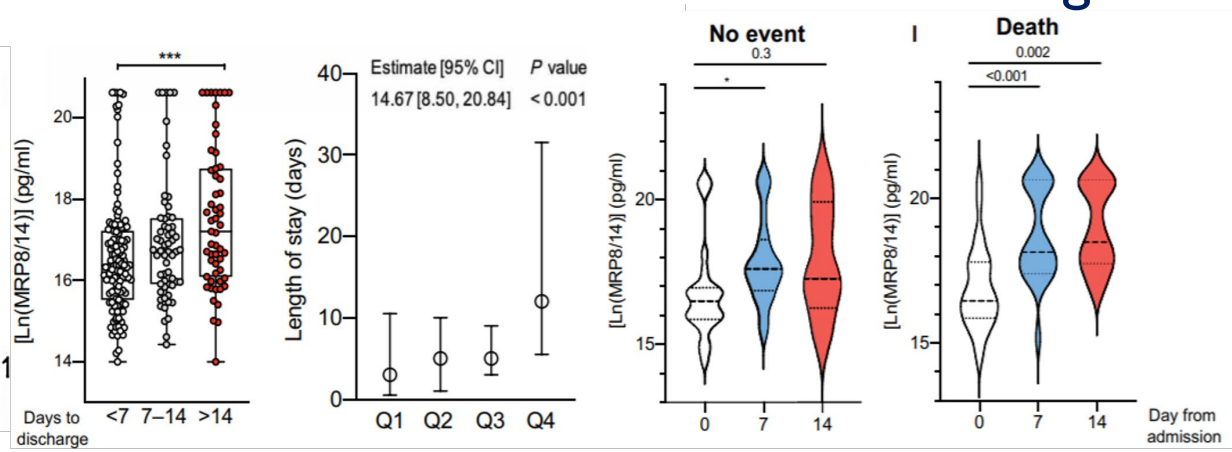
CONNECTS

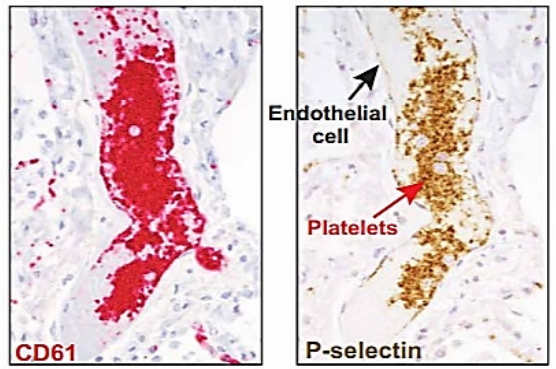
Mechanistic Studies in Parallel with Clinical Trials Inform Risk Stratification and New Targets

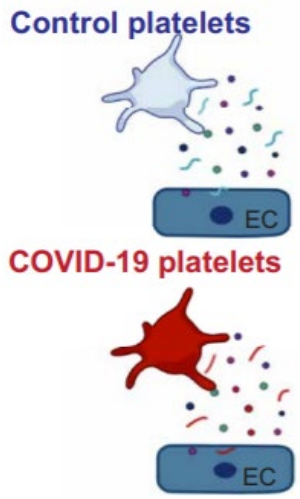


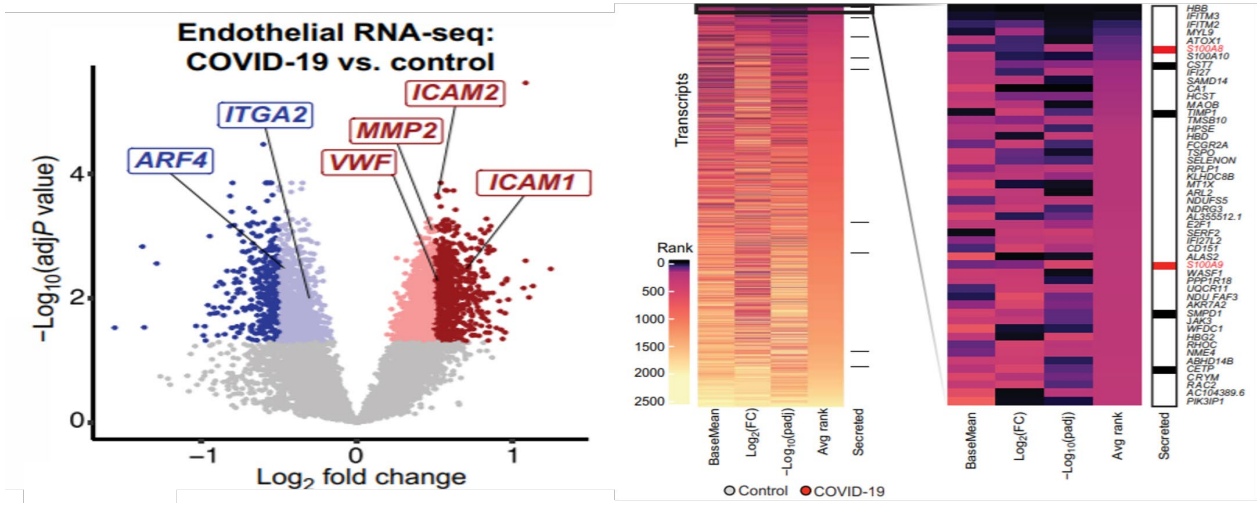
Chest X-Ray: BMJ 2020;370:m2426
http://dx.doi.org/10.1136/bmj.m2426











Demonstrated that platelet-derived factors promote an inflammatory hypercoagulable phenotype, and are significant contributors to poor clinical outcomes in COVID-19 patients

→ Testing anti-platelet agents

ACTIV-4HT: A Phase III Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of RAAS and other HT-directed Agents in Hospitalized Adults with COVID-19

Prevention → Outpatient Asymptomatic → Outpatient Symptomatic → Emergency Department → **Hospital Vent/CPAP +** → **Hospital ICU** → Convalescence → Recovered

Patient Population: Moderately and severely ill adult hospitalized patients treated with oxygen for hypoxemia

Patients on O_2

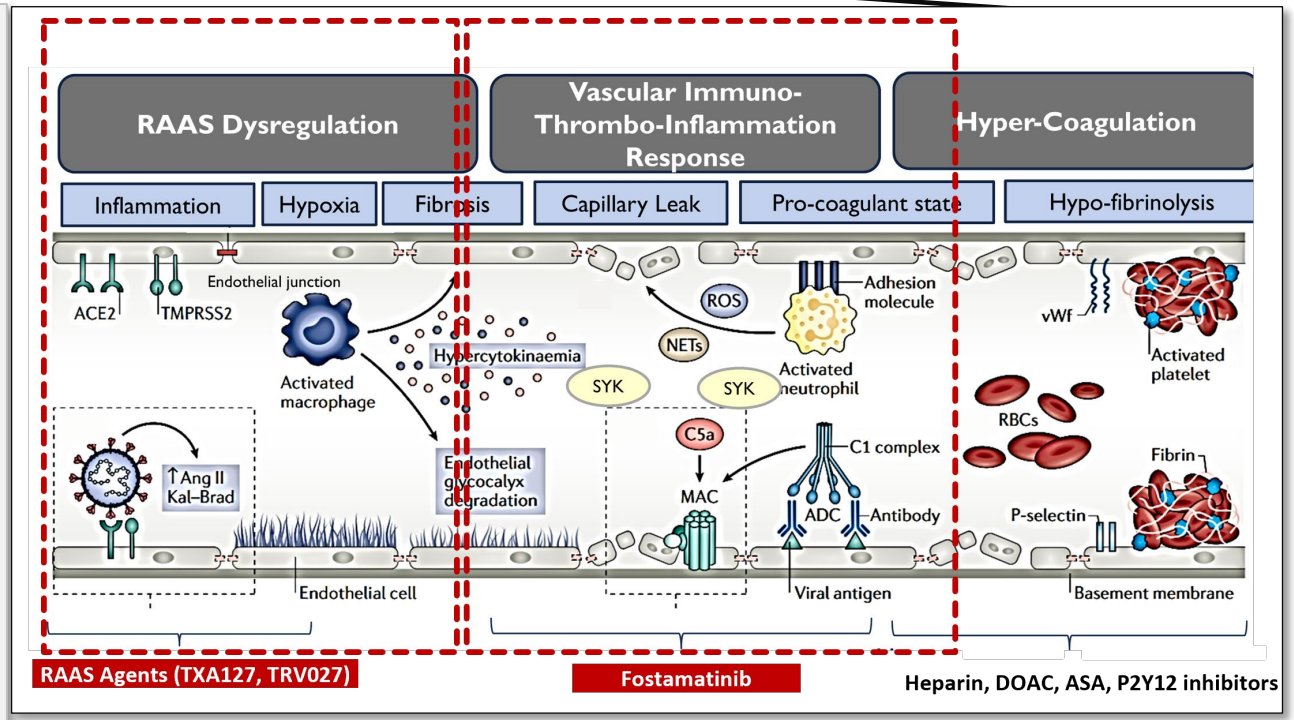
Interventions/Agents (Arms):

- Renin-Angiotensin-Aldosterone System (RAAS) Agents:
  - TXA127 and TRV027
- Inhibition of vascular inflammation:
  - Fostamatinib (spleen tyrosine kinase (SYK) inhibitor)
- Placebo

Target enrollment: 300 per arm

Primary Endpoint: Oxygen-free days from randomization through 28d

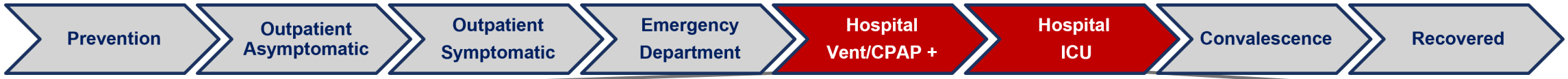
Secondary Endpoint: Mortality, WHO 8-point ordinal scale, support-free days through 28d



https://clinicaltrials.gov/ct2/show/NCT04924660?term=NCT04924660&draw=2&rank=1

Can RAAS-targeting agents and/or Fostamatinib prevent COVID-19 host-tissue responses: vascular injury, inflammation, fibrosis, capillary leakage, and thrombosis?

ACTIV-4HT: A Phase III Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of RAAS and other HT-directed Agents in Hospitalized Adults with COVID-19



Hospitalized Patients On Oxygen

Intervention: Fostamatinib (Spleen tyrosine kinase inhibitor)

Builds upon Phase II NHLBI study:

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Fostamatinib for the Treatment of Hospitalized Adults With Coronavirus Disease 2019: A Randomized Trial

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Phase II Trial of Fostamatinib: Safe in hospitalized patients requiring oxygen and associated w/ trend to clinical and biochemical improvement (esp. in severely ill patients)

ACTIV-4B: COVID-19 Outpatient Thrombosis Prevention Trial: A Multi-center Adaptive Randomized Placebo-controlled Platform Trial Evaluating the Efficacy and Safety of Anti-thrombotic Strategies in COVID-19 Adults Not Requiring Hospitalization at Time of Diagnosis

Prevention → Outpatient Asymptomatic → **Outpatient Symptomatic** → **Emergency Department** → Hospital Vent/CPAP-free → Hospital ICU → Convalescence → Recovered

Clinically Stable Symptomatic Outpatients

JAMA | Original Investigation

Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19
The ACTIV-4B Randomized Clinical Trial

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POPULATION

388 Women
269 Men

Outpatients with symptomatic COVID-19, platelet count >100,000/mm^3, and estimated glomerular filtration rate >30 mL/min/1.73m^2
Median age: **54** years

LOCATIONS

52
Sites in the US

INTERVENTION

657 Patients randomized
558 Patients analyzed

164	165	164	164
Aspirin 81 mg/d + matching placebo for 45 days	**Prophylactic apixaban** 2.5 mg twice/d for 45 days	**Therapeutic apixaban** 5 mg twice/d for 45 days	**Placebo** Placebo twice/d for 45 days

PRIMARY OUTCOME

Composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause

Anti-thrombotic prophylaxis (ASA, DOAC) is not indicated to reduce adverse cardiopulmonary outcomes in symptomatic but clinically stable COVID-19 outpatients

ACTIV-4C: A Phase III Multicenter, Adaptive, Randomized Platform Trial Evaluating the Safety and Efficacy of Antithrombotic strategies in COVID-19 Patients Following Hospital Discharge

Prevention → Outpatient Asymptomatic → Outpatient Symptomatic → Emergency Department → Hospital Vent/CPAP-free → Hospital ICU → **Convalescence** → Recovered

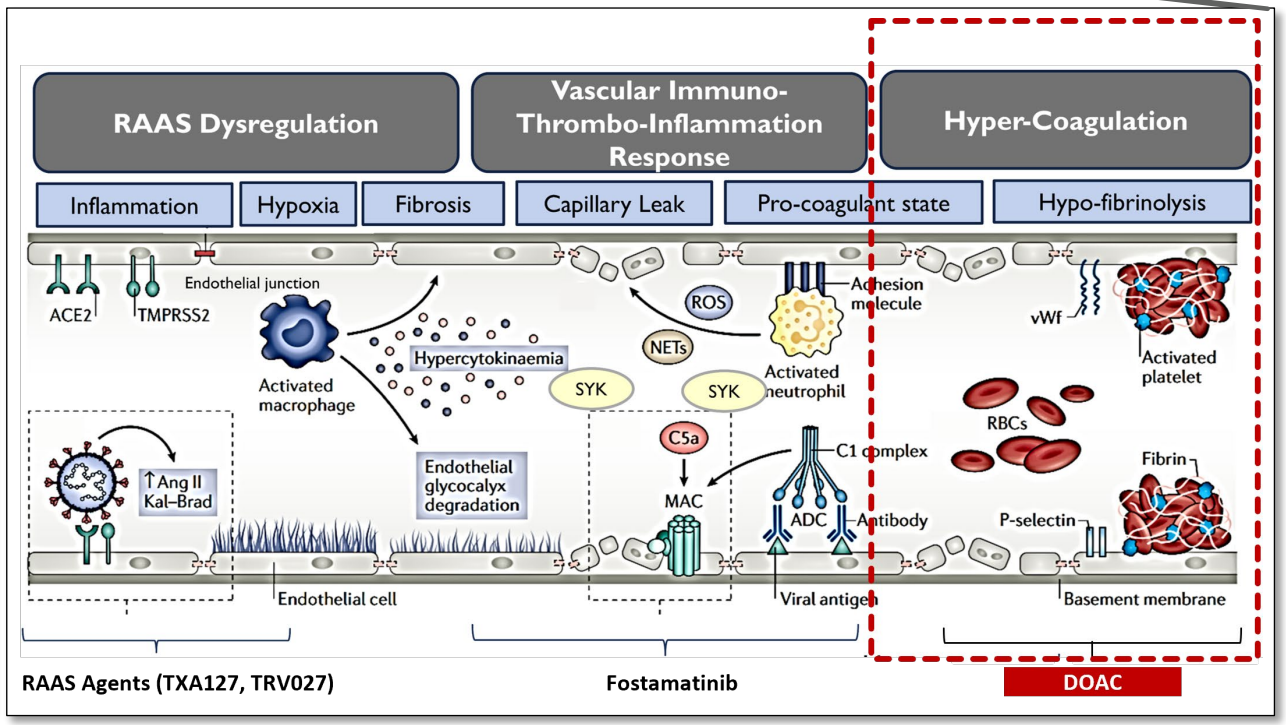
Intervention/Agent: Apixaban

Patient Population: Enrolling adults > 18 years of age with COVID-19 who are hospitalized ≥ 48 hours and ready for discharge

Primary Endpoint: Thrombotic Event; Binary composite endpoint of venous and arterial thrombotic complications and all-cause mortality

Secondary Endpoint: Individual outcomes of the composite primary endpoint, the time-to-event for the composite primary endpoint, and a clinical rank-based score

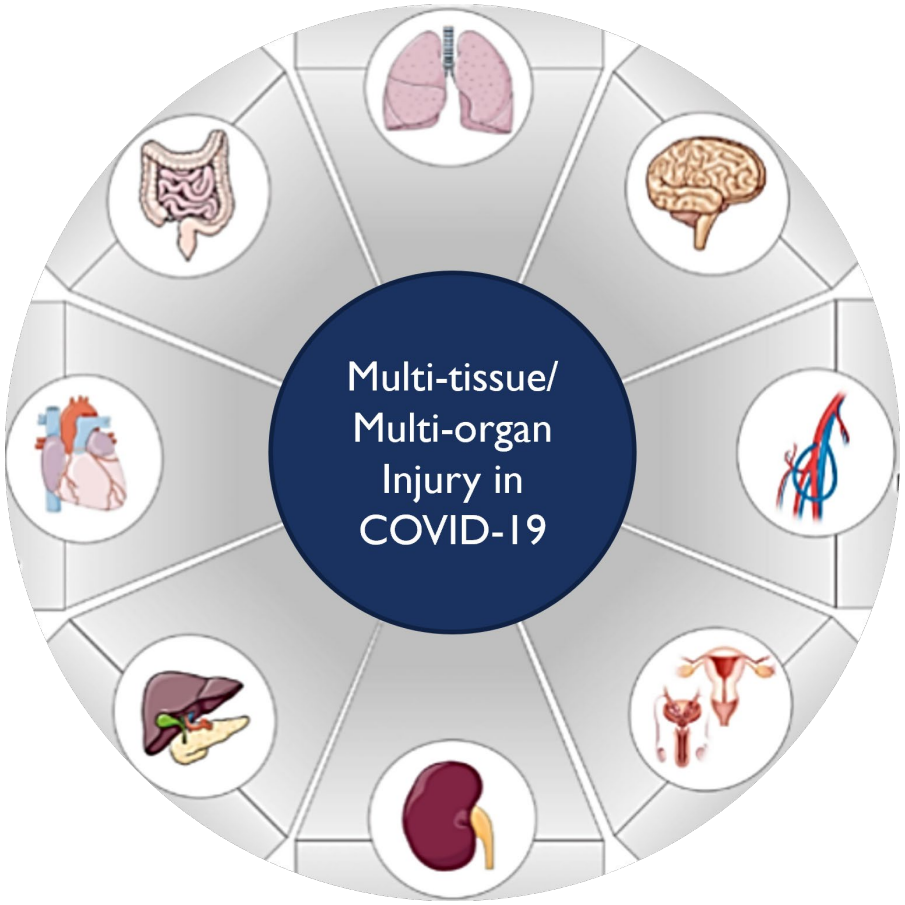
Clinicaltrials.gov:
https://clinicaltrials.gov/ct2/show/NCT04650087



Can anti-thrombotic therapy in the post-acute setting prevent thrombo-embolic events and improve survival after hospital discharge?

Development of Host Tissue-Directed Therapeutics: Vital to Future Pandemic Preparedness

1. **Initial phase of a viral pandemic:** specific anti-viral agents (i.e. vaccines, anti-virals, or monoclonals) not readily available
2. **Later phases:** Even in presence of specific antiviral reagents, delays in effective protection to all components of the population
3. **Subsequent phase of a viral pandemic:** Pathogen evolves, is able to evade specific antigen recognition upon which vaccine and passive immunization strategies rely, and/or is able to circumvent mechanisms of, for example, specific protease inhibitors
4. **Post-acute infection phase** may be associated with significant host tissue sequelae which will require monitoring and development of therapeutic and prophylactic interventions



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Patients & Researchers
Policymakers & Govt Agencies
Academic Health Centers
International Organizations
Community Organizations
Primary Care
Private Sector
Professional Societies/ Foundations
Patients Citizen-Science
NIH
Thank you to Patients, Researchers, NIH and HHS Staff, for your critical role in improving COVID-19 therapies