Beyond the tension of hypertension : focus on non-antihypertensive aspects of antihypertensive treatment

BEYOND THE TENSION OF HYPERTENSION

focus on non-antihypertensive aspects of antihypertensive treatment

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aan mijn ouders
aan Marleen, Tine, Jeroen en Stijn

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PART I
INTRODUCTION

chapter 1. pathophysiology and epidemiology of hypertension

1. blood pressure and blood pressure control

From a physiological point of view, systolic and diastolic blood pressure are determined by the mean arterial pressure (MAP) and the pulse pressure (ΔP) oscillating around this mean arterial pressure. Determinants of blood pressure are shown in Table 1.1.

Table 1.1. Determinants of blood pressure

components	mean arterial pressure	pulse pressure
nature	static	dynamic
main determinant vessels	resistance vessels: - small arteries - arterioles - capillaries	capacitance vessels: - small arteries - large arteries

Mean arterial pressure - the static component of blood pressure - is determined by cardiac output (CO) and systemic vascular resistance (SVR): MAP = CO x SVR.
The cardiac output is determined by the heart rate (HR) and stroke volume (SV): CO = HR x SV.
The systemic vascular resistance is a function of blood viscosity (η) and the resistance determined by small resistance vessels, which are predominantly arterioles and capillaries. This is described in more detail in chapter 2.
For a given stroke volume (SV), pulse pressure - the dynamic part of the blood pressure - is determined by the compliance (C) of arterial capacitance vessels, which are predominantly large arteries (1):
$\Delta P = SV / C$ (2,3)
Compliance is a quantitative measure of the buffering capacity of vessels. However, this formula of ΔP is incomplete since, apart from compliance of large vessels, not only stroke volume, but also the velocity of ejection of the blood from the heart and reflected pulse waves can influence pulse pressure [see part II chapter 1] (1).
In summary: systolic and diastolic blood pressure are a result of the cardiac pump function and the static and dynamic resistance (impedance) of the arterial tree. For a given heart function, arterioles and capillaries largely account for the static component of the blood pressure (MAP), while large arteries determine predominantly the dynamic part (ΔP) (1).
Short-term variability (over a 30-minute period) in arterial pressure of adult man is smaller than 10 % of the mean pressure. This is due to blood pressure control systems. The body has many systems for controlling the pressure, which has been extensively described (4,5). Examples of them are shown in Table 1.2.

Table 1.2. Examples of blood pressure controllers (4)

short-term	intermediate	long-term
baroreceptor reflex	renin-angiotensin system	kidney-fluid control
CNS ischaemic reflex	stress relaxation	
chemoreceptor reflex	capillary fluid shift	
	aldosterone	

Controllers based on the nervous system act within seconds and are thus short-term controllers. Intermediate pressure controllers function a few minutes after activation of the neural pressure controllers (6,4). Long-term control is achieved by the kidney-fluid system, which takes usually 2 to 4 days before pressure equilibrium has been reached (4).

2. epidemiology of hypertension

Hypertension, defined as a resting diastolic blood pressure over 95 mmHg, is a very common condition in westernised countries. 15 to 20 % of American adults, as evidenced by a National Health Survey, have hypertension (7); if hypertension is defined from a level of more than 90 mmHg, about one third of the population is affected (8). About 1 % of hypertensive patients develop malignant hypertension (9), characterized by an extremely high blood pressure accompanied by neuro-retinopathy with papilloedema and exudates with haemorrhages (10).
Hypertension can be secondary to different diseases and may be drug related (11). Examples of secondary hypertension are shown in Table 1.3. Ferguson reported that secondary hypertension was most frequently oral anticonceptive-induced (40 %); 30 % of secondary hypertension was due to renovascular disease, about 20 % due to chronic renal disease and about 2 % due to Conn's syndrome (12). In 90 to 95 % of cases the aetiology of hypertension is still largely unknown (9,12). This means that > 90 % suffer from primary or essential hypertension.

Table 1.3. Some examples of secondary hypertension

renal disease	adrenal disease	drugs	other
glomerulonephritis	Cushing's syndrome	contraceptive pill	pre-eclampsia
polycystic disease	Conn's syndrome	liquorice	coarctation of aorta
pyelonephritis	phaeochromocytoma	MAO-inhibitors	raised intracranial tension
renovascular disease		corticoids	
renin secreting tumor		sympathomimetics	

Essential hypertension is a multifactorial disease (13). Genetic as well as environmental factors and excessive psychological stress - can increase the risk for essential hypertension (14-16). High blood pressure before the age of 55 occurs 3.8 times more often among persons with a strong positive family history of high blood pressure (17). Williams believes that most familial aggregations of high blood pressure is due to genetic rather than due to shared familial environment (18), with

about 12 % of hypertensives suffering from familial dyslipidaemic hypertension. Different environmental risk factors relate to modern lifestyle, i.e. high salt intake, high dietary sodium/potassium ratio, caloric imbalance with resultant obesity, and high alcohol intake (19). An overview of published observations suggests that both genetic predisposition and environment work together to produce hypertension in most persons (18). For example, hyperinsulinaemia and insulin-resistance might be a genetic and/or environmental important risk factor for hypertension. The linkage between obesity and hyperinsulinaemia due to insulin resistance is well known (20). Hyperinsulinaemia could lead to hypertension through stimulation of 4 intermediate factors: renal sodium reabsorption and sodium retention (21), plasma norepinephrine concentration, vascular hypertrophy and intracellular calcium concentration (22). In addition, Reaven described a syndrome X, characterized by [1] resistance to insulin-stimulated glucose uptake, [2] glucose intolerance, [3] hyperinsulinaemia, [4] increased concentrations of very low density lipoprotein triglyceride, [5] decreased concentration of high density lipoprotein cholesterol and [6] hypertension (23). Reaven's syndrome X is thought to be linked with an increased risk for coronary artery disease. In family studies it occurred in 12 percent of all persons with essential hypertension, but in 25 % of those with hypertension beginning before the age of 60 (24). Syndrome X can also exist in persons who are otherwise thought as healthy (25). Reaven's syndrome X should be distinguished from another recently described Syndrome X, also of unknown aetiology, which includes typical angina, a positive exercise test, a normal coronary angiogram, and a normal resting cardiac function but a reduced coronary vasodilatory capacity (26).

3. Ill effects of hypertension

Malignant hypertension has a grave prognosis: 50 % of untreated patients die within 3 months and very few survive more than 1 year (10). Death is usually due to renal failure, often accompanied by heart failure and stroke. Cumulative death from malignant hypertension is positively related to the height of the blood pressure (27). Due to active treatment the morbidity and mortality risk of hypertension has been changed from malignant hypertension to hypertension-induced progressive atherosclerosis and its chief sequelae (28). The major target organs of hypertension are the blood vessels, heart, brain and kidneys (29). Major ill effects of hypertension are stroke, those due to cardiac hypertrophy and atherosclerosis - coronary atherosclerosis in particular - and to a lesser extent renal failure (30). In the Framingham study the annual incidence of coronary disease was 306/10,000 in hypertensive men versus 66/10,000 for stroke (31). Thus, the risk of coronary heart disease was 5 times more frequent than the risk of stroke.

chapter 2. functional and structural changes of the cardiovascular system in hypertension and their influence on morbidity and mortality

1. changes resulting in an increased mean arterial pressure[1]

In most cases of essential hypertension mean arterial pressure is increased. Mean arterial pressure is determined by cardiac output and peripheral resistance. In early hypertension, an increase in cardiac output might be the reason for the elevated blood pressure (15) with or without an increase in peripheral resistance. In established hypertension peripheral resistance is nearly always increased. This increase in peripheral resistance plays a key role in the onset and maintenance of essential hypertension. The factors that determine vascular resistance are the number of blood vessels [N], the length of the vessels [L], the blood viscosity [η], and the radius of the vessels [r]. The quantitative relationship between these variables and total resistance (R) is given by Poiseuille's law:

formula: $R = 8\eta L/N\pi r^4$

Although this is a relatively simple formula to describe, the actual physiology of resistance control and changes in hypertension is complex. This complexity is caused by the architecture of the vascular system, its heterogeneity, both within a given vascular bed and between different vascular beds, and the many factors influencing vascular resistance (Table 1.4).

Three mechanisms have been proposed to underlie the overall vascular resistance increase in hypertension: [a] rarefaction of arterioles and capillaries; [b] decreased internal diameter of the arterioles and small arteries; and [c] increase in arterial and arteriolar wall mass (32-36).

Traditionally, the decrease in internal diameter was regarded as the most important cause of resistance increase in hypertension. Modern views regard internal diameter as an important short-term controller of vascular resistance, whereas the number of small vessels and vascular mass are important in the long-term control of vascular resistance (32-33,35-38).

Table 1.4. Factors influencing vascular resistance

blood viscosity	smooth muscle activity	structural factors
haematocrit	myogenic response	wall/lumen ratio: -structural diameter -wall thickness -distensibility
velocity	electrolytes	network characteristics: -number -length -*branching pattern*
cell aggregation	nerves	
cell deformation	metabolites endothelium-derived substances	

[1] Part of this chapter is based on: Struyker Boudier HAJ, Van Bortel LMAB, De Mey JGR. Remodeling of the vascular tree in hypertension: drug effects. Trends Pharmacol Sci 1990, 11: 240-245.

Microvascular rarefaction can be observed as a feature of several tissues in early stages of development of hypertension. The nature of the mediators of microvascular rarefaction in hypertension is still unknown. One possibility is that it represents an adaptive response to increased microvascular pressure or flow (33,39). Alternatively, rarefaction may be the result of a decreased capacity of the hypertensive animal to form new blood vessels (angiogenesis).
Folkow has proposed that an increase in contractile mass is an important feature of the arterial and arteriolar vessel wall in hypertension (32). Increased vessel wall mass is part of a general process to remodel blood vessels in response to a variety of stimuli. The mediators of the increase in vessel wall mass are still largely unknown. However, there is increasing evidence that the endothelium plays a crucial role in controlling growth in the vessel wall. By sensing changes in local haemodynamics and by acting as an important source of molecules affecting growth, the endothelium is a unique controller of both vascular smooth muscle tone and vessel wall structure (40).

2. changes resulting in an increased pulse pressure

Ventricular ejection and large artery visco-elastic properties influence the level of pulse pressure (1). In essential hypertension, the increase in pulse pressure is predominantly due to stiffening of the large arteries. This is described in detail in part II, chapter 1. Different factors may contribute to the stiffening of large arteries, for example, a decreased connective tissue elasticity, atherosclerosis and a decrease in smooth muscle relaxation (41).
Systolic blood pressure is more closely related to pulse pressure, while diastolic pressure better reflects mean arterial pressure. The Framingham study and also other epidemiological studies have shown that the ill effects of hypertension are better correlated with the systolic than with the diastolic blood pressure (42-44), indicating an important role of the pulsatile stress (pulse pressure).
Increased pulse pressure is most pronounced in elderly hypertensive patients. It results in an increase in systolic pressure, while diastolic pressure tends to decrease in relation to the mean arterial pressure (1). Apart from combined systolo-diastolic hypertension, isolated systolic hypertension (ISH) occurs relatively often in elderly patients. The prevalence of ISH increases with age. It ranges from 7 % in individuals aged 60 to 69 years to more than 20 % in those aged 80 years and more (45-46). In isolated systolic hypertension mean arterial pressure and vascular resistance may be normal or only slightly elevated, while pulse pressure is increased (1).

3. left ventricular hypertrophy

Left ventricular hypertrophy, as detected by echocardiography, is present in approximately 20-50 % of hypertensive patients (47).

3.1. cardiac remodeling in hypertension

Mechanical overload increases wall stress of the left ventricle, which is considered the main pathogenic stimulus for cardiac hypertrophy (48). The true load for the heart is the impedance of the ascending aorta, being to the pulsatile pressure and flow what resistance is to continuous flow. In hypertensive heart disease, it depends on the arteriolar resistance, compliance of the large vessels (predominantly

the aorta), blood inertia and also on the reflected pressure waves (49). Thus, the compliance of large arteries plays an important role both in the onset and maintenance of cardiac hypertrophy in hypertension (50-51). The importance of mechanical factors is discussed in more detail in part II.
Mechanical overload is known to influence several (neuro)hormonal systems, including the sympathetic nervous system and the renin-angiotensin-aldosterone system. Overactivity of these systems seems to be important in driving the early asymptomatic remodeling process (52). Apart from the sympathetic nervous system and the renin-angiotensin-aldosterone system, other undefined cytokines and peptides are probably also involved (53). Cardiac hypertrophy is characterized by quantivite and qualitative changes in the myocardium and coronary arterioles: [1] myocyte hypertrophy; [2] slowing the maximal shortening velocity (V_{max}) of the myocytes due to an increased proportion of the ß isoform of myosin, which can totally replace the α isoform (54); [3] possibly altered calcium homeostasis in the myocyte; [4] hypertension-induced coronary artery hypertrophy resulting in a smaller compliance and higher coronary resistance; [5] increase in collagen content in the interstitium of the heart (55). Collagen may be produced in response to fibroblast stretch (56), and by activation of trophic factors including angiotensin II and aldosterone (57). In patients with hypertension, left ventricular mass is strongly correlated with plasma aldosterone levels (58). Recently, a role of aldosterone in the development of left ventricular fibrosis, associated with left ventricular hypertrophy, has been suggested (59). These findings suggest that the increased afterload for the heart in hypertension is the drive for (reversible) cardiac hypertrophy, while the elevated angiotensin II and aldosterone levels not only maintain hypertension by salt and water retention, but further impair cardiac function by (hardly reversible) fibrosis.

3.2. effect of cardiac hypertrophy on heart function.

Diastolic function is abnormal in hypertension. This abnormality is seen at a stage before left ventricular hypertrophy is obvious (60). It reflects chamber stiffness or relaxation abnormalities (61). Systolic function is, in general, normal in hypertensive patients with left ventricular hypertrophy (61). However, with progressive hypertrophy, systolic function may become impaired and may result in an initially asymptomatic state with decreased ejection fraction, which can further deteriorate to overt heart failure (62).

3.3. risk of cardiac hypertrophy

In hypertension, an increase in left ventricular mass provides the best prediction of (fatal and nonfatal) cardiovascular clinical events (63). Possible reasons why left ventricular hypertrophy might be such a lethal condition are: cardiac hypertrophy leads to [1] a mismatch between blood supply and non-vascular tissue resulting in a relatively 'starved' subendocardial region; [2] an increased basal myocardial oxygen demand due to increased mass and wall stress; [3] a markedly reduced coronary flow reserve (ability to dilate coronary arteries) making ischaemia more likely under stressful conditions (64); [4] an increase in ventricular arrhythmias and sudden death (65-66). This might be due to an excess of fibrous tissue, interference with coronary flow or disturbances in the ventricular pump function itself (62,64). The association of left ventricular hypertrophy and arrhythmia might also be due

to (impending) heart failure. This is supported by the observation that, in patients with heart failure, antihypertensive treatment with the ACE-inhibitor enalapril reduced mortality especially from progressive heart failure, while there was no effect on mortality from arrhythmia without previous worsening congestive heart failure (67-68).
In conclusion, cardiac hypertrophy is common in hypertension and is a lethal condition. Therefore, measurement of left ventricular mass might be a better tool for the evaluation of antihypertensive treatment.

4. (coronary) atherosclerotic disease

4.1. onset of atherosclerosis.

Vascular injury is a key event in the response-to-injury hypothesis of atherogenesis (69). The definition of endothelial injury has been problematic, since there may be a spectrum of changes in injured endothelium and many of these may have no morphologic manifestations. Fuster proposed 3 types of vascular injuries (Table 1.5), which might be involved in onset and progression of atherosclerosis (70).

Table 1.5. Types of endothelial injury

type	nature
type I	functional alterations of endothelial cells without morphologic changes
type II	endothelial denudation and intimal damage with intact internal elastic lamina
type III	endothelial denudation with damage of both intima and media

Endothelial injury (type I and II) may result in release of growth factors from one or more of the following cells: the endothelium, monocytes and platelets. Growth factors induce smooth-muscle cell migration and proliferation and possibly autogenous growth factor release by stimulated smooth-muscle cells.
All four principal cells involved in atherosclerosis - endothelium, smooth muscle cells, platelets, and monocyte/macrophages - either contain (e.g., platelets) or can synthesize and release chemo-attractants and growth factors (69). These interactions could then lead to fibrous-plaque formation and further lesion progression.
In spontaneous atherosclerosis, the tenet is that chronic minimal injury to the arterial endothelium is caused mainly by a disturbance in the pattern of blood flow in certain parts of the arterial tree, especially at bending points and areas near branching vessels (69,71-72). The influence of physical factors is discussed below.
In experiments in animals, chronic mild endothelial injury may also be potentiated by hypercholesterolaemia, circulating vasoactive amines, immunocomplexes, infection, and chemical irritants in tobacco smoke (73).
Atherosclerosis is of multifactorial origin. Its genesis is influenced by dyslipoproteinaemia, thrombotic events, haemodynamic/mechanical and endogenous chemical injury of the arterial intima (or media), as well as inflammatory and/or immune reactions of the arterial wall (74). Risk factors for atherosclerosis are: hypertension, cigarette smoking, glucose intolerance, insulin resistance, obesity, hypercholesterolaemia, hypertriglyceridaemia [?], and personality type (31).

Table 1.6. Possible biologic mechanisms of risk factors in atherogenesis.

	HL	IR	HT	SM	ES	GE
vascular injury (type I)	+	+	+	+	+	—
lipid deposition	+ +	+ +	—	—	—	+ +
monocyte/platelet deposition	+	+	—	—	—	—
fibrointimal proliferation	+	+ +	+	+	+	+
plaque disruption(type II/III)	+ +	+ +	+ +	+ +	+ +	—
Thrombosis	+	+	—	+ +	+	+

Adapted from Ip et al (73); HL: hyperlipidaemia; IR: insulin resistance; HT: hypertension; SM: smoking; ES: emotional stress; GE: genetics; + : mild; + + : severe; —: no effect.

Although atherosclerosis is a separate disease that has a natural history independent of hypertension, it is exacerbated by hypertension (29). Hypertension may initiate and perpetuate vascular injury, or both, and may enhance the resultant fibrocellular proliferative responses (29). However, there is some experimental evidence that hypertension by itself may not be a necessary or adequate atherogenic factor (75). But more importantly, hypertension can play a role in triggering acute plaque rupture caused by physical stress on the arterial wall.

4.2. progression to atherosclerotic disease.

In most growing lesions progression is probably rapid. Emerging evidence from autopsy studies (76) suggests that it follows recurrent minor fissures of the most fatty or atheromatous plaques with subsequent thrombus formation and fibrotic organisation. Most of the fissures probably reseal and incorporate thrombus at the same time but do not produce clinical symptoms. However, a deep plaque fissure or ulceration may lead to thrombotic occlusion and acute coronary syndromes. Increased shear forces in the area of stenosis, sudden changes in intraluminal coronary pressure or tone (77-78) and bending and twisting of an artery during each heart contraction may contribute to the disruption of these plaques. Computer modelling also showed that the distribution of circumferential tensile stress across the intima was radically altered by atherosclerotic plaques. Regions of high circumferential stress correlated well with the site of intimal tears found at necropsy (79). Clearly, the role of mechanical or physical stresses in plaque disruption requires further intensive investigation (70). In comparison with other large arteries, coronary arteries undergo an additional stress exerted by the contraction of the heart itself. It seems logical that both heart rate and contractility might influence this additional stress. This view is supported by the observation that ischaemic episodes (80), myocardial infarction (81,82) and sudden death (83,84) have a peak occurrence in the morning waking hours, which correspond closely with a peak in heart rate and blood pressure (85) and also in indices of coagulation (86-90) such as increased platelet and decreased fibrinolytic activity.
The relative prevalence of this process of plaque disruption with mural thrombus formation and organization, in comparison with the more progressive myointimal proliferative process due to chronic endothelial injury postulated by Ross is unknown. However, several groups (76,79,91-94) have clearly shown that thrombus formation, usually due to atherosclerotic plaque rupture plays a fundamental

role in the development of the acute coronary syndromes. The disrupted plaques are the so-called complicated plaques (70).
Recent evidence from a prospective angiographic study (95) suggests that severe stenoses tend to progress to total occlusion about 3 times more frequently than do less severe lesions, but this process only infrequently results in myocardial infarction. In contrast, 85 % of infarct-related lesions were not haemodynamically important (stenosis of less than 75 % of the diameter). In addition, other authors have found that about two third of the lesions responsible for myocardial infarction had a stenosis less than 50-70 % (96-99). Unlike small plaques, which may be lipid-rich and prone to disruption, severely stenotic plaques tend to be very fibrotic and stable (100). These findings support the concept that disruption of small plaques is important in the pathogenesis of acute myocardial infarction, whereas longstanding severe stenoses more commonly result in total vessel occlusion, with a small or silent infarction or no infarction at all, perhaps because of the presence of well-developed collateral vessels (101-103).
Although a substantial proportion of episodes of unstable angina and acute myocardial infarction is caused by plaque fissuring or rupture with superimposed thrombosis, other mechanisms that alter the balance between myocardial oxygen supply and demand also need to be considered (104). Vasospasm was found to be an important contributor to intermittent coronary artery occlusion in patients with acute myocardial infarction who were treated with streptokinase (105). Animal experiments showed that platelets contribute to a reduction in blood flow, either by transiently aggregating and occluding the vessel, by releasing vasoconstrictor substances like serotonin and thromboxane A_2 (106-109), or both (94). In addition, atherosclerotic arteries have an abnormal vasodilator function, perhaps related to a deficiency in the production of endothelium-derived relaxing factor (110).

5. stroke.

The prevalence of stroke is estimated to be 50 - 80 per 10000 population over the age of 25 years (111). Stroke is the third leading cause of death and an important cause of hospital admission and long-term disability in most industrialised countries. It accounts for 10-12 % of all deaths in industrialised countries (112). In addition, the cumulative risk of recurrence over 5 years is high, ranging from about a third to almost a half of people who have stroke (112). Risk factors for stroke are shown in Table 1.7.

Table 1.7. Factors that predict future occurrence of stroke.

physiological	behaviour	other
blood pressure	diet	social class
serum cholesterol	smoking	psychosocial factors
fibrinogen	alcohol	ethnic groups
body mass index	oral contraceptives*	age
blood sugar		

* only data on older oral contraceptives available

In patients with blood pressure ≧ 160/95 mmHg, the relative risk of stroke was 2.7 for men and 2.3 for women compared with normotensive men and women (113). Also in isolated systolic hypertension the risk of stroke was increased at least twofold (114). In addition, about 88 % of the deaths attributed to stroke are among people over 65 years (112). Stroke incidence rises exponentially with increasing age, with a hundred-fold increase in rates from about 3 per 10000 population per year in the third and fourth decades to almost 300 in the eight and ninth decades (115). There are 3 main classes of stroke: ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage (116). Raised serum cholesterol is strongly related to death from non-haemorrhagic stroke, but not from intracerebral and subarachnoid haemorrhage. The major risk factor for stroke, whether haemorrhagic or not is high blood pressure (116).

6. renal failure.

Renal dysfunction is almost always demonstrable in hypertensive patients, even in those with minimally elevated pressures. This often asymptomatic involvement may be detected by increased microalbuminuria, reflecting intraglomerular hypertension (117). It results from an increased preglomerular arteriolar flow and decreased resistance. This leads to glomerular hypertension, glomerular hyperperfusion and glomerular injury and sclerosis, referred to as nephrosclerosis (118-119). The loss of renal function is positively related to the blood pressure (120), but only a minority of hypertensives develop terminal renal failure. Renal failure represents either the effects of the malignant phase of hypertension caused by fibrinoid arterial necrosis or the progression of some primary renal disease unidentified in the search for a specific cause. Very rarely the kidneys may fail due to other forms of arterial disease, particularly atheroma of the larger vessels and nephrosclerosis (121). The elevated serum uric acid level present in one-third of untreated hypertensives possibly reflects nephrosclerosis (122). Hypertension accounts for 20 to 25 % of all causes of renal failure in the United States (123). The relative risk for hypertensive end-stage renal disease is about 5 % (124). It is more common in blacks than in caucasians.

7. conclusion

Except for isolated systolic hypertension, the onset and maintenance of hypertension is mainly based on functional and structural changes in arterioles and capillaries. The ill effects are not only due to the elevated pressure (i.e. stroke), but even more importantly to acceleration of atherosclerosis and cardiac hypertrophy.
In conclusion, the onset and maintenance of hypertension is predominantly due to changes in the microcirculation, while the majority of ill effects are due to pathological changes in the macrocirculation.
In isolated systolic hypertension both onset and ill effects are predominantly due to changes in the macrocirculation.

chapter 3. management of hypertension

1. reduction of high blood pressure

1.1. nonpharmacological management

Various nonpharmacological therapies are being widely advocated as initial therapy - at least for the first 3-6 months after recognition of hypertension - for most patients with a slightly elevated blood pressure (125-126). Different nondrug therapies have been proposed. Recently, their long-term effectiveness has been reviewed by Kaplan (127) and is shown in Table 1.8.

Table 1.8. Long-term effectiveness of proposed nonpharmacological treatment.

effective	minimal, if any	no evidence at all
overweight reduction	potassium	coffee reduction
salt restriction	magnesium	smoking reduction
physical exercise[1]	calcium	onions and garlic
less alcohol[2]	less fat intake	
relaxation therapy[1]		

[1] conflicting evidence; [2] less than 3 glasses per day.

There is large evidence that obesity is linked with a higher prevalence of hypertension (128-129). MacMahon et al (130) estimated that approximately 30 % of arterial hypertension can be attributed to obesity. Numerous studies of medical weight reduction have confirmed that weight loss is associated with a fall in blood pressure in severely obese hypertensive patients (131-133).

Before the introduction of thiazides in the late 1950s, it was known that salt restriction lowers blood pressure (134). Data from 11 adequately controlled studies showed that the average effect of 100 mmol/day reduction in sodium intake - which was about half the usual intake - induced a 5.4/6.5 mmHg fall in systolic and diastolic blood pressure, respectively (135). The higher the initial blood pressure (136) and the more rigid the salt restriction (137), the larger the fall in blood pressure. In contrast to the poor patient adherence to very rigid salt restriction, the acceptability and efficacy of moderate salt restriction (60-100 mmol/day) is good (138-139). However, such a modest salt restriction will induce only a significant fall in blood pressure in those patients, who are more sodium sensitive (127).

The effect of physical training on casual blood pressure has been extensively investigated. It has been recognized that blood pressure acutely decreases after physical exercise (140). It is not so clear whether exercise training may induce a more prolonged decrease in blood pressure. In a consensus statement by the World Hypertension League a small average decline of 4 mmHg for systolic as well as diastolic blood pressure is assumed (141). However, the majority of controlled longitudinal studies did not show a decrease in blood pressure at rest (142-143). Recently 3 studies have been published on the influence of exercise training on ambulatory blood pressure. Two authors did not find any influence neither on casual nor on ambulatory blood pressure (144-145), whereas the 3rd author

described a small decrease in diastolic blood pressure alone (146). Even if the effect of exercise training on blood pressure is small, physical exercise might play a role in the prevention of ill effects of hypertension. Indeed, exercise training decreases vascular resistance (144), which might be due to an increment in the size of the capillary bed of the skeletal muscle in combination with changes in regulatory effects of arterioles, i.e. decrease in sympathetic tone (147-149). This decrease in vascular resistance often did not result in a decrease in blood pressure because of a slight rise in cardiac index at rest (144,150-151). Regular exercise may also reduce the incidence of hypertension. Blair et al calculated that the relative risk for development of hypertension was 1.52 greater in men and women with low levels of physical fitness than in those with higher levels (152).

Most large-scale surveys find no higher blood pressures among those who consume 1-2 drinks per day. The consumption of more alcohol/day is associated with a higher prevalence of hypertension (153-155). One or two glasses of alcohol per day have been clearly associated with a lower mortality and morbidity rate from coronary heart disease than abstinence or higher amounts of alcohol (127). Therefore, for those who consume fewer than 3 drinks per day, no change in alcohol consumption seems necessary.

A variety of relaxation therapies such as yoga, psychotherapy, biofeedback, and transcendental meditation have shown to reduce blood pressure of hypertensive patients at least transiently (127). A longterm antihypertensive effect was found in a study by Patel et al (156), but not in another study (157).

The INTERSALT study suggested a beneficial effect of the combination of different nondrug therapies. It was calculated that a reduction of daily sodium intake of 100 mmol, from current UK levels of 170 to 70, an increase in potassium of 30 mmol, a reduction of body mass index of 5, and a reduction of alcohol in heavy drinkers to less than 3 drinks a day would correspond to 11 mmHg lower systolic blood pressure (158). Even if it were possible only to achieve half of these changes, mean blood pressure of the whole population would be lowered by 5 mmHg, which would correspond to an approximately 10% lower mortality from CHD and stroke (112). However, evidence for risk reduction from hypertension might never be established for some nondrug therapies, since efficacy of nondrug therapy is in general less effective than that of antihypertensive drugs and since they are also more difficult to monitor (127).

1.2. pharmacological management

1.2.1. history

Before the 1940s there was no effective way to lower raised blood pressure. Late in the 1940s ganglion blocking agents were introduced (159). These drugs were useful in the treatment of malignant hypertension, but in non-malignant hypertension, the decrease in supine blood pressure was small. These drugs blocked sympathetic as well as parasympathetic nerves, thereby inducing numerous side effects. In 1957 thiazide diuretics were introduced and the use of reserpine became also popular. These 2 drugs could be given together, resulting in a fall in diastolic blood pressure of 10-20 mmHg and, compared to older antihypertensive agents, they had relatively acceptable side effects. In 1959 the first adrenergic neuron blocker guanethidine was introduced. This drug was free of parasympathetic blockade. It acted through inhibiting the release of noradrenaline from nerve

endings, and was - like the earlier ganglion blocking agents - not very effective in lowering supine blood pressure. In the early 1960s methyldopa was introduced, like reserpine a centrally acting drug, but more effective than either reserpine and thiazides.
The use of ß-blockers as antihypertensive drugs was firstly reported by Prichard in 1964. Since that time their popularity has grown. In the 1980s ß-blockers were the most popular antihypertensive drugs in several European countries (160). In the last decade also calcium-antagonists and ACE-inhibitors became firstline antihypertensive agents (125).

1.2.2. most important antihypertensive drugs currently used

Most important antihypertensive drugs are shown in Table 1.9.

Table 1.9. Most important antihypertensive drugs currently used

class	subclass
ß-blockers	nonselective $ß_1$-selective with intrinsic sympathomimetic activity
calcium-antagonists	phenylalkylamines benzothiazepines dihydropyridines
diuretics	thiazides thiazides + potassium sparing diuretics aldosterone antagonists loop diuretics
ACE-inhibitors	
α-blockers	α_1-blockers
central α-agonists	
direct vasodilators	hydralazine group minoxidil nitrates
multiple action drugs	ß-blockade + vasodilation $5HT_2$-antagonism + α-blockade central $5HT_1$-agonism + α-blockade central α_2-agonism + imidazoline preferring receptor

Thiazide diuretics are the oldest antihypertensive drugs currently used. Initially, the increase in urinary salt and water excretion result in a reduced plasma volume and smaller preload for the heart. This reduction in preload results in a smaller cardiac output. However, after 8 weeks cardiac output is back to normal and intravascular volume is minimally reduced by 5 % or less, but systemic vascular resistance is decreased (161). To prevent hypokalaemia, thiazide diuretics are often combined with potassium sparing diuretics. The loop diuretics such as furosemide are less effective in controlling blood pressure compared to an equivalent dose of hydrochlorothiazide (162).
Although the antihypertensive mechanism of ß-blockers is still not fully understood, the effect is mainly due to $ß_1$-blockade. ß-blockers with vasodilating properties might be of interest since they do not increase vascular resistance (163).

Three groups of calcium-antagonists are currently used: the phenylalkylamines (verapamil), the benzothiazepines (diltiazem) and the dihydropyridine calcium-antagonists. The 3 groups differ in vascular selectivity. Verapamil is as (non)selective for the heart as for the vessels; diltiazem is 7 times more selective for the vessels, but still has a marked effect on the heart. The dihydropyridines are more selective for the vessels, but within this group vessel-heart selectivity ratio differs largely: e.g. 14 with nifedipine and 118 with felodipine (164).
The short-term antihypertensive effect of ACE-inhibitors may result from vasodilation by inhibition of the vasoconstrictor angiotensin II, by higher levels of the vasodilator bradykinin and by the loss of facilitated sympathetic nerve action (165). A lot of attention is paid to the long-term effects of ACE-inhibitors as inhibitors of the growth factor angiotensin II. This particular property might be important in cardiac and vascular remodeling and atherogenesis during hypertension (166).
Alpha-blockers have the theoretical advantage of improving the lipid profile in the plasma. All lipid subfractions and also the apolipoproteins are favorably influenced (161,167). The main disadvantage of alpha-blockers is the first dose hypotension and syncope, but also during chronic therapy orthostatic hypotension may occur. Orthostatic hypotension is reported in up to 20 % of patients, while syncope occurs in less than 2 % (168). Orthostatic side effects are less frequent in second generation α-blockers like doxazosin and terazosin than during prazosin (168).
Other antihypertensive drugs are less frequently used. Most of the centrally acting antihypertensive drugs have sedative side effects. Direct vasodilators like hydralazine and minoxidil cannot be used in monotherapy due to reflex tachycardia and salt and water retention (161). Nitrates predominantly dilate the smaller arteries (169), resulting in a smaller pulse pressure. Nitrates might be of interest especially in patients with isolated systolic hypertension since they reduce systolic pressure, without substantial decrease in diastolic pressure (170). The preservation of the diastolic pressure might be important for a good coronary circulation in these patients (171).
In the last few years also some new drugs with combined action were introduced like urapidil and ketanserin. Due to serotonin$_2$ antagonism ketanserin could inhibit platelet aggregation (172) and might be protective against coronary events (173).
The 1988 Joint National Committee on Detection, Evaluation and Treatment of High blood Pressure proposed 4 classes of antihypertensive drugs as firstline drugs: diuretics, ß-blockers, calcium-antagonists and ACE-inhibitors. Due to its beneficial effect on lipids, authors such as Kaplan judge selective α_1-blockers as suitable for initial therapy as the 4 aforementioned classes (168).

1.2.3. results of pharmacological treatment of hypertension

In contrast to the old antihypertensive drugs, modern antihypertensive drugs lower blood pressure effectively. Most antihypertensive agents of the different therapeutic classes exhibit similar response rates, approximately 30 to 60 % (174-175). Using the approach of sequential monotherapy and testing 2 or even 3 types of drugs consecutively, a higher number of patients, possibly reaching 70-80 % of the hypertensive population, could be treated by monotherapy alone (175).
The benefits of effective treatment in malignant hypertension rapidly became clear (30,176). In non-malignant hypertension results were not so pronounced. From

a meta-analysis of 14 placebo-controlled, randomized trials in subjects with non-malignant hypertension pharmacological treatment induced a 42 % reduction in the incidence of stroke and a 14 % reduction in coronary events (177). The reduction in stroke is better linked to the reduction in blood pressure than atherosclerosis (30). Recent data from patients with isolated systolic hypertension suggest a reduction by 36 % in stroke and of 27 % in coronary events (41).
A further reduction especially in coronary events would be desirable not only because of the small risk reduction obtained but also because the incidence of coronary heart disease (Table 1.10) is 2-5 times higher than that of stroke (30,31).

Table 1.10. Mortality in treated hypertensive patients (30)

ill effect	mortality (all causes)
ischaemic heart disease	36 %
stroke	18 %
other cardiovascular disease	8 %
renal failure	3 %

Different reasons for the rather poor effect of therapy on morbidity and mortality have been suggested such as poor blood pressure control and the adverse effects of the antihypertensive treatment itself promoting ill effects.

1.2.4. drug adherence

Faulty therapeutic compliance is probably the main cause of poor blood pressure control in the community (178). In the USA in the 1970s, the rule of the halves applied: half the hypertensives were unknown; of those that were known, only half were on treatment; of those on treatment only half had blood pressure under control. In other words, about 12 % of hypertensives were treated satisfactorily (116). By 1985, more than 75 % of those with high blood pressure were aware of it and 79 % were taking some action to control it (116). Other authors estimated that of those patients who continue to attend clinics for hypertension, one half to two thirds take enough pills to lower their blood pressure to normal (179-180).
Compliance with an antihypertensive drug regimen is related to frequency of dosing and was markedly better on a once daily regimen than on a three times daily regimen (181-182). Compliance appears to be better in rural family practices than in urban clinics. In an urban clinic only 38 % of patients took more than 75 % of their pills (183), whereas this was 79 % in a rural setting (184). Although there is some evidence that the intensity with which the physician prescribes medication correlates with the level of blood pressure control, it is also clear that as more pills are prescribed, a lower portion is taken (185). Compliance has been improved by different approaches such as a reduction of the number of pills, simplification of the drug regimen, maximum use of nondrug therapies, increased family involvement, home monitoring, self-help groups and patient rewards (180). Since patients with mild-to-moderate hypertension are often asymptomatic (186), it is very important that, in order to assure good patient compliance, antihypertensive drugs should not impair the quality of life. Better tolerated antihypertensive drugs with fewer side effects should therefore be helpful (187).

2. prevention of ill effects of hypertension

2.1. Treatment and prevention of cardiac hypertrophy.

In general, ventricular arrhythmias have been shown to diminish in parallel with the reversal of left ventricular mass (188-189). Preliminary data on 166 hypertensives followed up for 5 years showed that cardiovascular events occurred in only 6% of patients whose left ventricular mass decreased or was unchanged from baseline in contrast to 16% ($p < 0.05$) of patients whose left ventricular mass increased from baseline (190). It was concluded from this study that reduction of left ventricular mass during treatment of essential hypertension is associated with improved prognosis, and that measurement of left ventricular mass index may provide a better indication of the efficacy of treatment than the level of blood pressure.

In a meta-analysis of 109 treatment studies Dahlöf et al showed that all 4 classes of firstline antihypertensive drugs can reverse left ventricular hypertrophy in hypertensive patients (191). The average reduction in left ventricular mass was more pronounced with ACE-inhibitors compared to diuretics, calcium-antagonists and ß-blockers (Table 1.11). In this study no difference has been made between the ß-blocker subclasses. This study also includes ß-blockers with ISA, which are thought not to cause regression of left ventricular hypertrophy (62). As a consequence the average effect of the other subclasses of ß-blocking agents might be better. Also other antihypertensive drugs like α-blockers and methyldopa can reverse left ventricular hypertrophy while vasodilators like minoxidil and hydralazine did not (64).

Table 1.11. Effect of antihypertensive drugs on cardiac hypertrophy (191)

drug	change in left ventricular mass*
diuretics	-21.4 (-49 to -6)
calcium-antagonists	-26.9 (-42 to -12)
ß-blockers	-22.8 (-38 to -8)
ACE-inhibitors	-44.7 (-66 to -23)

* mean and 95% confidence intervals expressed in gram.

Recent survival trials on left ventricular dysfunction, such as the Veteran Administration-Heart Failure Trial (V-HeFT) I and II (192-193) have clearly shown that vasodilator therapy can prolong life expectancy in patients with severe left ventricular dysfunction. However, the V-HeFT II study showed that the ACE-inhibitor enalapril did increase survival much more than the combination of hydralazine-isosorbide dinitrate. In addition, enalapril provided a proportionately greater benefit in patients with dilated cardiomyopathy than in those with underlying ischaemic heart disease (192). This might indicate a predominant action of ACE-inhibitors on the remodeled heart. The benefical effect of ACE-inhibitors on mortality rates in patients with cardiac dysfunction has also been shown in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I; 67), the Study On Left Ventricular Dysfunction, using enalapril (SOLVD; 68), and in the Survival and Ventricular Enlargement Trial (SAVE; 194), using captopril.

Large survival trials have investigated the influence of drugs on reversal of cardiac hypertrophy. However, little is known on the effect of antihypertensive drugs in preventing cardiac hypertrophy. Mostly, cardiac hypertrophy develops more slowly in hypertension than after myocardial infarction, but the process might be very similar. In 2 studies - CONSENSUS II (195) and SMILE (Survival of Myocardial Infarction Long-term Evaluation; 196) trials - which initiated ACE-inhibitor therapy within 24 hours after myocardial infarction and registered the outcome for only 6 to 12 months, no beneficial effect on mortality was seen. Since cardiac remodeling takes some time (months) to appear, the lack of a positive outcome in these 2 studies might be due to the relatively short follow up time. This is supported by the observation that the differences in mortality rates in the SAVE trial only became clear after 1 year of treatment. In addition, in rats ACE-inhibitors showed a deleterious effect if given early after myocardial infarction, with a strong suggestion that the healing process of the heart after infarction was altered by ACE-inhibition (197). This could be an alternative explanation for the lack of a positive outcome in the CONSENSUS II and SMILE trials.
In conclusion, all firstline (and also some other) antihypertensive drugs can reverse cardiac hypertrophy, but ACE-inhibitors are more powerful in this respect. Survival studies in patients with cardiac dysfunction have shown a beneficial effect of ACE-inhibitors. However, no data are available on the effect of other drugs on survival in this condition. Prevention of cardiac hypertrophy is more difficult to study and no good data are available. However, primary prevention might be more important, since it is not clear whether fibrosis of the heart can be reversed.

2.2. prevention of ischaemic cardiovascular events

Three strategies can be imagined to prevent ischaemic cardiovascular events: (1) prevention of atherogenesis, (2) prevention of plaque rupture and (3) prevention of occlusive thrombosis and vasospasm.

2.2.1. **Prevention of atherogenesis** is complex for many reasons such as: [1] the origin of vascular injury is multifactorial; [2] many different cells and growth factors are involved, and [3] since early lesions already initiate at puberty, prevention should start preferably early in life. Nowadays prevention of atherogenesis regards mainly the prevention of risk factors like smoking, hypertension, hypercholesterolaemia, insulin resistance, emotional stress, and obesity. Influences on risk factors are discussed in section 2.2.4.
Antiproliferative properties of different substances like heparin (198-200), fish oil (201) and suramin (202) are being studied. Also of potential therapeutic value are other proliferative inhibitors like angiotensin II inhibitors (converting enzyme inhibitors and angiotensin II receptor antagonists). Altough some ACE-inhibitors might prevent intimal thickening in atherogenic animal models, their value in prevention of atherogenesis in man is not established, yet (203).
Another target can be to influence the role of lipids in atherogenesis. In this respect, the importance of lipoprotein modifications, especially oxidation, has renewed interest in antioxidants (204-205). In this context, probucol has been demonstrated to slow the progression of atherosclerosis in hyperlipidaemic rabbits (206).

Almost all classes of antihypertensive drugs tested have shown some favorable anti-atherogenic effect on some experimental model of hypercholesterolaemia (203). Of all antihypertensive drugs calcium-antagonists are best studied for their possible anti-atherogenic potency. They retard the progression of atherosclerosis (207). The mechanisms of action by which calcium-antagonists exert their anti-atherosclerotic effect have not been completely elucidated (208). In experimental models calcium-antagonists can beneficially modify many factors in the atherosclerotic process, such as endothelial damage and necrosis, platelet aggregation, release of platelet-derived growth factor, migration from media to intima, proliferation of smooth muscle cells, protein collagen synthesis, binding of lipoproteins to glycosaminoglycans (209). Recent reports indicate that nifedipine, verapamil and diltiazem exert antiperoxidative effects on membrane lipids, preventing oxidation of LDL, a modification thought to confer atherogenic properties to the lipoprotein (208). It is possible that the major anti-atherogenic effect of calcium-antagonists is related to their antiperoxidative properties.

2.2.2. Prevention of plaque rupture

Prevention of plaque rupture could be realized by stabilization of a weak plaque or by decreasing stresses at the plaque and the vascular wall. Since weak lipid-rich plaques are more rupture-prone, stabilization could be achieved by decreasing cholesterol levels. This hypothesis is supported by the results of studies on the effect of lipid lowering. In contrast to the small regression in atherosclerotic plaques on angiography, the reduction in the number of cardiac events was quite considerable in two of these studies (210-211). Therefore, it was suggested that the small increase in luminal diameter measured by means of angiography is more likely a marker of more important regression of the smaller, lipid-rich plaques. These smaller lipid-rich plaques may be undetectable angiographically, but represent the main clinical contributors to the acute coronary events (212).
The role of physical stress on plaque disruption needs further investigation. The major stresses on the vessel wall (circumferential and shear stress) are discussed in part II. As already mentioned, coronary arteries additionally suffer from stress of the pumping heart. Agents that lower heart rate and/or contractility might decrease coronary stress. ß-Adrenoceptor antagonists can provide secondary (213-214) and probably also primary (215) prevention of myocardial infarction. This favorable effect has been ascribed to a decrease of the stress on plaques and the risk of plaque rupture in the coronary arteries (216). Also non-dihydropyridine calcium-antagonists like verapamil (217) and diltiazem (218) might have their secondary prevention effect on the basis of the inhibition of plaque disruption.

2.2.3. The third strategy is the prevention of thrombosis and vasospasm. Since thrombus formation seems to be an important factor in the progression of coronary disease and in the conversion of chronic to acute events after plaque disruption, a promising approach is the prevention of these processes with the use of antithrombotic therapy. Antiplatelet agents might offer some promise in preventing the progression of small coronary atherosclerotic plaques (219), but the most beneficial effect of antiplatelet and anticoagulant agents has been observed in the prevention of acute coronary events (220-223). The best-studied, least toxic, and most widely used antithrombotic agent is aspirin. Aspirin interferes with platelet

activation. On the other hand anticoagulant agents interfere only partially with the coagulation system and are ineffective against platelet activation. In coronary artery disease, the overall antithrombotic effectiveness of aspirin and anticoagulant agents is clinically similar (224). Combination therapy with low-dose aspirin and anticoagulant agents may have additive effects (212).
Inhibition of coronary vasospasm can be achieved by different vasodilating drugs. Nitrates and calcium-antagonists are the most currently used. They have a direct vasodilating effect on smooth muscle cells of the vessel wall. In addition, calcium-antagonists can abolish endothelin-induced vasoconstriction (225). Also ACE-inhibitors can attenuate vasoconstriction in patients with coronary artery disease by increasing levels of vasodilating substances like prostacyclin and bradykinin, by decreasing levels of the vasoconstricting angiotensin II (226), and by attenuating sympathetic coronary vasoconstriction (227).

2.2.4. influence on risk factors for atherosclerosis.

Recently the influence of different antihypertensive drugs on insulin resistance have been shown. ß-Blockers like metoprolol and atenolol and the diuretic hydrochlorothiazide increase insulin resistance. Calcium channel antagonists verapamil and diltiazem are metabolically neutral, whereas nifedipine has a negative effect. Insulin resistance improves with the α-blocker prazosin and with the ACE-inhibitor captopril (228). In addition, dilevalol, a ß-blocker with vasodilating properties, also has a beneficial effect on insulin resistance (229). It has been suggested (230) that the beneficial effect of captopril on insulin resistance might be due to the increased bradykinin, which promotes the insulin-induced glucose uptake into skeletal muscle.
Two studies have shown that the ß-blockers atenolol and propranolol can convert type 'A' behaviour in a mellower type 'B' behaviour (231-232). The potential value of such a conversion can be deduced from the results of the Recurrent Coronary Prevention Project. This study showed that after a 4.5 years follow up period in postmyocardial patients, cardiac events and deaths were reduced by 39 % in those patients, whose type 'A' behaviour was modified towards a type 'B' pattern (233).
There is a continuous and graded relation between serum cholesterol levels and coronary heart disease death, with a 4 to 6-fold increase in risk from levels of 160 mg/dl to the highest cholesterol values (234-235). Lowering cholesterol in patients with hypercholesterolaemia decreases the risk of atherosclerotic complications and reduces mortality from coronary artery disease (210-211, 236-239). However, in a meta-analysis of 18 observational studies Jacobs et al showed the existence of a U-shaped relation between serum cholesterol and total mortality in men, and a flat relation in women (Table 1.12). This U shape resulted largely from a positive relation of total cholesterol with coronary heart disease death and an inverse relation with deaths caused by some cancers (e.g., lung but not colon), respiratory disease, digestive disease, trauma and residual deaths. One of the explanations might be that total cholesterol is lowered by some disease conditions themselves, such as wasting in cancer and pulmonary disease (240). But also the pattern of stroke is changed in patients with low serum cholesterol. Serum cholesterol is strongly related to death from non-haemorrhagic stroke. But men in the lowest category of serum cholesterol (< 4.14 mmol/l; 160 mg/dl) had higher death rates from both subarachnoid and intracerebral haemorrhage than other

men (116). The association between low cholesterol and intracerebral haemorrhage has also been observed in Japan (241-242), where the data pointed to a U-shaped relation.

Table 1.12. Risk ratios for deaths occurring ≧ 5 years after study baseline. (240)

blood cholesterol (mg/dl)	all causes	total cardiovascular	total noncardiovascular	total noncardiovascular noncancer
≦ 160	1.17 (3.6)	1.04 (0.8)	1.18 (2.3)	1.32 (5.3)
161-199	1.00	1.00	1.00	1.00
200-239	1.02 (0.8)	1.16 (3.6)	0.95 (-1.8)	0.89 (-2.5)
≧ 240	1.14 (5.1)	1.48 (9.5)	0.95 (-1.2)	0.87 (-3.6)

pooled data of 18 studies; data of men; ( ) number of standard deviations that the estimated hazard ratio departs from 0.

In a review of six randomised controlled primary prevention trials, Muldoon et al (243) found that lowering of raised serum cholesterol in middle-aged subjects by diet, drugs, or both was also associated with a significant decrease in the number of death from coronary heart disease but not in total deaths. When the World Health Organisation Study (244) results were excluded, there was no association between cholesterol reduction and cancer (243). In the World Health Organisation Study clofibrate was used. The use of this drug might be related to cancer (244). However, there was a significant increase (nearly 100%) in mortality due to suicides or violence: compared with control subjects, treated groups had 28 fewer deaths per 100000 from coronary heart disease and 29 excess deaths from suicides, homicides and accidents. The increase in deaths due to violence was present in all 6 trials suggesting that these findings are not due to chance alone. As with the large observational trials and the primary prevention trials, noncardiovascular deaths increased significantly in a meta-analysis of 7 secondary prevention trials (239).
In conclusion: Randomised controlled trials have demonstrated the benefit of cholesterol reduction as primary prevention to reduce coronary heart disease in middle-aged men. There is no clinical trial evidence that primary prevention will reduce overall mortality (245). The protection provided against coronary heart disease through cholesterol reduction may be the greatest in patients with the highest serum cholesterol concentrations before treatment (as was noted in the World Health Organisation study). If so, promotion of long-term survival might be best achieved by targeting intervention efforts primarily at those people who are at particularly high risk for death from coronary heart disease: those with exceptionally high serum cholesterol concentrations, history of coronary disease, or several risk factors in addition to hypercholesterolaemia (243). This view is also supported by a cost-effectiveness analysis (245). Further long-term studies and studies in women and elderly patients are needed.

Some antihypertensive drugs negatively influence the lipid profile, but they may exert some favorable effect on some experimental models of hypercholesterolaemia (203). For example ß-blockers may decrease the serum level of the protective HDL cholesterol and increase triglycerides, but they show an anti-atherogenic effect in animal models (246). What could be the reason for this surprising observation? Clinical and experimental data suggest that ß-blockers might increase the size of the LDL particles. Large LDL particles are less atherogenic (247). In addition, ß-blockers decrease LDL-binding to arterial proteoglycans, resulting in less accumulation of LDL in the arterial wall (247), an anti-atherogenic effect. Due to the increase in LDL size, the triglyceride core of the LDL particle increases. As the larger LDL is less atherogenic, one might speculate that ß-blocker-induced increase in triglycerides might actually signal a beneficial effect rather than a negative one (215). This example also suggests that drug-induced presence of a risk factor might not have the same meaning as the spontaneous presence of that risk factor.

2.3. prevention of stroke.

About 40 % of strokes can be attributed to systolic blood pressure of more than 140 mmHg (44). A high risk approach that sought to detect and treat those with casual systolic blood pressure of greater than or equal to 170 mmHg would potentially save 35 % of the excess deaths. However, most of the deaths attributable to a raised blood pressure come from the majority of the population with modest increases in pressure. Therefore, only an approach that lowered average population blood pressures would reduce the incidence of stroke associated deaths attributable to raised blood pressure (116). In the large treatment trials, people over 65 derive benefit from treatment (248); there are no grounds for assuming that the rise of blood pressure with age is "normal" and requires less attention in the elderly (116).

The majority of strokes are ischaemic strokes (249). Therefore, risk factors for stroke are about the same as the risk for atherosclerosis and serious cardiac events (249-250). Approaches to prevention of atherosclerotic disease have been discussed previously and might also be beneficial in preventing ischaemic stroke. Secondary prevention of ischaemic stroke can be made by antiplatelet drugs. No antiplatelet drug is clearly better, cheaper and less toxic than aspirin (249). Thromboxane A_2 antagonists and/or synthetase inhibitors can be prescribed for patients who cannot tolerate aspirin. The recommended dose of aspirin is 300 mg for almost instant inhibition of platelet aggregation, followed by 75-150 mg a day, presumably indefinitely (249). Studies on the value of aspirin in the cerebral condition are being established (251).

The priority of stroke prevention has to be on the one hand control of high blood pressure in hypertensive patients and on the other hand reduction of blood pressure in the whole population. Also the reduction of risk for atherosclerosis like reduction of smoking, reduction of excess alcohol to less than 3 glasses per day and dietary measures may likewise have an impact on stroke (116).

2.4. prevention of renal failure.

The reported mortality from hypertensive renal disease has declined dramatically over the past 20 years in both sexes (252). Diuretics have no direct effects on renal haemodynamics. Renal blood flow and glomerular filtration rate are not affected

by α-blockers, but tend to be reduced by ß-blockers. With selective $ß_1$-blockers, this effect decreases with time. In general, these effects are not a problem, except for hypertensives with increased peripheral resistance and declining cardiac output. In these patients renal function may be altered. Calcium-antagonists and ACE-inhibitors decrease renal vascular resistance. ACE-inhibitors and calcium-antagonists might diminish renal injury in experimental models (124). Long-term benefits of these agents in humans still need to be proven.

Lessons of the past 20 years have taught us that lowering blood pressure by any means (pharmacological and non-pharmacological) helps in reducing renal damage (124).

this thesis

It can be concluded with the 1988 Joint National Committee on Detection, Evaluation and Treatment of High blood Pressure, that it is not enough to lower blood pressure in hypertensive patients; the goal of treatment should be to improve longevity, reduce minor complications, and improve the quality of life (125). Longevity can be improved by prevention of the ill effects of hypertension. The most important ill effects are stroke, (coronary) atherosclerotic disease, and cardiac hypertrophy leading to arrhythmia and/or heart failure.
The prevention of ill effects and the preservation of quality of life go beyond the reduction of the blood pressure in the restricted sense. Therefore, prevention of ill effects and preservation of quality of life are called non-antihypertensive aspects of antihypertensive treatment. Nevertheless, these aspects can be substantially influenced by the reduction in blood pressure.
The ill effects and their management have been introduced in the previous chapters. Most research in this regard has focussed on prevention of atherosclerotic disease. Studies have been made on the effects of reduction of hyperlipidaemia and of antithrombotic treatment. However, there are also arguments for an important role of physical factors in the ill effects of hypertension. For example, the incidence of stroke decreases with decreasing blood pressure (114); systolic ventricular wall stress is thought to stimulate cardiac hypertrophy (48); in the response-to-injury hypothesis, physical factors might induce intimal lesions of the vessel wall, which might - together with other promoting factors - lead to the formation of an atherosclerotic plaque (69,71-72). Even more important in atherosclerotic disease might be the physical stress on the arterial wall, which might induce plaque rupture leading to rapid progression of plaques or to acute thrombotic occlusion of the vessel (77-78). Part II of this thesis will deal with these physical factors and the influence of antihypertensive drugs in this respect. Chapter 1 reviews the physical factors on the vessel wall and the influence of antihypertensive therapy in this regard. Subsequently, non-invasive investigation of the effect of two antihypertensive drugs on the vessel wall properties of the common carotid artery is presented: chapter 2 investigates the effect of the non-selective calcium-antagonist verapamil and chapter 3 the effect of nebivolol, a selective β_1-adrenoceptor antagonist with vasodilating properties.
Preservation of quality of life is an important aim of medicine in general and an important tool to improve drug adherence. Perceived quality of life is the balance between positive and negative influences of a treatment. Positive influences on quality of life are mostly the disappearance of symptoms of the disease. The negative influences are in general side effects of the drug. Since mild-to-moderate hypertension is in general asymptomatic, side effects of drugs may easily reduce quality of life. Therefore, the influence of antihypertensive therapy on quality of life is very important for the hypertensive patient and also for a successful antihypertensive treatment. This non-antihypertensive aspect of antihypertensive treatment is discussed in part III. Firstly, the Inventory of Subjective Health (ISH), a general health profile is introduced. In chapter 1 the effect of nebivolol on quality of life as measured with the ISH questionnaire is compared with the effect on a 5-point perceived health scale and with the influence on side effect diaries.

Chapter 2 compares the quality of life during antihypertensive therapy with the highly selective $ß_1$-adrenoceptor antagonist bisoprolol with the quality of life during treatment with the ACE-inhibitor enalapril. Chapter 3 compares the influence on exercise tolerance of two ß-blocking drugs (atenolol and nebivolol) and reviews the effect of antihypertensive therapy on exercise tolerance. Finally part IV discusses different aspects of current antihypertensive treatment and formulates issues for future research.

PART II.
INFLUENCE OF PHYSICAL FACTORS ON THE VESSEL WALL

In part I evidence was discussed that physical stress at large arteries may be important in the development of cardiac hypertrophy, progression of atherosclerosis, occurrence of acute coronary events and stroke. Morbidity (42-43) and mortality (44) from hypertension are better correlated with systolic than with diastolic blood pressure, indicating a major role for the pulsatile stress in the ill effects of hypertension. The pulsatile stress is a circumferential stress which induces degeneration of the vascular media (253). Pulsatile stress in the vessel wall is a physical factor determined by a number of variables, which are discussed in chapter 1. Shear stress is the tangential stress at the vessel wall and acts predominantly on endothelial cells. Shear stress can be subdivided into a mean and a pulsatile shear stress. Mean shear stress is determined by variables like blood viscosity, mean blood velocity and the diameter of the vessel. Pulsatile shear stress is also influenced by vessel wall properties.
Chapter 1 reviews how antihypertensive drugs - in addition to their blood pressure lowering effect - influence physical factors, which seem to determine risks associated with hypertension. Chapter 2 and 3 describe experiments on the non-invasive measurement of vessel wall properties of the common carotid artery and the effect of 2 antihypertensive drugs (verapamil and nebivolol, respectively) on these large artery properties.

chapter 1. physical factors on large arteries and antihypertensive therapy [1]

1. pulsatile stress in the arterial wall

Pulsatile stress can be compared with forces inducing material fatigue (253). Important stress factors are peak force [systolic blood pressure], change in force [pulse pressure], velocity of this change, and frequency [heart rate] (253). Stress factors and their determinants are shown in Table 2.1.

Table 2.1. Determinants of pulsatile circumferential stress

stress factor	determinants
peak stress (= systolic pressure)	mean arterial pressure pulse pressure
change in stress (= pulse pressure)	vessel wall properties stroke volume (pulse wave reflections)
velocity of change (= dp/dt)	vessel wall properties cardiac inotropy
stress frequency (= heart rate)	cardiac chronotropy

[1] based on: LM Van Bortel, AP Hoeks, MJ Kool, HA Struyker Boudier. Introduction to large artery properties as a target for risk reduction by antihypertensive therapy. J Hypertens 1992, 10(suppl 6):123-126.

Vessel wall properties of large arteries are important determinants of this pulsatile stress, since a decrease in compliance will affect 3 stress factors: peak force, change in force, and velocity of this change.

1.1. Vessel wall properties of large arteries

Vessel wall distensibility and arterial compliance are important vessel wall properties. Distensibility is a two-dimensional entity defined by the relative change in cross-sectional area of the vessel per change in pressure. Distensibility is an important determinant of the pulsatile stress on the vessel wall. Compliance is a three-dimensional entity, defined by the change in volume per change in pressure. Compliance reflects the buffering capacity of the large vessels and is therefore an important determinant of the afterload for the heart. In the literature, the term compliance is often used for compliance as well as distensibility. This confusion remained until a few years ago, since no means were available to measure distensibility as well as compliance accurately. A few years ago, in Maastricht as well as in Lausanne, non-invasive echo-Doppler techniques were developed, which can measure vessel wall properties of large arteries accurately. With the technique developed by Dr Hoeks and co-workers in Maastricht, large artery diameter and change in diameter during the heart cycle of different large arteries can now be measured. From these data and the pulse pressure, both distensibility and compliance can be calculated. Chapters 2 and 3 describe two studies, as examples of the results obtained with this (first generation) non-invasive technique.

Table 2.2. Effect of firstline antihypertensive drugs on stress determinants.

determinant	MAP	AC	PWR	CI	HR
calcium-antagonists					
- dihydropyridine	•	•	•		
- non-dihydropyridine	•	•	(•)	•	•
ß-blockers					
- non-selective	•			•	•
- selective $ß_1$	•	•		•	•
- vasodilating#	•	•	•	(•)	•
ACE-inhibitors	•	•	•		
diuretics	•			(•)	

ß-blockers with vasodilating properties without ISA. MAP is mean arterial pressure; vessel wall properties are arterial compliance (AC) including the effect on pulse wave reflections (PWR); CI is cardiac inotropy; HR is heart rate. • is a beneficial effect decreasing pulsatile stress; (•) a beneficial effect might be present.

In hypertensive (254) and aging subjects (255-256) arteries become less elastic leading to a decrease in distensibility and compliance. Large artery compliance can be increased by antihypertensive drugs such as calcium-antagonists (257-261), ACE-inhibitors (261-263), ß-blocking agents with vasodilating properties (264-268) and nitrates (261,269). Apart from metoprolol (270), all $ß_1$-blockers (266,271) also improve compliance. At higher doses $ß_1$-blockers loose selectivity. This might be an explanation for the difference between metoprolol (100 mg twice daily) and

other selective $ß_1$-blockers on large artery compliance. Since a higher blood pressure, by itself, decreases arterial distensibility (169), the beneficial effect of some antihypertensive drugs on large artery compliance might, in part, be due to the decrease in blood pressure. Despite a marked fall in blood pressure, the non-selective ß-blocker propranolol (264), diuretics (272), vasodilators of the hydralazine group (273) and the centrally acting alpha$_2$ agonist clonidine (274) do not increase arterial compliance. The effect of alpha-blocking agents is not clear. On the one hand ketanserin (α + serotonin$_2$-antagonist) improves arterial compliance (270), while urapidil (α-adrenoceptor antagonist + central serotonin$_{1A}$-agonist) does not (268).
It is clear that the effect of different antihypertensive drugs on large artery compliance is not uniform. Is this effect also dependent on the condition of the vessel wall? In a recent study, described in chapter 2, this question was addressed using the calcium-antagonist verapamil (258). The results of this study suggest that verapamil given for 1 month is less effective on arterial compliance when structural changes are present. All studies concerning the effect of antihypertensive drugs on large artery compliance mentioned are acute or short-term chronic studies (up to 3 months of therapy). Consequently, effects on arterial compliance in these studies are likely to be due to functional rather than to structural changes. It is not clear whether a decrease in compliance due to structural changes can be improved. Prospective long-term studies are not available.

1.2. pulse wave reflections

In conditions with substantially decreased arterial distensibility, as in hypertensives and older subjects, pulse wave velocity increases and early wave reflections, originating from artery transitions with different impedance, can boost the systolic pressure in the ascending aorta (169), resulting in a substantially higher systolic stress on the heart and central arteries (169). Recent studies have shown that this distorted wave reflection can be reduced or almost abolished by some antihypertensive drugs. Beneficial effects in this respect have been described for nitrates (275-276), calcium-antagonists and ACE-inhibitors (169). Also ß-blocking agents with vasodilating properties like dilevalol might decrease wave reflections (266). Nitrates have a particular property. Low-dose nitrates selectively dilate smaller arteries with almost no effect on arteriolar tone (169). This results in a decrease in systolic stress and pulse pressure in central large arteries without substantial decrease in mean and diastolic pressure (170,269). These drugs might be useful in the treatment of isolated systolic hypertension, since - apart from a reduction in the harmful systolic pressure - during nitrate treatment diastolic pressure is preserved or may rise, resulting in a better perfusion of the heart.

1.3. other determinants of pulsatile stress

Determinants of pulsatile stress factors are shown in Table 2.1. Mean arterial pressure can be influenced by decreasing arteriolar tone (systemic peripheral resistance) or by decreasing cardiac output. This decrease in mean arterial pressure is achieved by classical antihypertensive therapy. A lower stroke volume decreases pulse pressure. Velocity of change in pulse pressure can be decreased by a slower cardiac contraction. Stress frequency is coupled to heart rate. Consequently (Table 2.2), beta-blocking drugs, verapamil and diltiazem might have a beneficial effect on

large arteries by decreasing heart rate (stress frequency) and cardiac inotropy (stroke volume and velocity of change in pulse pressure).

2. shear stress

Plaque formation correlates best with low mean shear stress and with oscillations in shear stress direction, and not with relatively high levels of wall shear stress where flow remains laminar and unidirectional (72). At arterial bifurcations, shear stress is relatively high in the region of the flow divider, while preferential sites of plaque formation are the lateral walls opposite to the central flow divider, regions of low shear stress (72).

With low shear stress particle residence time is increased. This means that the duration of exposure of the endothelial surface to circulating atherogenic agents or to conditions favoring transendothelial diffusion of atherogenic particles is increased in low shear regions (277). In this respect accumulation of monocytes, thrombocytes, and granulocytes on endothelial lumen surfaces may also be increased by a low wall shear stress (278-279). Endothelial cells exposed to high shear stress are mechanically stiffer than control cells. The increase in stiffness might strengthen endothelial integrity, which may protect against atherosclerosis (280). In addition, microfilament bundles may modulate endothelial permeability and prevent influx of macromolecules such as low density lipoproteins or cellular components like monocytes. In regions of low-shear endothelial microfilament bundle formation is attenuated and makes the endothelial junctions more leaky. The higher residence time of (atherogenic) particles toghether with the more leaky endothelial junctions at regions of low shear stress makes them more prone for initiation of atherosclerosis, especially in atherogenic conditions such as hypercholesterolaemia (280). In general, the coronary arteries may be extensively involved by atherosclerosis, while arteries with less complex unidirectional flow pattern, such as the renal and mesenteric vessels, tend to be spared in regions beyond their ostia (281-282). If cyclic reversal in flow direction favors plaque formation -and such oscillations occur mainly during systole - coronary arteries should be expected to be especially vulnerable, for in the course of the cardiac cycle, coronary arteries are subjected to two prominent changes in flow velocity during systole (283), compared with a single oscillation for other major visceral arteries. Individual differences in heart rate would therefore be expected to exert a long-term selective effect on the coronary arteries by doubling the systolic exposure to oscillations in flow direction. In addition, at a higher heart rate, diastolic period - during which flow is unidirectional and relatively increased - is shortened while systole is relatively uninfluenced by the heart rate (72). As in the case of pulsatile circumferential stress, heart rate might also be an important determinant of shear stress. The importance of heart rate in coronary artery disease has been emphasized recently. Perski et al described an association between minimum heart rate and both the extent of coronary atherosclerosis and its progression in patients after myocardial infarction (284).

High shear forces induce platelet aggregation in vitro as well as in animal models of coronary artery thrombosis (285). In man, tears in the vascular wall can occur at sites with high shear, especially adjacent to ectatic calcified lesions (79).

From these studies it can be hypothesized that, with an intact endothelium, high shear promotes endothelial integrity and function and protects the vessel against atherogenesis. However, if the endothelium is impaired or lost, high shear stress

might be harmful and could promote atherogenesis or acute coronary syndromes. Endothelial dysfunction, like disturbed endothelial-dependent vasodilation, has been shown in different conditions such as atheromatosis, hypercholesterolaemia, ischaemia, and hypertension (286).

In hypertension shear stress is decreased (287), which might make the endothelium more prone to atherogenesis. Data on pharmacological modulation of shear stress are scarce. The ß-blocker atenolol does not change shear stress whereas carteolol increases shear stress (267).

It seems too early to get a clear understanding of the impact of changes in shear stress on ill effects of hypertension. Nowadays shear stress cannot be measured accurately in man. Much progress in the understanding of the effect of shear stress on the vessel wall might be made, when new techniques, which can measure shear stress more accurately, will be available. These techniques are being developed.

3. conclusion

Pulsatile stress plays an important role in the genesis of the complications of hypertension. Vessel wall properties have a central role as determinants of pulsatile stress factors and can be improved by several (but not all) classes of antihypertensive drugs. Improvement of vessel wall properties of large arteries seems a logical strategy in treatment of hypertension. However, long-term prospective studies are needed correlating different aspects of vessel wall stress with morbidity and mortality in hypertension. Other important issues for future research are reversal of structural vessel wall changes, effects on local wall tension, determination of the relative impact of different stress factors of the pulsatile stress and impact of shear stress.

chapter 2. the effect of verapamil on carotid artery distensibility and cross-sectional compliance in hypertensive patients[2]

introduction

Distensibility and compliance are vessel wall properties of large arteries, which are decreased in hypertension. Distensibility reflects the elasticity of the artery and is a determinant of the stress on the vessel wall. Compliance reflects the buffering capacity of large arteries and is an important determinant of the afterload on the heart. This and also the effect of antihypertensive therapy have been reviewed in the previous chapter.

The aim of the present prospective study was to investigate the effect of oral, chronic verapamil treatment on the distensibility and cross-sectional compliance of the common carotid artery in hypertensive subjects following a double-blind, crossover protocol. A calcium-blocker was chosen because this type of antihypertensive drug has a relaxing effect on smooth muscle cells (288). The common carotid artery was used in this study because it is easily accessible to ultrasound, while it is known to be more distensible (average relative diameter increase in systole of 9.6% (255) to 14.2% (289)) than, for instance, the femoral artery (relative diameter increase in systole of about 3% (290)). The relative diameter changes of the common carotid artery during the cardiac cycle were recorded on-line with a high resolution multigate pulsed Doppler system (291). This system also allows the on-line recording of velocity profiles (255,292-294). From the width of these profiles, absolute internal diameters can be determined. Arterial pulse pressure was estimated from brachial artery cuff blood pressure measurements and arterial distensibility and cross-sectional compliance were calculated as previously described in detail (295).

materials and methods

The study was performed on 19 patients with essential hypertension (10 males and 9 females) with diastolic blood pressures > 90 mmHg, but < 120 mmHg. Nine patients were younger than 40 years and 10 were 60 years and older. After a washout period of at least 4 weeks, in which all antihypertensive drugs and diuretics were withdrawn, the patients entered a double-blind, randomized, placebo-controlled, crossover study. Patients were given verapamil tablets (120 mg) or apparently identical placebo tablets three times daily for 4 weeks. This period was followed by another 4-week crossover period. In the 4th week of each double-blind period, blood pressure and heart rate were measured, and ultrasound investigation of the common carotid artery was performed. The age of the patients varied from 21 to 73 years (mean of 49 years) and their weight averaged 82 kg (range of 52-103 kg). They all had normal serum protein and albumin levels, and normal liver function tests. Serum creatinine levels were < 134 μmol/l. None of them suffered from symptomatic atherosclerotic disease.

[2] based on: T Van Merode, L Van Bortel, FAM Smeets, R Böhm, J Mooij, KH Rahn and RS Reneman. The effect of verapamil on carotid artery distensibility and cross-sectional compliance in hypertensive patients. J Cardiovasc Pharmacol 1990, 15:109-113.

The ultrasound investigations were performed 2 hours after the last dose. The subjects were in the supine position with the head tilted slightly to the contralateral side. Both the right and left common carotid artery were examined. The relative diameter changes ($\Delta d/d \times 100\,\%$) of the common carotid artery during the cardiac cycle were recorded on-line with a multigate pulsed Doppler system (Fig 2.1), the characteristics of which have been described in detail before (255,291-292). The diameter changes were recorded in the plane of the carotid artery bifurcation. The assessment of vessel wall displacement is based upon the processing of low frequency Doppler signals, originating from the sample volumes coinciding with the anterior and posterior walls. The Doppler signals originating from the walls are 30-100 times higher in amplitude than the signals originating from the slowly moving blood cells close to the vessel wall and, hence, mask the signals induced by these cells completely. The small size of the sample volume (1.2 mm^3 at a depth of 15 mm) excludes contamination with other slowly moving structures. To insure that the initial relative change at the beginning of the cardiac cycles is constant, it is reset to zero by a trigger derived from the R wave of a standard lead of the ECG. The relative diameter changes can be determined with an absolute accuracy of 0.5 % (291), comparing favorably to the peak excursions observed. This means that for a relative excursion of, for instance, 7.0 %, a relative change in diameter between 6.5 and 7.5 % can be measured. The multigate pulsed Doppler system also allows the on-line recording of velocity profiles in arteries, i.e., the velocity distribution of the cross-section area of the vessel, at discrete time intervals during the cardiac cycle (292-294). From the width of the velocity profiles, the systolic diameter of the artery can be assessed (Fig 2.1) rather accurately (295) with an error of about 0.7 mm. Since the diameter, as determined in this way, is dependent on the angle of interrogation, the values measured were corrected for this angle, i.e. 60° in the present study.

During the ultrasound measurements, systolic and diastolic blood pressure and heart rate were measured in the supine position with a semi-automated device (Dinamap). With this technique, the arterial pulse pressure (systolic minus diastolic blood pressure) can be measured adequately (296). The systolic and diastolic pressures were recorded at least 6 times during the Doppler investigation, and the average value of the last 4 recordings was taken as the patient's reading. The pulse pressure was assessed on the right arm and the left arm, and the average value of these two readings was used for further calculations. This was allowed because no significant difference between the average blood pressure values of left and right arm was found.

The peak systolic value of $\Delta d/d \times 100\,\%$, the absolute diastolic diameter (d) and the pulse pressure (Δp) were used to calculate the distensibility coefficient (DC) and the cross-sectional compliance (CC) as previously described (295) with the use of the following equations:

$$DC = 2\Delta d/d \,/\, \Delta p \qquad (1)$$

$$CC = \Delta d/d \,/\, 2\Delta p \times \pi d^2 \qquad (2)$$

Differences between the values in the placebo and verapamil periods were evaluated for statistical significance according to the non-parametric Koch procedure for crossover design (297). In this procedure, the possible effects of treatment, interaction, and order of administration were tested for significance.

A p-value of < 0.05 was considered to indicate a statistically significant difference.

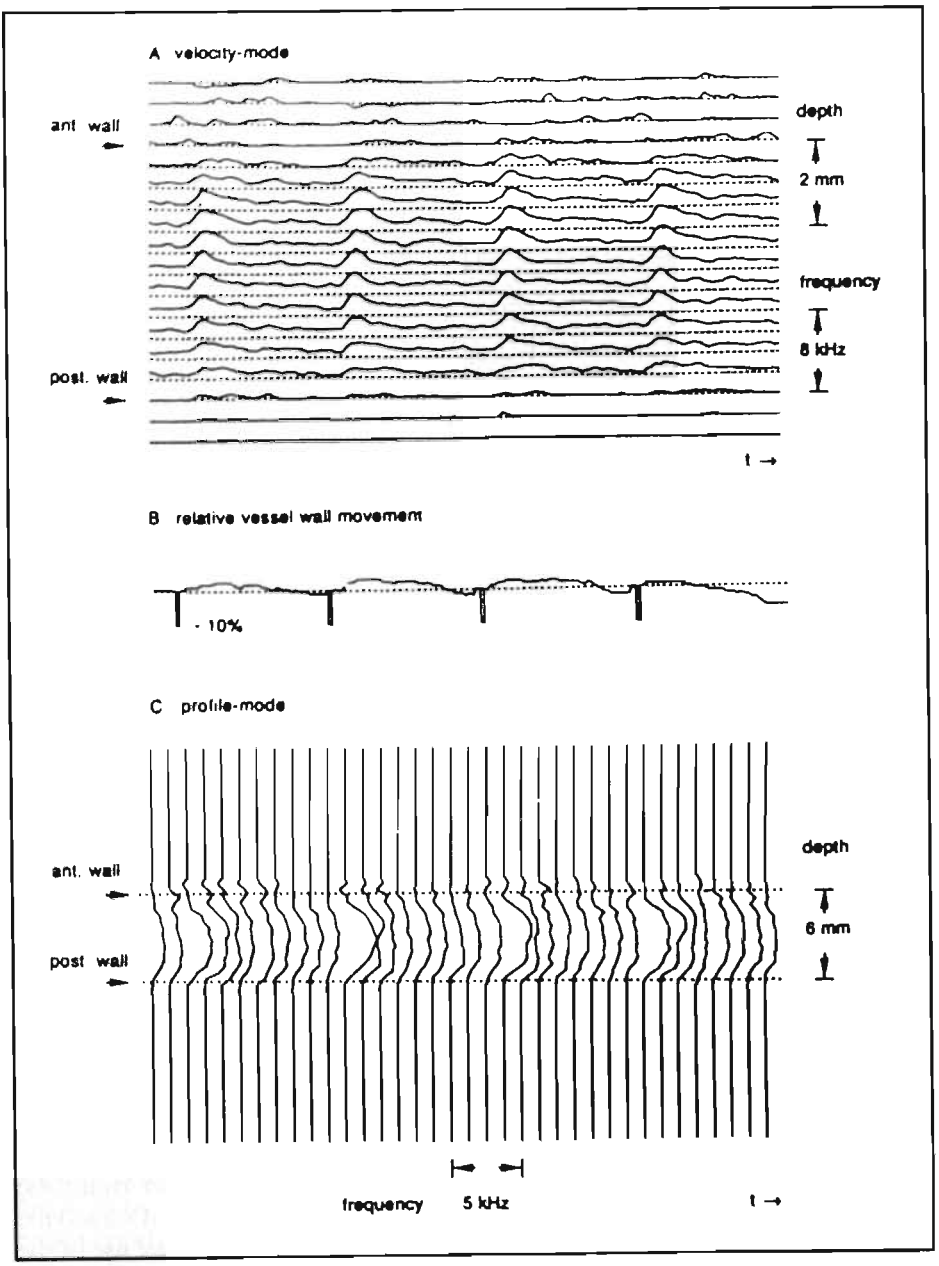

Fig. 2.1 The instantaneous mean velocity wave forms (velocity mode: A), relative vessel wall movements (B), and axial velocity profiles (profile mode, C), as recorded in the common carotid artery of a patient aged 48 years. Only the first three relative diameter tracings were taken to assess the patients' reading. The last tracing is an artifact due to transducer movement. The dotted lines indicate the width of the profiles during systole from which the arterial diameter was estimated.

results

On average, mean systolic and diastolic blood pressures were higher during placebo than during verapamil treatment (153/95 vs. 147/92 mmHg). There were no significant effects of interaction and order of administration. The results of treatment are depicted in Table 2.3.

Table 2.3. Arterial diameter (d), relative diameter changes (Δd/d), distensibility (DC), cross-sectional compliance (CC), and pulse pressure (Δp) for the right (R) and left (L) common carotid artery during verapamil and placebo periods

		Placebo	Verapamil
Diameter (mm)	R	7.2 ± 0.2	7.5 ± 0.2
	L	7.3 ± 0.2	7.2 ± 0.2
Δd/d (%)	R	4.5 ± 0.5	5.3 ± 0.4[a]
	L	4.4 ± 0.4	5.4 ± 0.4[a]
DC (10^{-3}/kPa)	R	10.7 ± 1.1	13.1 ± 1.0[a]
	L	10.5 ± 1.0	13.3 ± 1.0[a]
CC (mm^2/kPa)	R	0.34 ± 0.04	0.43 ± 0.03[a]
	L	0.34 ± 0.04	0.40 ± 0.03
Δp (mmHg)		64 ± 2	61 ± 2

[a] statistically significant difference between placebo and verapamil; data are mean ± SEM.

The relative change in artery diameter during the cardiac cycle was significantly higher during verapamil treatment than during the placebo period, for both the left and the right common carotid artery ($p < 0.02$ and $p < 0.05$, respectively). The distensibility coefficient (DC) was significantly increased during verapamil treatment, as compared to the placebo period for both left and right common carotid artery ($p < 0.01$ and $p < 0.05$, respectively). The cross-sectional compliance (CC) was increased during verapamil treatment, but reached the level of significance only for the right common carotid artery ($p < 0.05$). The p-value for the left common carotid artery was 0.16. The common carotid artery diameter and the arterial pulse pressure were not significantly different during verapamil and placebo treatment.

Changes in blood pressure, heart rate and vessel wall properties were also examined in the subgroups of young (21-40 years) and elderly (60-73 years) patients (Table 2.4). In elderly patients, blood pressure was higher and vessel wall properties lower. During verapamil the decrease in blood pressure was more pronounced in elderly patients, while the increase in distensibility and compliance was higher in young patients.

Table 2.4. Haemodynamic effects of verapamil after 4 weeks 3x120mg per day in young and elderly hypertensive patients.

	young (n = 9)		elderly (n = 10)	
	placebo	verapamil	placebo	verapamil
SBP (mmHg)	148 ± 4	140 ± 4[a]	159 ± 5	146 ± 4[a]
DBP (mmHg)	87 ± 3	80 ± 3[a]	92 ± 2	83 ± 2[b]
ΔP (mmHg)	61 ± 2	61 ± 3	67 ± 3	63 ± 3
HR (b/min)	74 ± 5	70 ± 4	76 ± 3	70 ± 3[b]
D (mm)	6.9 ± 0.3	7.3 ± 0.4	7.5 ± 0.2	7.8 ± 0.3
DC (10^{-3}/kPa)	13.1 ± 1.6	16.5 ± 1.2	8.5 ± 1.1	10.0 ± 0.8
CC (mm^2/kPa)	0.38 ± 0.06	0.51 ± 0.04	0.30 ± 0.05	0.35 ± 0.04

SBP: systolic blood pressure; DBP: diastolic blood pressure; ΔP: pulse pressure; HR: heart rate; D: diameter; DC: distensibility coefficient; CC: compliance coefficient; Data are presented as mean ± SEM; [a]$p < 0.05$,[b]$p < 0.01$ statistical difference versus placebo.

discussion

The findings in the present study indicate that chronic treatment with the calcium-antagonist verapamil increases distensibility and cross-sectional compliance of the common carotid artery in hypertensive patients. These improvements have to be considered as changes in arterial wall distensibility because no significant differences in arterial diameter could be detected between treatment with the compound and placebo. The latter observation is interesting because verapamil apparently improves arterial wall distensibility without dilating the artery significantly.

That the improvement of cross-sectional compliance during verapamil treatment did not reach the level of significance for the left carotid artery is probably caused by the slightly, but non-significantly, smaller mean carotid artery diameter (maybe due to a stray value) on that side, especially since the distensibility is significantly improved. One should keep in mind that slight differences in diameter do have a great impact on cross-sectional compliance, because of the second power of this measure in the equation to calculate this parameter (see equation 2).

The improvement of the reduced vessel wall distensibility in hypertensive patients through chronic treatment with verapamil could result in a better management of the systolic flow jet from the heart, and may help to protect the patient against atherosclerotic complications of hypertension.

The diminished arterial wall distensibility, which means a stiffer behavior, in young hypertensive patients indicates that in these patients the arteries age faster (298). Therefore, antihypertensive treatment should not only aim at lowering arterial blood pressure, but also at improving the distensibility of the arteries. In this context, it should be kept in mind that improved arterial wall compliance during anti-

hypertensive treatment may be achieved through arterial dilation without an effect on arterial wall distensibility. Although through this compensating mechanism arteries are able to better store volume energy, it remains to be seen whether dilation alone prevents the arteries from early aging. Further studies are required to assess the true value of these findings.

As expected blood pressure was higher in older patients and distensibility and compliance of the common carotid artery (CCA) were smaller. Despite the larger decrease in systolic blood pressure and pulse pressure during verapamil treatment in eldery patients, the change in vessel wall properties was smaller. This difference can hardly be explained by the difference in blood pressure alone, since in elderly patients blood pressure during verapamil was even lower than during placebo in young patients, but distensibility remained lower in the elderly. These data are compatible with a stiffer large vessel in the elderly and strongly suggest structural changes in the CCA of the elderly. These results suggest that verapamil given for 1 month has less effect on arterial distensibility and compliance when structural changes are present.

A criticism of the method, as used in the present study, could be that pulse pressure was measured at the brachial rather than the common carotid artery. This was necessary because a non-invasive method to measure pressure in the latter artery is not available. In this approach, it is assumed that the pulse pressure in the brachial artery is representative of that in the common carotid artery. An indication of this assumption is the positive relationship between this pulse pressure and the relative diameter increase of the common carotid artery during systole, as found in a previous study (295), examining age-related changes in distensibility and cross-sectional compliance in a similar way. However, early reflected pulse waves can occur especially in elderly patients. These pulse wave reflections can raise the pulse pressure in the ascending aorta and probably also in the carotid artery. The pulse pressure in the brachial artery is in general not influenced by pulse wave reflections (169,299). It cannot be excluded that in the elderly patients of the present study the pulse pressure in the carotid artery is influenced by early reflected pulse waves. If this is the case, then compared to the younger patients pulse pressure would be higher and the vessel wall properties lower than measured. As a result the difference in distensibility and compliance between young and elderly patients would even be more pronounced.

In conclusion, the results of this study indicate that verapamil administration in hypertensive patients increases both carotid artery distensibility and cross-sectional compliance. Although increased compliance probably compensates for a decrease in arterial elasticity, it does not necessarily protect the arteries against aging faster in hypertensive patients. The improvement in distensibility, as found with chronic treatment with verapamil in this study, could be even more important in this respect.

chapter 3. effect of nebivolol on distensibility and compliance of the common carotid artery[3]

introduction

In hypertension large arteries are aging faster and atherosclerosis, a major cause of morbidity and mortality, is developing earlier than in normotensive patients (300). Therefore, the goals of modern antihypertensive treatment will be not only normalization of blood pressure and preservation of quality of life, but also prevention of atherosclerotic disease (125).

Not only in patients with essential hypertension (301) but also in borderline hypertensive patients (298) compliance of large arteries is diminished. Since stiff arteries manage the systolic pressure pulse from the heart less adequately, endothelial injury and plaque rupture may occur more frequently in these vessels. Thus, improvement of the vessel wall properties of large vessels might protect them from atherosclerotic disease. The influence of physical factors on large vessels has been discussed in chapter 1.

In this study the effect of nebivolol on vessel wall properties (distensibility and compliance) of the common carotid artery are investigated with a high resolution multigate pulsed Doppler system. Nebivolol is a selective β_1-adrenoceptor antagonist with vasodilating properties (302). Five mg once daily has on average a good antihypertensive effect (303-304).

materials and methods

After a 4-week single blind run-in period, during which all antihypertensive drugs and diuretics were withdrawn, 29 patients (21 males, 8 females; aged 25-70 yr) entered the study.

The study was a double-blind, randomized, placebo controlled crossover study. The study design is shown in Fig 2.2. In each crossover period, patients were given 5 mg nebivolol or apparently identical placebo once daily for 4 weeks. At the end of each 4-week period, arterial blood pressure, heart rate and vessel wall properties were measured. Measurements were performed at a fixed time of the day, which was for each patient a fixed time after daily dose intake as well.

All patients suffered from essential hypertension and were recruited from outpatient clinics. None suffered from symptomatic atherosclerotic disease. Diastolic blood pressure was > 90 mmHg but < 120 mmHg at the end of the 4-week washout period. All patients had normal liver function tests and normal serum protein and albumin levels. Serum creatinine levels were < 134 μmol/l. The study was approved by the Medical Ethical Committee of the University of Limburg. All patients gave their written informed consent.

[3] based on:
- LMAB Van Bortel, T Van Merode, FAM Smeets, RS Reneman, JMV Mooij, HAJ Struyker Boudier. Nebivolol improves the vessel wall properties of the common carotid artery. Drug Invest 1991, 3(suppl 1):61-63.
- T Van Merode, LM Van Bortel, FA Smeets, RS Reneman, R Böhm, KH Rahn. Verapamil and nebivolol improve carotid artery distensibility in hypertensive patients. J Hypertens 1989, 7(suppl 6):262-263.

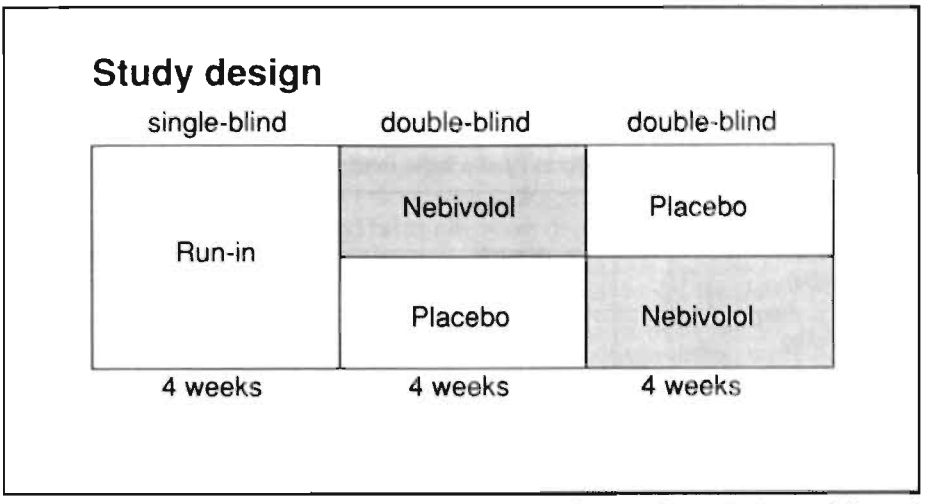

Fig. 2.2. Study design: a 4-week single blind placebo run-in period was followed by 2 4-week double blind crossover periods (nebivolol, placebo).

Vessel wall properties of the common carotid artery were measured with a multigate pulsed Doppler system, as described previously (292). The relative change in diameter of the right common carotid artery during the heart cycle was recorded on-line. From the width of the on-line recorded velocity profiles in the artery, the diameter of the common carotid artery can be measured. The relative change in diameter can be recorded with an absolute accuracy of 0.5 % (292). The diameter, as determined with this technique, is dependent on the angle of interrogation. Therefore, the values measured, were corrected for this angle, 60° in the present study.

Simultaneously with the Doppler recordings of the common carotid artery, arterial blood pressure and heart rate were measured with a semi-automated device (Dinamap, Critikon, Tampa, USA). Blood pressure and heart rate were recorded at least 6 times during Doppler investigation. The average value of the last four recordings was taken as the patient's reading. Pulse pressure was calculated from the average values of the readings on the right and left arm. All measurements of vessel wall properties and arterial blood pressure were performed in supine position after 15 minutes of rest.

From the diameter (D), the relative change in diameter during the heart cycle ($\Delta D/D$) and the pulse pressure (ΔP), distensibility coefficient (DC) and cross-sectional compliance coefficient (CC) were calculated:

formula: $DC = 2(\Delta D/D)/\Delta P$

formula: $CC = (\Delta D/D).\pi D^2/2\Delta P$

Statistical analysis was performed according to the non-parametric Koch procedure for the two-way crossover design (297), which allows testing for treatment, period and interaction effects. A p-value < 0.05 was considered a significant difference.

results

All patients completed the study. No serious adverse events occurred. No statistically significant interaction or period effects were seen between the two crossover periods. Data on haemodynamics are shown in Table 2.5.

Table 2.5. Haemodynamic effects of 4 weeks nebivolol 5 mg once daily

	P	N
SBP (mmHg)	155 ± 3	145 ± 3***
DBP (mmHg)	97 ± 2	90 ± 2***
ΔP (mmHg)	62 ± 2	62 ± 2
HR (b/min)	80 ± 3	69 ± 2***

P: placebo; N: nebivolol; SBP: systolic blood pressure; DBP: diastolic blood pressure; ΔP: pulse pressure; HR: heart rate; *** $p < 0.001$ statistical difference between placebo and nebivolol; Data are presented as mean ± SEM.

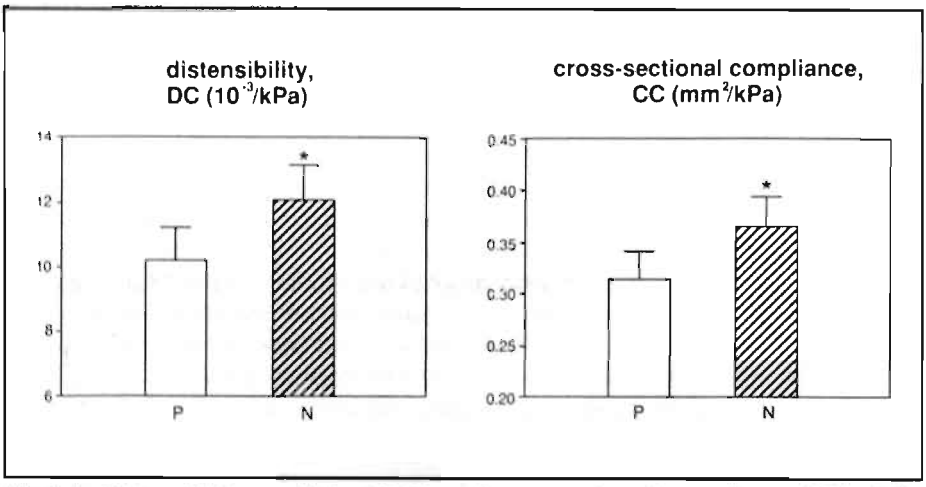

*Fig 2.3. Distensibility coefficient (DC) and cross-sectional compliance (CC) of the common carotid artery during placebo (P) and nebivolol (N). Data are mean ± SEM. * $p < 0.05$, difference between double blind placebo and nebivolol.*

Nebivolol decreased heart rate, systolic and diastolic blood pressure ($p < 0.001$). Pulse pressure did not differ between placebo and nebivolol.

The diameter of the common carotid artery did not differ between placebo (7.4 ± 0.2 mm) and nebivolol (7.5 ± 0.3 mm). The effect of nebivolol on the distensibility coefficient and cross-sectional compliance of the common carotid artery is shown in Figure 2.3. With placebo, distensibility of the common carotid artery was 10.2 ± 1.1 10^{-3}/kPa and compliance was 0.31 ± 0.03 mm^2/kPa. These two vessel wall properties increased ($p < 0.05$) during nebivolol treatment (distensibility: 12.1 ± 1.1 10^{-3}/kPa; compliance: 0.37 ± 0.03 mm^2/kPa).

discussion

Distensibility and compliance are vessel wall properties of large arteries. Accurate non-invasive measurements of these vessel wall properties can be obtained by means of recently developed echo-Doppler techniques. In this study a first generation device developed by Dr Hoeks and coworkers was used. The technique, its accuracy and limitations have been discussed in chapter 2.

Nebivolol is an antihypertensive drug with ß-blocking and vasodilating properties. As expected blood pressure and heart rate were decreased after 4 weeks treatment with nebivolol.

The results of the present study also indicate that nebivolol favorably influences distensibility and cross-sectional compliance of the common carotid artery. The improved compliance was the result of an increased distensibility, without change in diameter of the common carotid artery. These findings might result in a better management of the systolic pressure pulse. The increased distensibility, the lower systolic blood pressure and heart rate might decrease the load on the vessel wall and as a consequence help to protect the common carotid artery (and perhaps also other large arteries) from accelerated aging and atherosclerotic disease. The increased compliance might result in a smaller afterload for the heart, and as a consequence help to prevent cardiac hypertrophy.

As discussed in chapter 1, large artery compliance is improved by ß-blocking drugs with vasodilating properties (264-268) like nebivolol and dilevalol and also by those with intrinsic sympathomimetic activity like pindolol. Non-selective ß-blockers without ISA like propranolol (264) did not improve compliance, while selective $ß_1$-adrenoceptor antagonists like bisoprolol (271) and atenolol (266) improved compliance, but metoprolol (270) did not maybe because of loss of selectivity due to a higher dose.

In conclusion, in patients with essential hypertension, 5 mg nebivolol once daily had a good antihypertensive effect and improved vessel wall properties of the common carotid artery. This might help to prevent or delay cardiovascular disease in these hypertensive patients.

PART III
QUALITY OF LIFE PERCEPTION DURING ANTIHYPERTENSIVE TREATMENT

introduction

Effective antihypertensive therapy is important since the risk of cardiovascular complications related to hypertension increases continuously with increasing levels of both systolic and diastolic blood pressure (125). Effective antihypertensive therapy is influenced by both the prescribed antihypertensive drug and patient's drug adherence. Different classes of antihypertensive drugs are now available that can effect a comparable reduction in blood pressure. In contrast, patient's drug adherence is in general poor, as described in part I. Efforts should be made to improve it. In this respect quality of life perception during antihypertensive treatment is important. Since patients with mild-to-moderate hypertension are in general asymptomatic (186), therapy is not likely to improve functional status and sense of well-being, but can cause new symptoms and result in poorer adherence to therapy if the unwanted effects are substantial. As a result, it is not only important to control blood pressure but also to preserve the patient's quality of life (305-306).

Standardized information on quality of life has proven to be an important research tool in the development of drugs with equal therapeutic benefit (307-308). A quality of life measurement instrument must be reproducible and must have been validated. In addition, it has to detect clinically important changes; in other words, it has to be responsive (309). Information on quality of life can be obtained by general health profiles or disease-specific measures. General health profiles can identify aspects affected by the disease and its management. However, general measures may fail to examine adequately detailed aspects of treatment for specific symptoms or functions related to a disease (305). Choosing a good questionnaire is important, but avoiding systematic bias in questionnaire administration may even be more important. Inconsistencies in administration can be avoided by using trained interviewers or by using traditional self-administered questionnaires (309).

The Inventory of Subjective Health is a general health profile, which was originally developed by Dirken for detecting stress in the work place. Seven of its core items are identical to the items in the somatic subscale of the "John Hopkins Symptom Checklist" (HSCL). As it proved to be a sensitive instrument for health problems, it has been validated (310-311) and used in the last decade in numerous Dutch surveys - also in hypertension (312) - to indicate subjective health status. This health profile measures subjective physical well-being, also the physical well-being influenced by psychological or emotional factors. It consists of a self-administered questionnaire containing 47 yes/no questions about self-experienced health. The lower the score, the better the subjective perception of well-being. Since the items of the Inventory of Subjective Health are mutually dependent, classical multivariate techniques are not appropriate for analysis (313).

In physically active patients, exercise tolerance may be an important determinant of quality of life. During normal and recreational physical activity maximal work capacity will usually not be reached. In contrast, prolonged exercise at a sub-

maximal exercise level is regularly achieved. Therefore, endurance performance at a submaximal level rather than the maximal exercise capacity is the major exercise-related determinant of patient's quality of life. A reduction in endurance capacity during ß-adrenoceptor blockade has been well documented (314-320).
Chapter 1 investigates the effect on quality of life - as measured with the Inventory of Subjective Health (ISH) - of placebo and antihypertensive treatment with nebivolol, a $ß_1$-adrenoceptor antagonist with an ancillary property. The ISH-score is compared with the results of perceived health rating and side effect diaries.
Since ACE-inhibitors are assumed to preserve quality of life better than other antihypertensive drugs, chapter 2 investigates the effect on quality of life of the ACE-inhibitor enalapril compared with the effect of the selective $ß_1$-adrenoceptor antagonist bisoprolol.
Chapter 3 investigates exercise tolerance with 2 different ß-blocking agents. The effect of different antihypertensive drugs on exercise tolerance is also discussed.

Appendix to introduction
The Inventory of Subjective Health

The items of the Inventory of Subjective Health (circle yes or no).

1.	Are you regularly bothered by coughing?	yes	no
2.	Do you often have pains in the chest or heart region?	yes	no
3.	Do you regularly have unpleasant cold fingers, hands or feet?	yes	no
4.	Is your appetite less good than you consider normal?	yes	no
5.	Does your stomach often feel full and bloated?	yes	no
6.	Do you get short of breath easily?	yes	no
7.	Do you often have an unpleasant or sweetish taste in your mouth?	yes	no
8.	Are you often bothered by pricking or watering eyes?	yes	no
9.	Are you bothered by roaring in the ears?	yes	no
10.	Do you feel fit lately?	yes	no
11.	Do you often have to clear your throat?	yes	no
12.	Do you often have sneezing fits?	yes	no
13.	Do you often feel hungry?	yes	no
14.	Do you often feel tight in the chest?	yes	no
15.	Do your bones or muscles ever ache?	yes	no
16.	Do you generally move your bowels every day?	yes	no
17.	Do you often feel tired?	yes	no
18.	Do you sometimes sweat heavily even when it is not hot?	yes	no

19.	Are you often bothered by itching?	yes	no
20.	Are you often bothered by headaches?	yes	no
21.	Do you often feel dizzy?	yes	no
22.	Do you often have indigestion?	yes	no
23.	Do you often feel sleepy or sluggish?	yes	no
24.	Do your arms and legs often go dead or tingle?	yes	no
25.	Do you often get upset?	yes	no
26.	Do you think you are too thin?	yes	no
27.	Do you think you are overweight?	yes	no
28.	Do you often feel listless?	yes	no
29.	Are you accident prone?	yes	no
30.	Does alcohol effect you more than it used to? (if you never drink alcoholic beverages put a circle around 'no')	yes	no
31.	Are you often irritable?	yes	no
32.	Do you feel tired now and then at the end of a strenuous day?	yes	no
33.	Do your hands often shake?	yes	no
34.	When you get home after work, do you fall asleep in your chair right away?	yes	no
35.	Do you often have palpitations of the heart or throbbing in your heart region?	yes	no
36.	Do you think you suffer from excessive thirst?	yes	no
37.	Do you often have pains in the stomach region?	yes	no
38.	Do you often have pains in or around the eyes?	yes	no
39.	Is your nose often blocked?	yes	no
40.	Do you fall asleep easily and do you sleep well?	yes	no
41.	Are you bothered by weak or aching feet?	yes	no
42.	Are you often bothered by acne or boils?	yes	no
43.	Do you often feel nervous?	yes	no
44.	Do you generally get up feeling tired and not rested in the morning?	yes	no
45.	Do you often have stomach trouble?	yes	no
46.	Are you often troubled by backache?	yes	no
47.	Are you often bothered by sleeplessness?	yes	no

chapter 1. Effect of placebo and antihypertensive treatment with nebivolol on haemodynamics and quality of life as measured with the Inventory of Subjective Health[1]

introduction

Nebivolol is a newly developed selective $beta_1$-adrenoceptor antagonist with an unusual haemodynamic profile. In contrast to other beta-adrenergic antagonists, nebivolol acutely lowered arterial blood pressure in spontaneously hypertensive rats. In healthy volunteers, nebivolol (5 mg) lowered systemic vascular resistance during daily oral treatment and did not impair left ventricular function (302). This suggests the presence of a pharmacologic ancillary vasodilating property, apart from the $beta_1$-adrenoceptor antagonism. The nature of this ancillary property is still unknown. In vitro and in vivo studies did not show alpha-, $serotonin_2$-, calcium-antagonism, nor a direct vasodilating action. There was also no evidence for intrinsic sympathomimetic activity (302). In hypertensive patients, the antihypertensive effect of nebivolol 5 mg once daily was greater than that of 2.5 mg once daily. Ten mg/day did not enhance the antihypertensive effect (303-304). This study investigates the antihypertensive efficacy, adverse effects and influence on quality of life perception of a 4 and 8-week treatment with nebivolol 5 mg once daily.

materials and methods

Patients

131 patients were recruited from outpatient clinics. At the end of a 4-week single blind placebo run-in period 10 patients did not meet the blood pressure entry criteria and 7 were excluded for other reasons. 114 patients with essential hypertension were selected and entered the study. Demographic data are shown in Table 3.1. Inclusion criteria were a diastolic blood pressure between 95 mmHg and 120 mmHg or a diastolic blood pressure between 90 and 94 mmHg with a systolic blood pressure of more than 160 mmHg at the end of the 4-week run-in period. Serum levels of ALAT and ASAT did not exceed twice the upper limit of normal. Serum levels of creatinine were lower than 190 μmol/l. Fifty six patients regularly consumed 2 glasses (< 1 up to 10) alcohol per day. Twenty nine patients smoked 11 (1-30) cigarettes per day. Fifty-two of 114 patients were receiving other non-antihypertensive medications during double blind treatment. At baseline, 3 patients showed clear ECG signs of left ventricular hypertrophy with strain. Five patients had ECG parameters compatible with an old inferior wall and 2 with an old anterior wall infarction. Three patients had ECG signs of ischaemia of the inferior wall. Two complete right bundle branch block and 1 ECG with atrial fibrillation were seen.

[1] based on: LMAB Van Bortel, JGS Breed, J Joosten, JA Kragten, FAT Lustermans, JMV Mooij. Nebivolol in hypertension: a double blind placebo-controlled multicenter study assessing its antihypertensive efficacy and impact on quality of life. J Cardiovasc Pharmacol 1993, 21:856-862.

Table 3.1. Demographic data (n = 114)

Male/female	76/38
Race	Caucasian 112 Black 1 Asian 1
Age (years)	54 ± 1 (25-77)
Height (cm)	169 ± 1 (150-191)
Weight (kg)	78 ± 1 (48-127)

Data are mean ± SEM and (range)

Study design

The study design is shown in Figure 3.1. After a 4-week single blind placebo run-in period, during which all antihypertensive drugs were withdrawn, 114 patients entered a double blind placebo-controlled multicenter study. Major exclusion criteria were a systolic blood pressure of more than 200 mmHg and a diastolic pressure of more than 120 mmHg, a heart rate lower than 50 beats/min, atrioventricular block (second and third degree), signs of heart failure, clinically relevant impaired renal and liver function, uncontrolled diabetes, severe vascular disease, clinically relevant signs of bronchospasm, a history of cerebrovascular accident or myocardial infarction within 3 months preceding the study, poor general condition or life expectancy, lack of compliance or pregnancy.

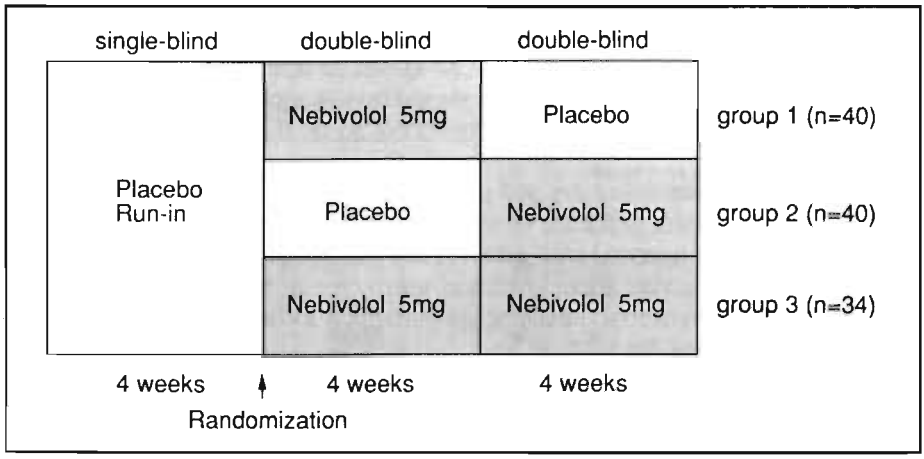

Fig 3.1. Study design: A 4-week single blind placebo run-in period was followed by 2 4-week double blind periods: nebivolol-placebo, placebo-nebivolol, or nebivolol-nebivolol.

Selected patients were randomized into 3 groups and were given nebivolol 5 mg solution (5 ml) or placebo identical in appearance. Group 1 consisted of 40 patients and received nebivolol in the first double blind 4-week period followed by placebo

in the second 4-week period. Group 2 consisted of 40 patients and was given placebo followed by nebivolol. Group 3 was given nebivolol for 8 weeks.
At the end of each 4-week period supine blood pressure and heart rate were measured, a 12-lead electrocardiogram (ECG) was recorded and blood was taken for determination of haematologic and biochemical parameters. All measurements were performed at a fixed time of the day, which was for each patient a fixed time after daily dose intake as well. Time between dose intake and measurements varied between patients from 3 to 10 hours. At the same visit a quality of life questionnaire was filled out. In addition, patients were asked to rate their perceived health. During week 3 and 4 of each 4-week period, prevalence and duration of side effects were assessed with a diary.
Volunteers were asked about their compliance. Volunteers' compliance was also checked by assessing the amount of drug returned. The study was approved by the ethical committee of each participating center. All patients gave their written or witnessed oral informed consent.

Methods

Blood pressure and heart rate were measured after 15 minutes of supine rest and after 2 minutes standing. Data are means of 3 consecutive measurements in each position. Heart rate was measured by counting radial pulse during 30 seconds. Blood pressure was measured with a sphygmomanometer at the right arm and preferably by the same investigator. Diastolic blood pressure was defined at Korotkoff V. Response rates were calculated from patients in groups 1 and 2 (n = 68) with supine diastolic blood pressure at randomization (baseline) of 95mmHg or more. Patients were considered as responders if diastolic blood pressure during double blind treatment was normalized ($\leqq$ 90mmHg) or if diastolic blood pressure was decreased with at least 10 %.
Quality of life was measured with the Inventory of Subjective Health (ISH). This self-administered questionnaire contains 47 questions about common complaints that may be present or absent for some time. The ISH score is a valid indicator of subjective health status (310-311). The lower the score, the higher the perception of well-being.
Perceived health was rated on a 5-point scale from very good(= 1) to very bad(= 5). This is a valid predictor of mortality over a 10-year period (321).
Adverse effects were assessed with a diary. Each day 1 page had to be filled in. Each page contained questions about common symptoms in hypertension, including those known to be related to beta-blocker therapy. If a complaint was not listed it could be added to the list.
ECG parameters were calculated from an electrocardiogram recorded at 50mm/sec. Parameters were means of at least 5 heart cycles. QT-time was corrected for heart rate by the QT_c formula of Bazett (322): $QT_c = QT / \sqrt{RR}$.
At the end of the visit, non-fasting blood samples were taken for determination of haematologic and biochemical parameters. Haematologic parameters consisted of red and white blood cell counts, platelet count, haemoglobin, haematocrit and 1-hour red blood cell sedimentation rate (ESR). Biochemical parameters were serum levels of sodium, potassium, calcium, total protein, albumin, uric acid, urea, creatinine, total bilirubin, ASAT, ALAT, GGT, alkaline phosphatase, total cholesterol and glucose.

Statistical methods

All data are presented as mean ± S.E.M. Data after 4 weeks of nebivolol and double blind placebo were analysed in groups 1 and 2 (n = 80), which form a crossover design. Statistical analysis was performed according to the non-parametric Koch procedure for the two-way crossover design (297) using the Mann-Whitney U-test. Comparative data analysis within group 3 (n = 32) was made by the Wilcoxon m.p.s.r. test. Haemodynamic data after 8 weeks of treatment with nebivolol (group 3) were also compared with those after 4 weeks of treatment with nebivolol (group 2; n = 40), which, for both groups, comprises 8 weeks after initial randomization. Statistical analysis of this parallel design was performed with the Mann-Whitney U-test. Comparison with baseline was made with the Wilcoxon m.p.s.r. test when appropriate. Baseline was defined as the end of the 4-week placebo run-in period, which was at randomization. A p-value < 0.05 was considered a significant difference.

results

At the end of each 4-week period, patients returned the drugs left and were asked about their drug compliance. From patients' answers about their drug adherence (mean 98 %; range 91-100 % of prescribed dose taken) and from the assessment of the amount of drug returned, patients' compliance was estimated as more than 90 %. Two patients dropped out. Both were randomized to group 3. One patient dropped out because of recurrent peptic ulcer. The second patient withdrew consent. The weight of patients did not change throughout the study.

Four weeks of treatment with nebivolol

Four weeks treatment with nebivolol was compared with 4 weeks double blind placebo in a crossover design (groups 1 & 2). No statistically significant carry-over effects were seen between the two crossover periods. Except for supine systolic blood pressure, also no period effects were present.
Data on blood pressure and heart rate are shown in Fig 3.2.

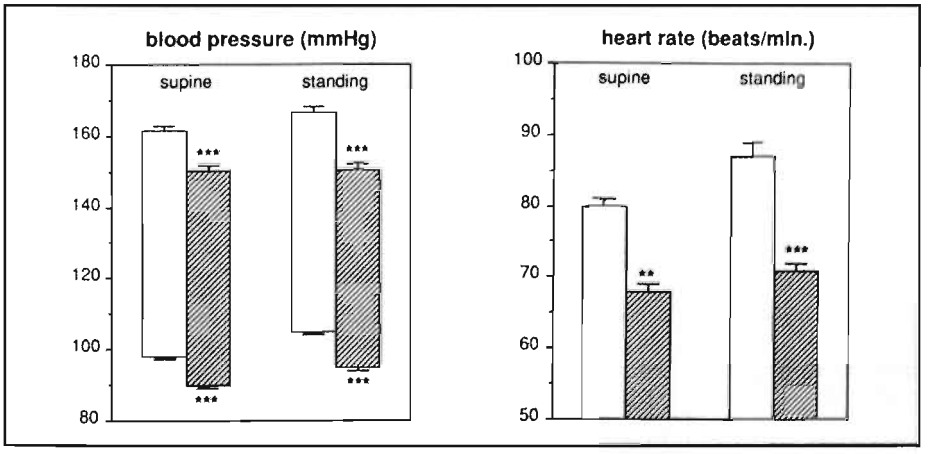

Fig 3.2. Supine and standing systolic blood pressure, diastolic blood pressure and heart rate after 4 weeks treatment with (▨) nebivolol versus double blind (□) placebo (n = 80). Data are mean ± SEM. ** $p < 0.01$, *** $p < 0.001$.

During nebivolol treatment, statistically significant decreases ($p < 0.0001$) in systolic and diastolic blood pressure as well as in heart rate were seen. In the supine position, blood pressure decreased from 161 ± 2/98 ± 1 mmHg during placebo to 150 ± 2/90 ± 1 mmHg during nebivolol, and heart rate from 80 ± 1 to 68 ± 1 b/min. In standing position blood pressure was 166 ± 2/105 ± 1 mmHg during placebo and decreased to 150 ± 2/95 ± 1 mmHg during nebivolol. Heart rate was 87 ± 2 b/min during placebo and 71 ± 1 b/min during nebivolol. Blood pressure response rate to a 4-week treatment with nebivolol 5 mg once daily was 65 % (Fig 3.3). Response rate to placebo was 25 %.

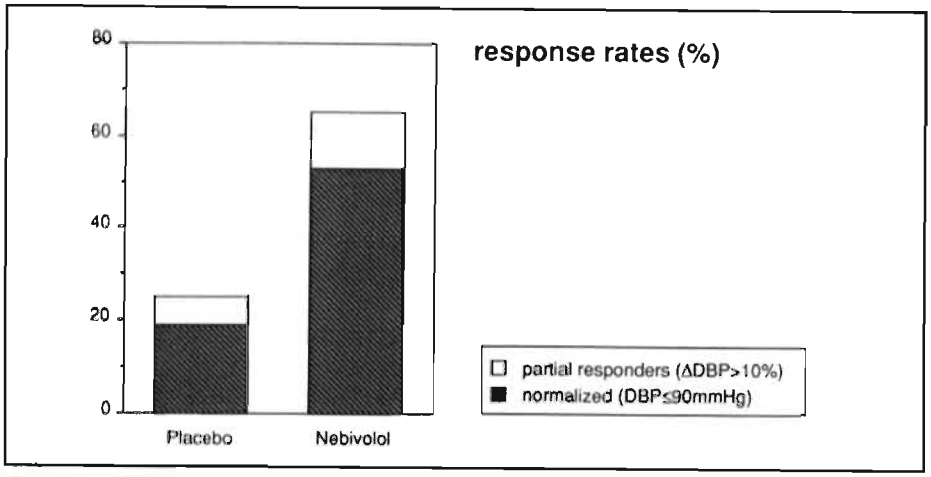

Fig. 3.3. Blood pressure response rates (%) after 4 weeks treatment (n = 68).

ECG parameters are shown in Table 3.2. The PQ interval increased with nebivolol and QRS-time remained unchanged. As a result of the reduction in heart rate QT-interval increased. QT-time corrected for heart rate showed a shortening of QT_c during nebivolol. Two ECG's showing left ventricular hypertrophy with strain at baseline changed during double blind treatment: strain disappeared in one instance during nebivolol and in the other instance during placebo following the nebivolol treatment sequence. One right bundle branch block disappeared during nebivolol and was again present during the consecutive placebo period. The other ECG's remained unchanged in shape throughout the study.

Table 3.2. ECG parameters at baseline and after 4 weeks of treatment (groups 1 and 2).

	Baseline	Placebo	Nebivolol
PQ (ms)	168 ± 3	169 ± 3	175 ± 3***
QRS (ms)	86 ± 2	86 ± 2	86 ± 2
QT (ms)	366 ± 3	367 ± 3	390 ± 4***
QT_c (ms)	409 ± 3	412 ± 3	398 ± 3*

* $p < 0.05$; *** $p < 0.001$ double blind placebo versus nebivolol

Quality of life perception - as measured with the Inventory of Subjective Health - was evaluable in 79 patients. The ISH score was 11.2 ± 0.8 at the end of the run-in period and decreased ($p < 0.001$) to 9.5 ± 0.7 during double blind placebo and nebivolol (Fig 3.4). Perceived health rated on a 5-point scale ($n = 79$) was 2.32 ± 0.07 at the end of the run-in period (Fig 3.4). During placebo perceived health was 2.25 ± 0.06 and did not differ ($p > 0.5$) during nebivolol treatment (2.23 ± 0.06). Baseline values did not differ significantly from the 2 double blind periods.

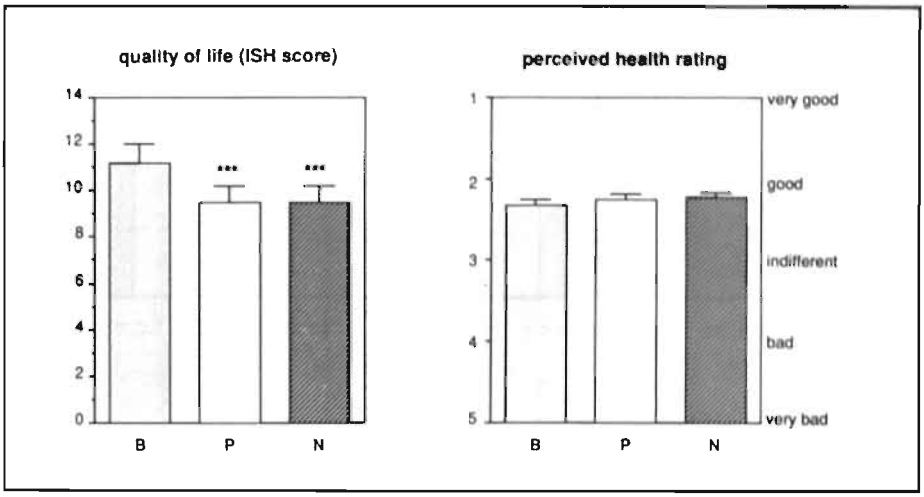

*Fig 3.4. ISH score and perceived health rating after 4 weeks treatment (nebivolol and placebo) and at baseline (n = 79). The lower the score, the better the subjective well-being and perceived health. Data are mean ± SEM. B(baseline); P(placebo); N(nebivolol). *** $p < 0.001$ (difference versus baseline).*

Adverse effects were recorded in a diary. Diaries of 79 (all but 1) patients, who filled in at least 7 days, were analysed. Complaints were rated for presence in days per 100 patient days. Most relevant out of 65 complaints are shown in Fig 3.5. Only 3 complaints were statistically different between placebo and nebivolol. Headache decreased ($p < 0.01$) from 15.0 with double blind placebo to 9.4 days/100 patient days with nebivolol. Difficulty falling asleep (sleep problems) decreased ($p < 0.02$) from 13.3 to 10.8 days/100 patient days during nebivolol treatment. Complaints of dry mouth also decreased statistically during nebivolol. Although often a trend was seen, other complaints did not differ statistically between nebivolol and placebo. The total number of complaints during double blind placebo was 333 complaints/100 patient days and 312 complaints/100 patient days during nebivolol. The difference was not statistically significant.

Table 3.3 lists the most relevant laboratory data after 4 weeks treatment with double blind placebo and nebivolol. In addition, it shows the number of patients with laboratory values within the normal range at baseline but with abnormal values during double blind placebo and nebivolol, respectively. For the laboratory data, which are not listed, this number of patients did not differ with more than 1 between placebo and nebivolol.

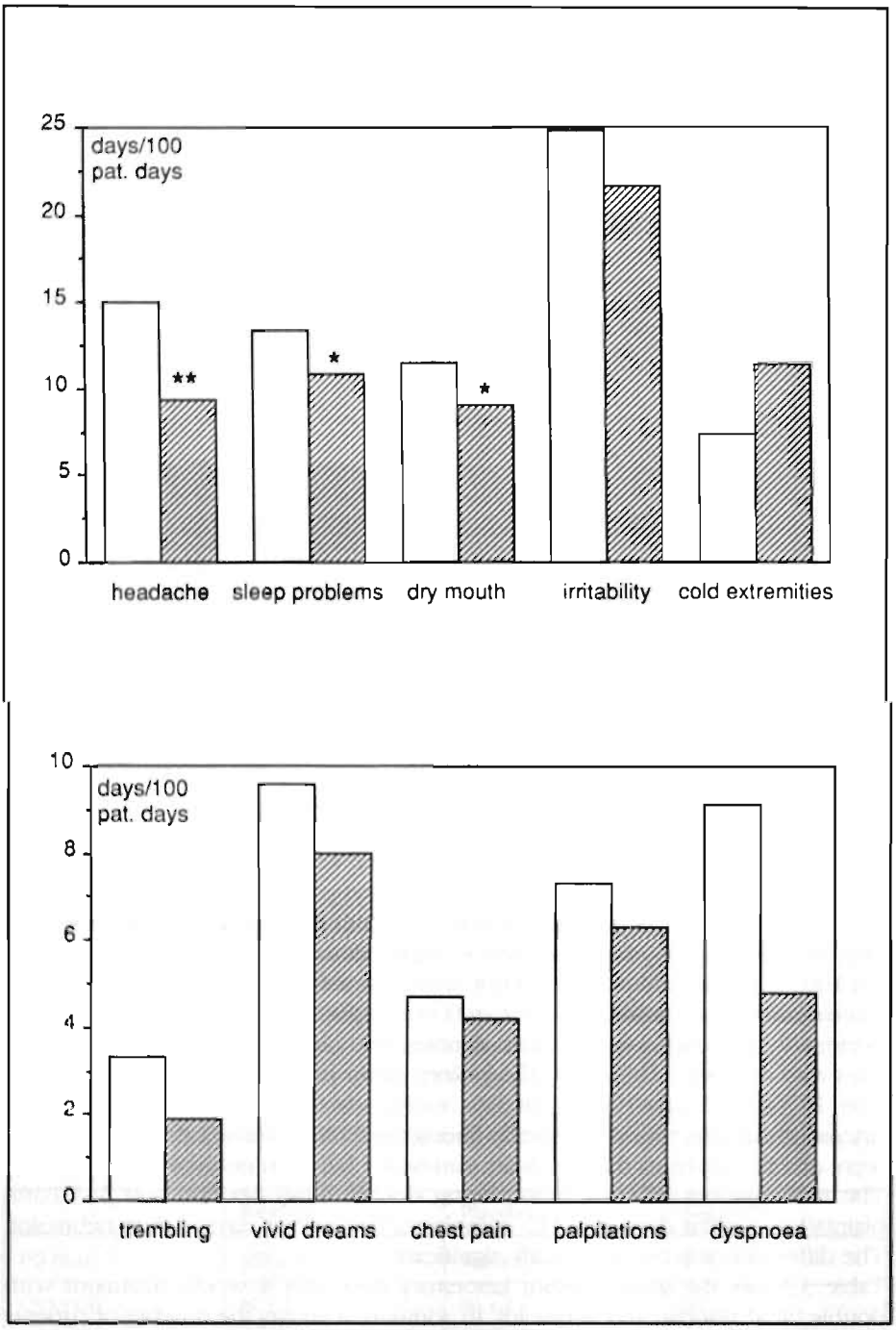

*Fig 3.5. Adverse effects after 4 weeks nebivolol (▨) versus placebo (□): most relevant out of 65 complaints. Data are means. * $p < 0.05$, ** $p < 0.01$. "Vivid dreams" is the sum of 2 complaints: many dreams and nightmares; "Irritability" is the sum of nervousness and rapidly irritated.*

Table 3.3. Laboratory data after 4 weeks of treatment (groups 1 and 2).

	Mean value ± SEM			Changes from baseline		
	Baseline	Placebo	Nebivolol	Change	Placebo (n)	Nebivolol (n)
ESR (mm)	12 ± 1	11 ± 1	11 ± 1	↑	10	8
Platelets (giga/l)	255 ± 13	246 ± 12	239 ± 14**	↓	0	0
Calcium (mmol/l)	2.33 ± 0.02	2.35 ± 0.01	2.35 ± 0.01	↑	3	1
Glucose (mmol/l)	5.8 ± 0.3	5.8 ± 0.3	5.6 ± 0.2	↑	4	5
Total cholesterol (mmol/l)	6.4 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	↑	4	7
Alkaline phosphatase (U/l)	86 ± 3	83 ± 3	82 ± 3	↑	1	3
GGT (U/l)	33 ± 3	34 ± 3	37 ± 4	↑	2	2
ALAT (U/l)	18 ± 2	17 ± 1	19 ± 3	↑	2	2
Urea (mmol/l)	6.1 ± 0.2	6.1 ± 0.2	6.5 ± 0.2**	↑	3	3
Creatinine (μmol/l)	92 ± 3	95 ± 3	96 ± 3	↑	2	1
Uric acid (μmol/l)	320 ± 12	327 ± 11	344 ± 13*	↑	1	1
Potassium (mmol/l)	4.2 ± 0.1	4.3 ± 0.1	4.7 ± 0.2*	↓ ↑	5 1	6 2

statistical difference versus placebo * $p < 0.05$; ** $p < 0.01$; (n) Number of patients with value within normal range at baseline and abnormal value during double-blind placebo or nebivolol.

Eight weeks of treatment with nebivolol

Eight weeks treatment with nebivolol are compared with 4 weeks in group 3. Data on blood pressure, heart rate, quality of life and ECG are shown in Table 3.4. Shape of ECG's remained unchanged throughout the study.

Table 3.4. Data after 4 and 8 weeks nebivolol (group 3).

haemodynamics	baseline	4 weeks	8 weeks
supine SBP (mmHg)	165 ± 3	148 ± 3	142 ± 3*
supine DBP (mmHg)	101 ± 1	91 ± 2	87 ± 2**
supine HR (b/min)	82 ± 2	68 ± 2	69 ± 2
standing SBP (mmHg)	165 ± 3	147 ± 4	144 ± 4
standing DBP (mmHg)	106 ± 1	93 ± 2	92 ± 2
standing HR (b/min)	88 ± 2	71 ± 2	72 ± 2
inventory of subjective health			
score	13.1 ± 1.6	11.3 ± 1.6	11.5 ± 1.5
perceived health rating			
score	2.43 ± 0.12	2.32 ± 0.10	2.31 ± 0.09
electrocardiogram			
PQ (msec)	170 ± 4	175 ± 4	174 ± 4
QRS (msec)	87 ± 2	88 ± 2	89 ± 2
QT (msec)	367 ± 6	394 ± 4	394 ± 5
QTc (msec)	420 ± 5	406 ± 4	404 ± 4

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; differences between week 4 and 8: * $p < 0.05$; ** $p < 0.01$. Data are mean ± SEM.

Heart rate and standing blood pressure did not differ between 4 and 8 weeks treatment with nebivolol. The decrease in supine blood pressure was larger after 8 weeks than after 4 weeks treatment. This could, at least in part, be due to a hidden placebo effect. Therefore, results after 8 weeks nebivolol (group 3) were compared with those after 4 weeks nebivolol (group 2). In group 2, supine blood pressure was 165 ± 3/101 ± 1 mmHg and heart rate was 78 ± 2 b/min. In the standing position these values were 167 ± 3/107 ± 1 mmHg and 82 ± 2 b/min, respectively. Decreases from these baseline values are shown in Fig 3.6. Supine and standing blood pressures and heart rates tended to decrease somewhat less after 4 than after 8 weeks of nebivolol. The differences between week 4 and 8 were not statistically significant.

Diaries for side effects of 31 patients (all but 1), who filled in at least 7 days, were analysed. The number of patients with complaints did not differ between week 4 and 8 of treatment with nebivolol, but was lower than at baseline.

No clinically relevant differences in laboratory values were seen between week 4 and week 8. The number of patients - with a normal laboratory value at baseline and abnormal value during the double blind periods - did not differ with more than 1 between week 4 and week 8.

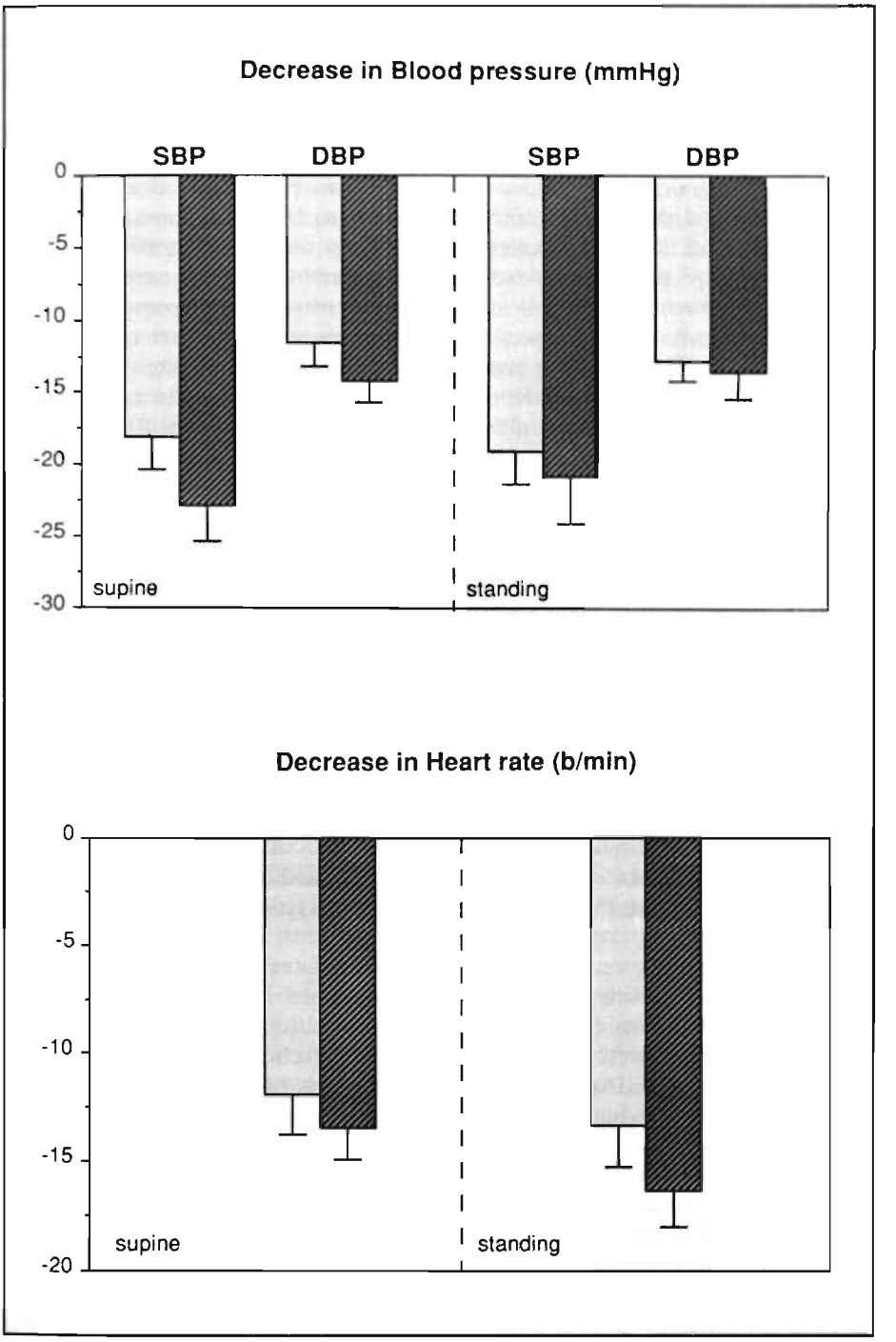

Fig 3.6. Decrease in supine and standing systolic blood pressure, diastolic blood pressure and heart rate after 4 (□; group 2) and 8 (▨; group 3) weeks nebivolol. Data are mean ± SEM.

discussion

Nebivolol is an antihypertensive drug with beta-blocking properties. As a result resting supine and standing heart rate decreased during treatment with nebivolol. The decrease in heart rate was not larger after 8 than after 4 weeks of nebivolol. Although heart rate at rest is also largely determined by vagal tone, these data suggest that steady state beta-blocking effect was reached within 4 weeks.

Nebivolol 5 mg once daily induced a good antihypertensive effect in supine (10/8 mmHg) and standing (16/10 mmHg) position. After 2 minutes standing no signs of orthostatic hypotension were present. Response rate to placebo was 25 %. Response rate to 5 mg nebivolol was 65 %. Comparable response rates have been described for placebo (323-324) and antihypertensive monotherapy (324-326). A fixed dose of nebivolol was used in the present study in contrast to other studies investigating response rates. The antihypertensive effect in the supine position was higher after 8 than after 4 weeks of treatment with nebivolol. In addition, the standing blood pressure did not differ between week 4 and week 8. This indicates absence of drug tolerance over the 8-week period. Could the larger antihypertensive effect (in supine position) after 8 weeks be due to a period effect? Comparison of week 8 in group 3 with week 8 in group 2 (4 weeks placebo followed by 4 weeks nebivolol) can correct for a possible hidden period effect. Differences in antihypertensive effect at week 8 between group 2 and 3 were not statistically significant. It seems reasonable to suggest that a period effect might be present.

ECG changes during nebivolol are those associated with other beta-blocking agents (327-328). PQ-time increased during nebivolol treatment, but no atrioventricular block of the second or third degree occurred. QRS-time was not changed. QT-time increased, but heart rate corrected QT-time (QT_c) was shorter than during placebo. Changes in the electrocardiogram did not differ between week 4 and 8 with nebivolol.

After a 4-week treatment period, no clinically important changes in mean values of laboratory data were found between nebivolol and double blind placebo. Similar to other beta-blockers (329-330) blood urea, uric acid and potassium increased slightly with nebivolol. Platelets showed a slight decrease. But for each of these 4 laboratory items, similarly few patients had a normal value at baseline and an abnormal value during treatment with nebivolol or placebo. As a consequence, the differences are not likely to be of clinical relevance. Liver enzymes and total cholesterol showed no clinically relevant changes during nebivolol. Since no fasted blood samples were taken, serum levels of HDL cholesterol and triglycerides were not determined. During nebivolol serum levels of plasma glucose did not differ from the double blind placebo period and were similar after 4 and 8 weeks of treatment. It is not clear whether glucose tolerance is less impaired with nebivolol than with other beta-blocking drugs. The effects of nebivolol on blood biochemistry are in accordance with those found by Chan et al (331). In this latter placebo-controlled study with 16 patients in the nebivolol group, fasted serum triglycerides levels did not increase during nebivolol.

It is generally accepted that quality of life trials have to be large, usually 150-200 patients per treatment group, owing the variability of data collected (332). This variability in collected data is in part due to the interindividual variability in studies with a parallel groups design. Quality of life perception depends upon different conditions such as age, sex and social status (333-336). In a study with a crossover

design, differences in overall quality of life scores between ketanserin and placebo could be shown with only 17 patients (337). Therefore, the crossover approach has been suggested as useful with agents that have no carry-over effect (338). In the present placebo-controlled study, no carry-over effect was seen as measured with the Koch procedure for the two-way crossover design. The ISH score did not differ between double blind placebo and nebivolol. This indicates that during a 4-week treatment with nebivolol 5 mg/day quality of life perception was preserved. Quality of life perception improved during both nebivolol and placebo versus baseline. This improvement versus baseline might be due to the participation in the trial (339). As a consequence an absolute change in quality of life can only be demonstrated in a placebo-controlled study and not by comparison with pretreatment baseline measurements. The majority of studies investigating quality of life are not placebo-controlled but comparative (338). As a result, in those studies the only conclusion can be that one drug is better than another. Comparison with the baseline status might be misleading, and might induce incorrect conclusions. Like the ISH score, the rating of perceived health did not differ between nebivolol and double blind placebo. It also tended to be better during both placebo and nebivolol versus baseline. These data are consistent with the results of the ISH score. ISH scores and perceived health rating did not differ between week 4 and week 8 of treatment with nebivolol. This indicates that quality of life perception was very constant and preserved for at least 8 weeks.

Adverse effects were registered with a diary. As with other beta-blocking drugs (340-341), the prevalence of headache decreased during nebivolol. Nebivolol might be devoid of CNS adverse effects, since sleep problems occurred less frequently and vivid dreams were not increased but even tended to decrease. During nebivolol dyspnoea tended to be less frequent than during placebo. This is unusual for a beta-blocking drug, and no β_2-agonistic effect of nebivolol is known, which might induce bronchodilation. The lower incidence of dyspnoea during nebivolol might in part be due to the exclusion from the study of patients with overt signs of bronchospasm. In addition, it might reflect a lower incidence of the "shortness of breath" feeling due to hyperventilation. This hyperventilation can be improved by beta-blocker induced decrease in nervousness.

The favorable adverse effect profile, the total number of complaints, which did not differ and even tended to decrease slightly (6 %) during nebivolol, and the fact that during the study only 2 patients (< 2 %) dropped out, indicate that nebivolol is well tolerated and support the results of the quality of life assessments.

In conclusion, nebivolol 5 mg once daily is an effective antihypertensive agent, with response rates comparable to those of beta-blocker monotherapy. No signs of drug tolerance were seen. Nebivolol 5 mg once daily has a favorable adverse effect profile and preserves quality of life as measured with the Inventory of Subjective Health and perceived health rating. As far as the electrocardiogram and blood analyses are concerned, treatment with nebivolol 5 mg once daily seems to be safe. Whether glucose tolerance is preserved during nebivolol needs further investigation.

The present study also indicates that an absolute change in quality of life perception cannot be claimed by comparison with baseline, since participation in a trial already influences quality of life perception. The study also supports the validity of the Inventory of Subjective Health as a measure for general well-being, since results were in accordance with both the perceived health rating and the side effect diaries.

chapter 2. Do ACE-inhibitors preserve quality of life better than other antihypertensive drugs? A comparative study between enalapril and bisoprolol[2]

introduction

Quality of life has become a relevant measure of efficacy in clinical studies. Its use is spreading and its importance growing as a valid indicator of whether or not a medical treatment is beneficial (342).

Short-term therapy with angiotensin-converting-enzyme (ACE)-inhibitors for hypertension is effective and well-tolerated, and compared to beta-blockers, may cause fewer adverse reactions (313). This study investigates the antihypertensive effect and influence on patients' quality of life perception of the highly selective β_1-adrenoreceptor blocker bisoprolol compared to the ACE-inhibitor enalapril.

material and methods

Patients

Fifty-seven patients with mild-to-moderate essential hypertension were eligible. Fifty-four patients (37 males, 17 females; 14 smokers, 40 non-smokers) were selected to enter the active treatment period. Patients were from 20 to 69 years (mean 50 years) old, their height ranged from 148 to 190 cm (mean 172 cm) and their weight from 60 to 119 kg (mean 82 kg). Eighteen patients were not treated with any antihypertensive drug before starting the study. The other 36 selected patients were treated for hypertension for 4.8 ± 0.8 years (0 - 18 years) with different drugs (Table 3.5). Ten patients were treated for concomitant diseases at study entry. Concomitant medication consisted of clofibrate, simvastatin, omeprazol, prednisolone, tryptizol, lithium carbonate, dosulepine, disopyramide, baclofen and acitretine. Three eligible patients did not enter the study. Two of them had normal blood pressure after the run-in period and 1 withdrew consent.

Study design

After an initial screening visit, eligible patients started the study with a 2-week run-in period, during which all antihypertensive drugs were withdrawn. At the end of the run-in period patients were selected. Included were patients with a supine diastolic blood pressure higher than 95 mmHg but lower than 115 mmHg. Major exclusion criteria were a systolic blood pressure higher than 200 mmHg, a heart rate lower than 50 beats/minute, an atrioventricular block of the second or third degree, signs of heart failure, diabetes, impaired renal (creatinine > 140 μmol/l) or liver function or lack of compliance. Selected patients entered a multicenter double blind comparative two-way crossover study. Patients were given in random order bisoprolol (Emcor^R) 5mg tablets or enalapril (Renitec^R) 10mg tablets once daily for 8 weeks. The first treatment period was immediately followed by the second. If after 4 weeks of each 8-week treatment period diastolic blood

[2] based on: JGS Breed, R Ciampricotti, GP Tromp, FA Valster, E Lageweg, LMAB Van Bortel. Quality of life perception during antihypertensive treatment: a comparative study between Bisoprolol and Enalapril. J Cardiovasc Pharmacol 1992, 20:750-755.

pressure was higher than 90 mmHg, doses were doubled (bisoprolol 10 mg or enalapril 20 mg). At the end of the run-in period and at the end of each 8-week treatment period blood pressure and heart rate were measured and a quality of life questionnaire was filled out. Patients were also asked for possible complaints. A 12-lead electrocardiogram was taken and serum levels of sodium, potassium, creatinine and glucose were determined. In each patient, measurements were performed at the same time of the day. At the end of the double blind study patients were asked with an open question to indicate the treatment period during which they judged their subjective well-being better. The study was approved by the ethical committee of each participating center. All patients gave their written or witnessed oral informed consent.

Table 3.5. Antihypertensive treatment before starting the study

no antihypertensive drugs n = 18	
antihypertensive monotherapy n = 19	n
diuretics (1)	4
beta-adrenoreceptor antagonists (2)	6
calcium-antagonists (3)	3
ACE-inhibitors (4)	6
antihypertensive double therapy n = 16	
(1) + (2)	1
(1) + (3)	1
(1) + (4)	5
(2) + (3)	2
(2) + (4)	4
(3) + (4)	3
antihypertensive triple therapy n = 1 (2) + (3) + (4)	

Methods

Two consecutive measurements of blood pressure and heart rate were performed after at least 3 minutes of supine rest and after 2 minutes in upright position. Means of these 2 values were used for statistical analysis. Heart rate was measured by counting the radial pulse frequency and blood pressure was measured with a mercury sphygmomanometer. Diastolic blood pressure was defined at Korotkoff V. Quality of life was assessed by the Inventory of Subjective Health. This validated questionnaire consists of 47 yes/no questions (310-311). The lower the score, the higher the perception of well-being. Patients were asked to judge their subjective well-being over the last 2 weeks. Only spontaneously mentioned adverse effects were registered by the physician. Patients were not asked for any particular complaint. At the end of the observation period, patients were asked which period they preferred for continuation of their treatment. Subsequently, the treatment code was broken by the treating physician, and the drug given in the preferred period was prescribed.

Statistical methods

Data are presented as mean ± S.E.M. Measurements at the end of each 8-week treatment period were used for statistical comparison. Statistical analysis was performed according to the nonparametric Koch procedure for the two-way crossover design using the Mann-Whitney U test (297). Apart from "efficacy" analysis on all patients who completed the study, an intention-to-treat analysis was performed according to the "last observation carried forward" principle (343). Data from the intention-to-treat analysis are presented. A p-value lower than 0.05 was considered as significant.

results

Nine patients did not complete the study (Table 3.6). One patient had an overt lack of compliance during bisoprolol treatment and was therefore excluded from the study and study-analysis. Eight patients dropped out because of side effects. Seven of them during treatment with enalapril and 1 during bisoprolol.

Table 3.6. Dropouts

	patient number	treatment period	reason of dropout
	(1)	1	withdrawal of consent
during bisoprolol	(2)	2	tiredness, arrhythmia
during enalapril	(3)	1	headache, dizziness
	(4)	1	edema
	(5)	1	headache, dizziness, gastric pain, impotency, intolerance for alcohol
	(6)	1	cough, gastric and throat pain
	(7)	2	dizziness
	(8)	2	dizziness, palpitations
	(9)	2	dyspnoea

The "intention-to-treat" population contained 53 patients, while the "efficacy analysable population" - all patients who completed the study - consisted of 45 patients.

Neither in the efficacy analysis nor in the intention-to-treat analysis was any carry-over effect seen between the two crossover periods. Apart from a period effect ($p < 0.04$) in supine diastolic blood pressure in the efficacy analysis - which was not present in the intention-to-treat analysis - no period effects were seen between the two crossover periods. No qualitative differences in treatment effects were present between the efficacy and intention-to-treat analysis. This means that a statistically significant difference in treatment effect in the efficacy analysis was also statistically significant in the intention-to-treat analysis and vice versa.

Figure 3.7 shows the data on blood pressure. Standing blood pressure decreased similarly from 161 ± 2/104 ± 1 mmHg to 143 ± 3/91 ± 2 mmHg during enalapril and 145 ± 3/89 ± 1 mmHg during bisoprolol. Supine blood pressure decreased from 163 ± 2/102 ± 1 mmHg to 148 ± 3/90 ± 1 and 144 ± 3/86 ± 1 mmHg during enalapril and bisoprolol, respectively. Supine diastolic blood pressure was lower ($p < 0.02$) during bisoprolol than during enalapril.

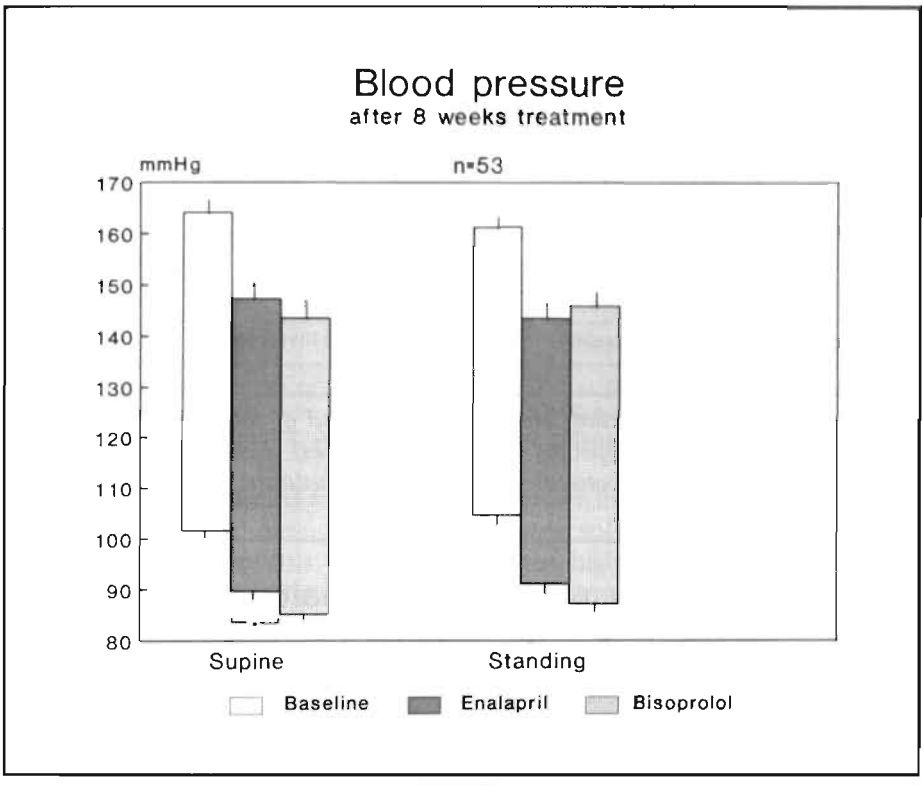

*Fig 3.7. Supine and standing systolic and diastolic blood pressure at the end of the run-in period and during enalapril and bisoprolol treatment (8 weeks). Data are mean ± SEM. * $p < 0.02$, difference between bisoprolol and enalapril treatment.*

Heart rate (Figure 3.8) was 84 ± 2 b/min in upright position and 78 ± 2 b/min in supine position. During bisoprolol, heart rates were lower ($p < 0.001$) in both standing (66 ± 2 b/min) and supine position (63 ± 1 b/min) compared to those during enalapril (79 ± 2, 73 ± 2 b/min, respectively).
Figure 3.9 shows scores of well-being as measured with the Inventory of Subjective Health. Scores were 15.8 ± 1.0 at baseline and did not differ between enalapril (14.7 ± 1.1) and bisoprolol (14.0 ± 1.1). The 95 % confidence intervals of the differences in well-being scores between bisoprolol and enalapril ranged from -0.65 to 2.15. The retrospectively calculated power to detect a difference in quality of life score between the 2 drugs was 17 %.

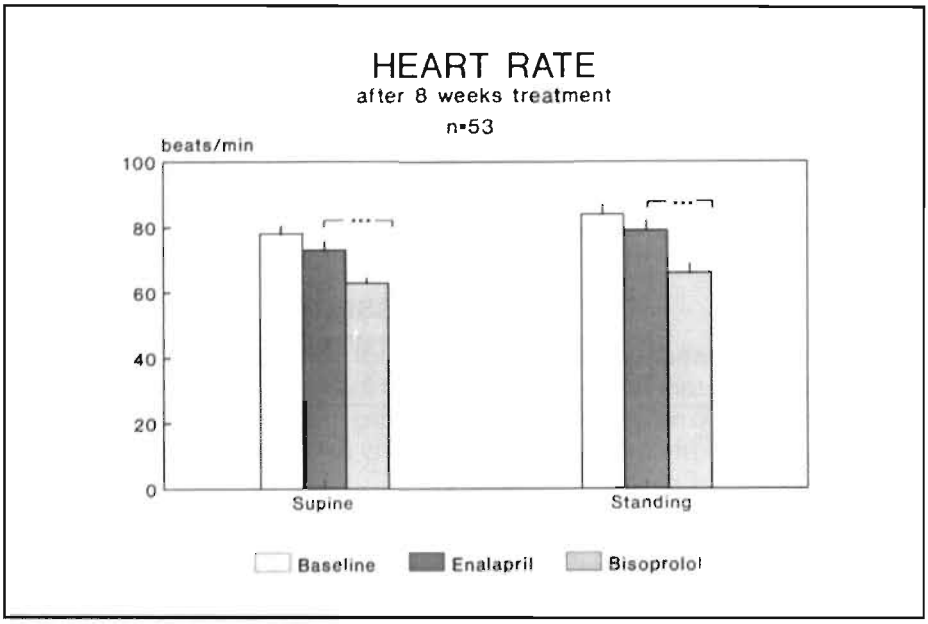

*Fig. 3.8. Supine and standing heart rate at the end of the run-in period and during enalapril and bisoprolol treatment (8 weeks). Data are mean ± SEM. *** $p < 0.001$, difference between bisoprolol and enalapril treatment.*

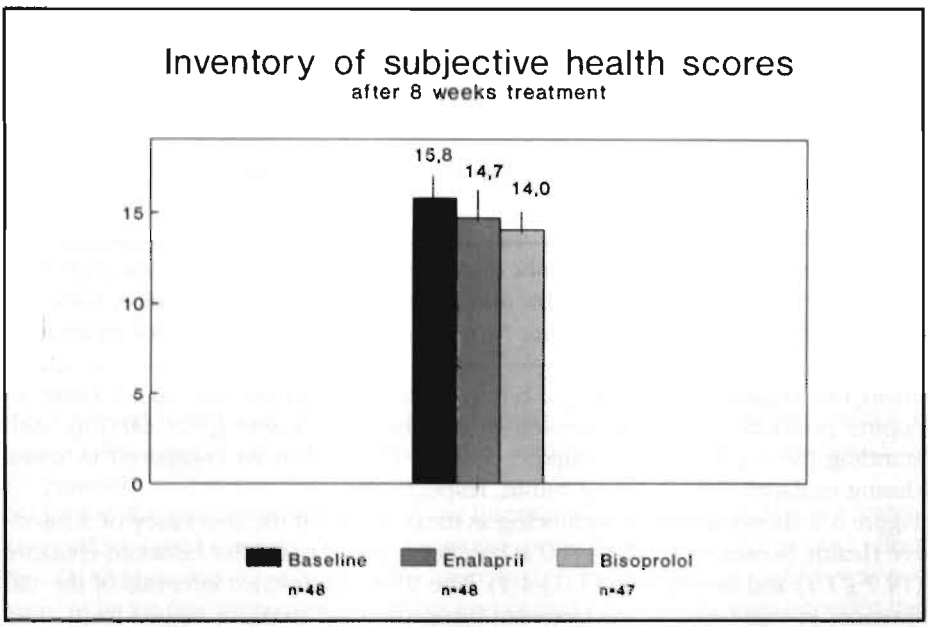

Fig. 3.9. Subjective well-being scores as measured by the inventory of subjective health at the end of the run-in period and during enalapril and bisoprolol treatment (8 weeks). Data are mean ± SEM; the lower the score, the higher the subjective well-being.

Table 3.7. Adverse effects

	run-in	enalapril	bisoprolol
fatigue	3	10	6 (7)
headache	4	7 (9)	1
dizziness	0	2 (4)	4 (6)
gastroenteric	0	2 (3)	2
throat complaints	0	3 (4)	1
cough	0	3 (4)	0
nervousness	1	2	1
palpitations	0	1	0 (2)
dyspnoea	0 (1)	1 (2)	1 (2)
sexual disturbances	0	1 (2)	0
other complaints	1	8 (10)	7
TOTAL	9 (10)	40 (51)	23 (29)

Figures represent the number of patients with a complaint in the efficacy analysable population (n = 45). Figures in brackets show the number of patients with a complaint in the intention-to-treat population (n = 53) if different from the efficacy analysable population.

Spontaneously mentioned adverse effects are shown in Table 3.7. Total number of complaints increased during enalapril and bisoprolol versus baseline. However, the number of complaints during enalapril was higher than during bisoprolol. During enalapril, headache and cough were regularly mentioned. Complaints of fatigue were also more frequent during enalapril than during bisoprolol. Slightly more dizziness was reported during bisoprolol treatment.
Fourty-five patients completed the study. At completion 31 patients preferred bisoprolol treatment and 11 preferred enalapril treatment. Three patients gave no preference for either drug (Figure 3.10).

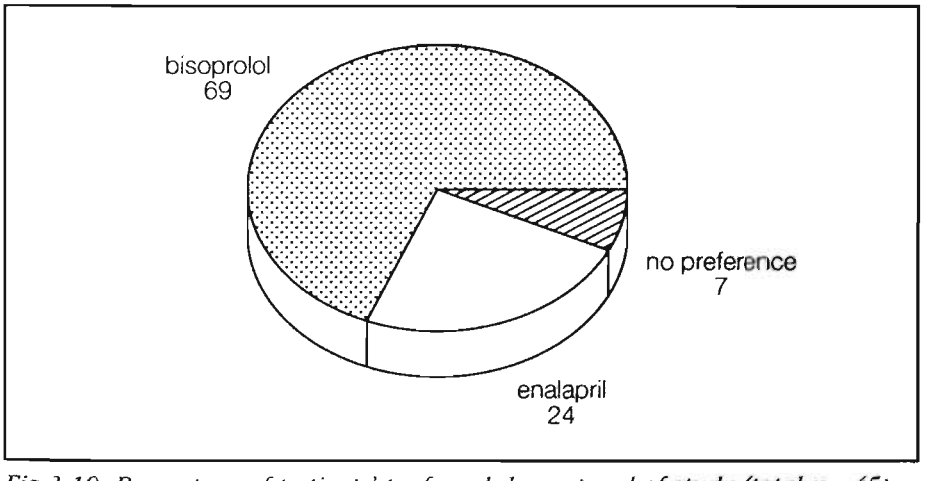

Fig 3.10. Percentage of patients' preferred drug at end of study (total n = 45).

At the end of the run-in period serum creatinine and random glucose levels averaged 91 ± 4 μmol/l and 5.5 ± 0.1 mmol/l respectively. Serum sodium was 141 ± 0.3 mmol/l and serum potassium 4.2 ± 0.1 mmol/l. In all 4 parameters, no clinically relevant changes were found during the observation period. Body weight was 82 ± 2 kg at baseline and did not change throughout the study.
Apart from a lower heart rate during bisoprolol, no clinically relevant changes in ECG were noted between the two treatment periods.

discussion

The decrease in blood pressure was at least as great with bisoprolol as with enalapril. Supine diastolic blood pressure was even lower during bisoprolol than during enalapril. A partial contribution of a slight period effect - present in the efficacy but not in the intention-to-treat analysis - in this difference cannot be excluded. As expected for a beta-adrenoreceptor antagonist, bisoprolol decreased heart rate significantly compared to enalapril.
Eight patients dropped out because of side effects. Only 1 patient dropped out during bisoprolol treatment. Patient 8 (Table 3.6) dropped out early in the second treatment period (enalapril) because of different complaints. One of them was palpitations, which might also be a bisoprolol withdrawal effect. Patient 9 dropped out during enalapril, but had already complaints of dyspnoea during bisoprolol treatment and even during the run-in period.
The adverse effects of ACE-inhibitors, such as cough, throat complaints and headache - were more often present during enalapril treatment. Fatigue is a well-known side effect of classical beta-blockers. It is remarkable that fatigue was more frequently reported during enalapril than during the highly selective beta-blocker bisoprolol. Dyspnoea and sexual disturbances were less frequently present during bisoprolol. The total number of side effects was much higher during treatment with either agent than at baseline. This is in contrast to the results of the quality of life score. A possible explanation could be that at the end of the run-in period the physician did not interpret a complaint as an adverse effect. The total number of spontaneously mentioned complaints was lower during bisoprolol than during enalapril. It is not clear whether this is due to fewer or less severe side effects or due to a better subjective well-being perception.
In a study with a crossover design, difference in overall quality of life scores between ketanserin and placebo was shown with only 17 patients (337). Therefore, the crossover approach has been suggested useful with agents that have no carry-over effect (338). The present comparative study uses the crossover design with a sample size of 54 patients, which is 3 times that of the above-mentioned placebo-controlled study. No carry-over effect was present as measured with the Koch procedure for the two-way crossover design.
The quality of life score, as measured with the Inventory of Subjective Health, was better during treatment with bisoprolol and enalapril than at the end of the run-in period. The results for enalapril are in accordance with other studies, where global scores of quality of life were improved with enalapril versus baseline (313,341). This improvement versus baseline might - at least in part - be due to the participation in the trial (339). A real improvement in quality of life can only be proven in a placebo-controlled study. In the present study, no statistically significant difference in quality of life scores was observed between the two drugs. This is in

accordance with results of other recent studies, comparing quality of life during treatment with the selective β_1-adrenoceptor antagonist atenolol versus an ACE-inhibitor (341,344). However, in the present study, the score of the Inventory of Subjective Health even tended to be somewhat better during bisoprolol treatment than during enalapril. A larger sample size might provide a statistically significant difference. Since - with the sample size used- retrospectively, the power of the test to detect a difference in score between the 2 drugs is not more than 17 %, the sample size needed for 80 % power has to be substantially larger. Moreover, a small but statistically significant difference does not imply clinical relevance. The fact that 31 (69 %) of the 45 patients, who made a blinded treatment choice at completion of the study, have selected the bisoprolol treatment period, and that less adverse effects were reported during bisoprolol, suggests that the slightly (but not statistically significant) better quality of life score during bisoprolol might be of clinical relevance.

In conclusion: in patients with mild-to-moderate hypertension, bisoprolol decreased blood pressure at least as well as enalapril. At the dosages used, bisoprolol had less side effects than enalapril. The well-being score during bisoprolol treatment tended to be better than during enalapril and more patients mentioned to feel better during bisoprolol. This study does not confirm the assumption that ACE-inhibitors may cause fewer side effects than beta-blocking agents, and certainly not than selective β_1-blockers.

chapter 3. Exercise tolerance during antihypertensive treatment[3]

introduction

Beta-blocking agents are widely used in the treatment of hypertension and cardiac diseases. Patients treated with these drugs often complain of fatigue during exercise. Maximal exercise capacity (345-349) and endurance performance (314-320) are diminished during beta-adrenoceptor blockade in hypertensive as well as in normotensive subjects. Drug-induced changes in haemodynamics predominantly influence maximal exercise capacity, altough metabolic effects play an important role during endurance performance (350). A decreased exercise performance can alter the quality of life of physically active patients. On the other hand, beta-blocking agents can increase exercise capacity in patients with angina pectoris by delaying pain and other ischaemic signs. These anti-ischaemic effects of beta-blocking drugs are outside the scope of this study.

Nebivolol is a newly developed selective $beta_1$-adrenoceptor antagonist with a particular haemodynamic profile. This profile has been described in chapter 1. In hypertensive patients, the antihypertensive effect of nebivolol 5 mg once daily was greater than that of 2.5 mg once daily. Ten mg/day did not enhance the antihypertensive effect (303-304).

In this study, the effects of nebivolol on maximal and endurance exercise performance were compared with those of atenolol. The haemodynamic and metabolic effects of the two drugs during exercise were also studied. Since atenolol and nebivolol are antihypertensive drugs, comparison of dosages, inducing a similar blood pressure lowering effect at rest, is clinically relevant.

In a pilot study, atenolol 100 mg and nebivolol 5 mg once daily decreased blood pressure equally in healthy subjects. The equipotent antihypertensive effect of atenolol 100 mg and nebivolol 5 mg once daily has also been shown in hypertensive patients by means of 24-hour ambulatory blood pressure monitoring (351).

subjects and methods

Subjects

Before the study,volunteers underwent a progressive maximal exercise test for determination of maximal aerobic work capacity (W_{max}) on a bicycle ergometer. Females started the exercise test at 50 W, while males started at 100 W workload for 5 minutes. Subsequently, workload was increased every 3 minutes by 50 W (or 25 W if heart rate was more than 160 beats/min), until exhaustion. Volunteers who were able to perform an endurance exercise test (at 70 % of the predetermined W_{max}) for at least 30 minutes were selected.

Twenty-one apparently healthy volunteers entered and completed the study. Volunteers (males 15; females 6) were 23 ± 1 yr (19-31 yr); their weight was 71 ± 2 kg (53-86 kg) and their height was 178 ± 2 cm (160-192 cm). In all volunteers serum levels of liver enzymes were less than 3 times the upper limit of normal and serum creatinine was < 115 μmol/l. Volunteers were active in sports at least on a recreational level. Their maximal aerobic exercise capacity ranged from 160 to 367 W.

[3] based on: LMAB Van Bortel, MA van Baak. Exercise tolerance with nebivolol and atenolol. Cardiovasc Drugs Ther 1992, 6:339-247.

Study design

Volunteers entered a double blind placebo-controlled three-way crossover study and were given in random order nebivolol (solution) 5 mg, atenolol (tablets) 100 mg, and placebo once daily for 2 weeks each, following the double dummy technique. Between treatment periods, there was a 3-week drug-free wash-out period. Atenolol and placebo tablets as well as nebivolol and placebo solution were identical in appearance. On day 10 of each treatment period, volunteers performed a progressive maximal exercise test. On day 14 a submaximal endurance test until exhaustion (at 70 % of predetermined W_{max}) was performed on a bicycle ergometer (Lode, Groningen, The Netherlands). Exhaustion was defined as the moment at which pedalling rate could not be maintained above 50 rpm. Exercise tests were performed when peak effects of atenolol and nebivolol were anticipated, 3-4 hours after the last administration of the drug. Exercise tests in each subject were also carried out on the same time of the day. Volunteers were asked to keep all factors - and especially physical exercise - as constant as possible throughout the whole study period. In addition, subjects were asked not to consume alcohol, coffee, or nicotine on the day of the test and to avoid strenuous physical exercise during 24 hours preceding the test. Volunteers were also asked to take a small meal 2 hours before the test. The study was approved by the Ethical Committee of the University of Limburg. All volunteers gave their written informed consent. Volunteers were asked about their compliance. Volunteers' compliance was also checked by counting tablets and by measuring plasma levels of the drugs.

Protocol of the maximal exercise test

After cannulation of an antecubital vein blood was drawn for baseline analysis. Resting blood pressure and heart rate were measured in sitting position after 10 minutes of rest. Exercise started at 100 W or 50 % of the predetermined maximal work capacity (W_{max}) if < 100 W for 6 minutes. Subsequently, workload was increased with 10 % of predetermined W_{max} every 3 minutes until exhaustion. At 100 W or 50 % of predetermined W_{max} blood pressure was measured and cardiac output was assessed using the CO_2 rebreathing technique (352-353). Variation of this technique is less than 5 % during exercise (354-355).
Throughout the test minute ventilation (V_E), O_2 consumption (VO_2) and respiratory exchange ratio (R) were measured continuously and averaged per 30 s. During the last 30 s of each work load, at exhaustion and after 3 min recovery, systolic blood pressure (up to 80 % W_{max}), heart rate and perceived exertion were measured and venous blood was drawn for determination of lactate, glucose, potassium, glycerol and non-esterified fatty acid (NEFA) concentrations.

Protocol of the submaximal endurance test

After cannulation of an antecubital vein blood was drawn for baseline analysis. Resting blood pressure and heart rate were measured in sitting position after 10 minutes of rest. Submaximal exercise at 70 % of the predetermined maximal work capacity was performed until exhaustion or for 90 min. At regular time intervals (5, 10, 15, 20, 30, 40, 50, 60, 70, 80 and 90 min) during exercise, at exhaustion, and at min 3, 6 and 10 during recovery, systolic blood pressure, heart rate and perceived exertion were measured and blood was drawn for determination of

haemoglobin, haematocrit, potassium, glucose, glycerol, NEFA and lactate. From changes in haemoglobin and haematocrit, changes in plasma volume during exercise were calculated according to Costill and Fink (356).

Methods

Heart rate (HR) was measured by ECG and blood pressure with a mercury sphygmomanometer (resting diastolic blood pressure: Korotkoff V; diastolic blood pressure at 100 W or 50 % W_{max} exercise: Korotkoff IV). Minute ventilation (V_E), oxygen consumption (VO_2), respiratory exchange ratio (R) and cardiac output (Q; CO_2 rebreathing) were measured with an automated device (Eos sprint, Jäger, Freiburg, Germany). Perceived exertion was measured using the Borg scale (357). Blood was immediately centrifuged for 1 min. Serum and plasma were rapidly frozen in dry ice and stored at -70°C until assayed. Plasma levels of glucose and lactate (Cobas auto-analyzer) and serum levels of glycerol (a modification of the triglyceride (Neutralfett) test combination Boehringer Mannheim) were measured enzymatically. Serum NEFA concentrations were determined colorimetrically (358). Plasma levels of K^+ were determined by flame photometry (Instrumentation Laboratory 243). Plasma levels of atenolol and nebivolol were determined at baseline (3 hours after the last administration of the drug) and assayed by HPLC (359-360).

Data analysis

Data are presented as mean ± S.E.M. Data in figures are shown by bars and curves. X-axis of maximal exercise curve figures show data at rest, at 100 W and at increasing workloads, expressed as percentage of the predetermined W_{max}. X-axis of endurance exercise curve figures is a time axis, representing the number of minutes cycled by the subjects. Bars and curves show means of all 21 volunteers. This means that in each crossover period all volunteers cycled up to 80 % or more of their predetermined W_{max} during the maximal exercise test and for at least 20 minutes during the endurance test. The last point during exercise is the value at exhaustion, which is shown at the appropriate average workload or exercise time. Recovery starts at exhaustion. Therefore, values representing exhaustion and 0 minutes of recovery are identical.

Statistical analysis was performed by non-parametric analysis of variance and Zerbe's randomization test for curves (361) with Scheffe's procedure for intergroup comparison. $P < 0.05$ was considered statistically significant. The following calculations were made: stroke volume (SV) = Q/HR; mean arterial pressure (MAP) = diastolic blood pressure (DBP) + 1/3 (systolic blood pressure (SBP) - DBP); total peripheral resistance (TPR) = MAP/Q.

results

No major changes in volunteers' physical activity were reported during the study. Volunteer compliance was good as measured by counting tablets (never less than 13 tablets were taken during the 14-day period), measuring solution volume and by detection of atenolol and nebivolol in plasma samples. All volunteers had detectable plasma levels of atenolol and nebivolol in the appropriate period. Plasma levels of atenolol ranged from 129 to 959 ng/ml. Apart from 3 subjects with higher nebivolol plasma levels (8.5, 14.6, and 17.8 ng/ml, respectively), plasma

levels of nebivolol ranged from 0.17 to 3.07 ng/ml. Data on resting blood pressure and heart rate are shown in Fig 3.11. Mean arterial pressure (MAP) at rest was 91 ± 1 mmHg (SBP: 118 ± 3 mmHg; DBP: 77 ± 1 mmHg) and decreased ($p < 0.01$) similarly during atenolol (83 ± 2 mmHg) and nebivolol (84 ± 2 mmHg). Heart rate was 82 ± 4 b/min during placebo and decreased ($p < 0.001$) during atenolol (62 ± 2 b/min) and nebivolol (68 ± 3 b/min).

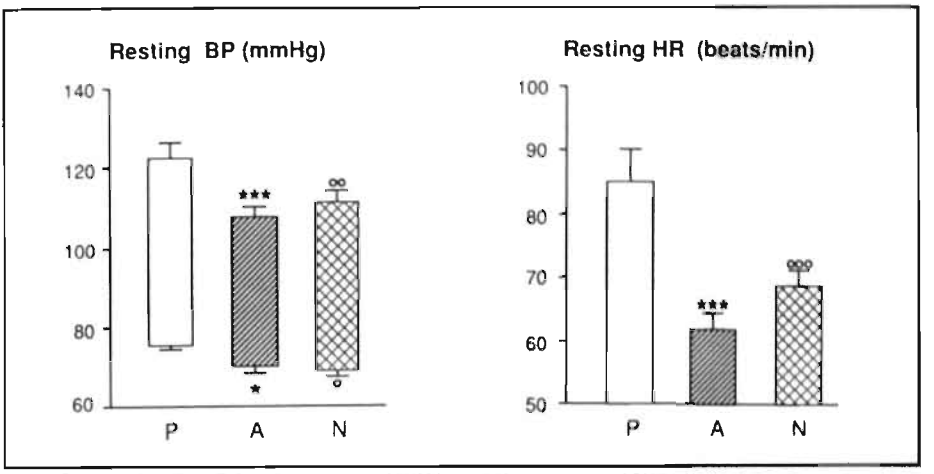

Fig. 3.11. Resting blood pressure (BP) and heart rate (HR) for placebo, atenolol and nebivolol. □ *placebo ;* ▨ *atenolol ;* ▩ *nebivolol ;* $*p < 0.05$, $***p < 0.001$ *(atenolol-placebo) ;* $°p < 0.05$, $°°p < 0.01$, $°°°p < 0.001$ *(nebivolol-placebo).*

Haemodynamics during exercise at 100 W are shown in Table 3.8. MAP and heart rate decreased ($p < 0.005$) during atenolol and nebivolol at 100 W exercise. The atenolol induced heart rate reduction was larger ($p < 0.005$) than that due to nebivolol. At 100 W exercise, stroke volume increased ($p < 0.001$) similarly during atenolol and nebivolol. In contrast to atenolol, nebivolol tended (ns) to increase cardiac output. Nebivolol decreased ($p < 0.03$) calculated total peripheral resistance during exercise (100 W).

Table 3.8. Haemodynamics during exercise at 100 W (mean ± S.E.M.)

	Placebo	Atenolol	Nebivolol
Heart rate ($b.min^{-1}$)	121 ± 4	94 ± 3*	102 ± 3°°
Systolic BP (mmHg)	153 ± 4	134 ± 3*	138 ± 3°
Diastolic BP (mmHg)	75 ± 3	71 ± 2	70 ± 2
Mean arterial pressure (mmHg)	101 ± 3	92 ± 2*	92 ± 2°
Cardiac output ($l.min^{-1}$)	14.3 ± 0.6	14.2 ± 0.8	15.0 ± 0.8
Stroke volume (ml)	121 ± 6	156 ± 11*	152 ± 11°
Total peripheral resistance ($mmHg.min.l^{-1}$)	7.2 ± 0.2	6.8 ± 0.3	6.5 ± 0.3°

* Significant difference between placebo and atenolol; ° Significant difference between placebo and nebivolol; ° Significant difference between atenolol and nebivolol

Systolic blood pressure and heart rate curves during exercise are shown in Fig 3.12. Rise in systolic blood pressure was significantly smaller with atenolol than with nebivolol during endurance performance and tended to be smaller during maximal exercise. Exercise-induced tachycardia was less depressed with nebivolol than with atenolol during maximal and endurance exercise. Maximal heart rate averaged 187 b/min during placebo and decreased to 161 b/min with nebivolol (14 %) and 140 b/min with atenolol (25 %).

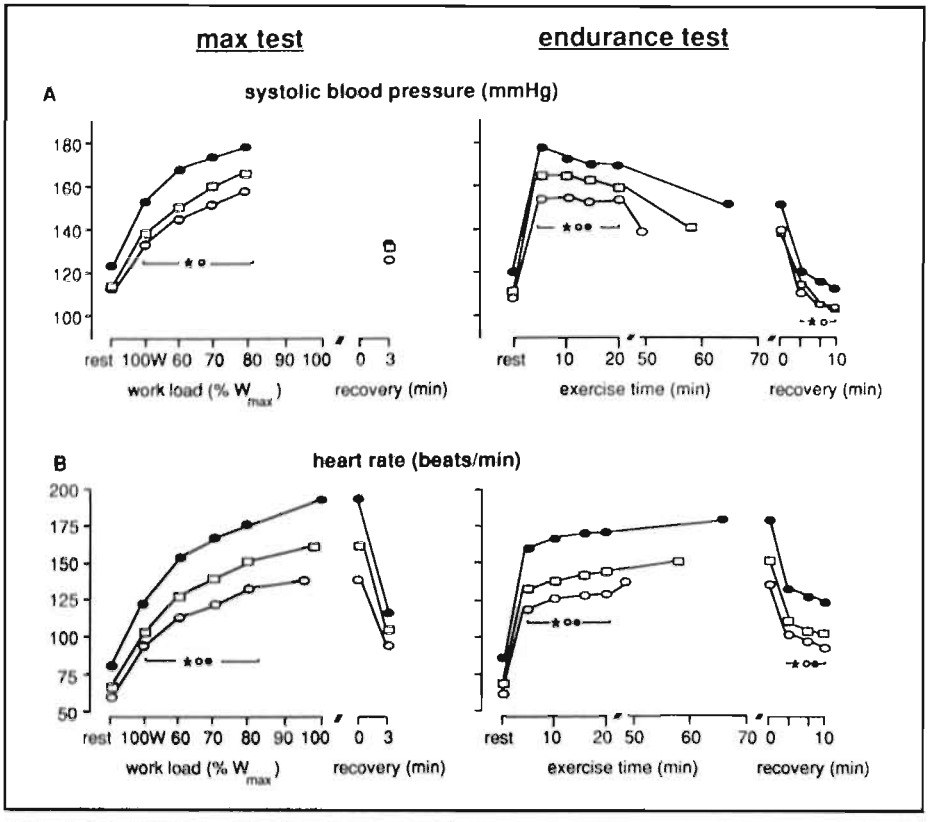

*Fig. 3.12. Systolic blood pressure and heart rate curves during maximal and endurance exercise tests. ● placebo ; ○ atenolol ; □ nebivolol. Significant difference between: *atenolol-placebo, °nebivolol-placebo, °atenolol-nebivolol. Fig. A: SEM did not exceed 6 mmHg for placebo and nebivolol and 5 mmHg for atenolol. Fig. B: SEM did not exceed 5 beats/min for placebo and 3 beat/min for atenolol and nebivolol.*

Maximal work load was 263 ± 15 W during placebo, 251 ± 15 W during atenolol ($p < 0.02$) and 256 ± 16 W during nebivolol (n.s.). VO_{2max} was 3.40 ± 0.17 l/min during placebo and was decreased ($p < 0.03$) during atenolol (3.22 ± 0.19 l/min) and was 3.37 ± 0.19 l/min (n.s.) during nebivolol (Fig 3.13). Submaximal endurance time was reduced from 65 ± 5 min during placebo to 50 ± 5 min during atenolol ($p < 0.001$) and was not significantly affected during nebivolol (61 ± 5 min) (Fig 3.13).

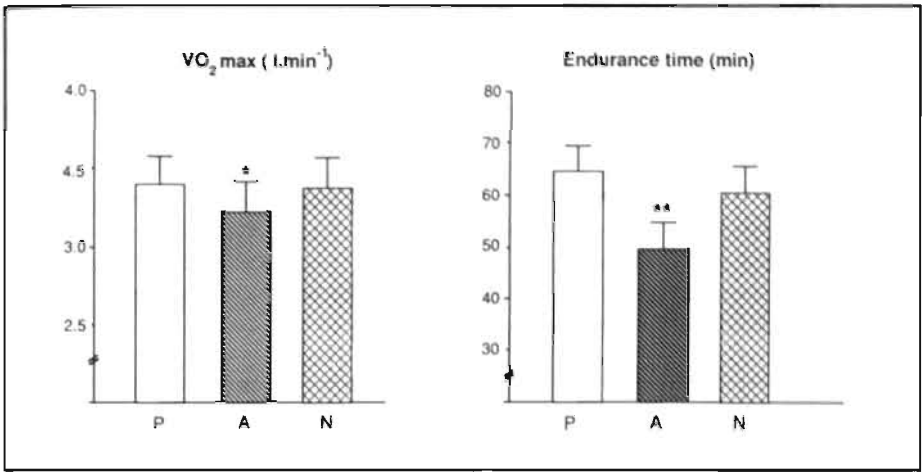

Fig. 3.13. Maximal oxygen consumption (VO_{2max}) and endurance exercise time during placebo, atenolol and nebivolol. □ *placebo ;* ■ *atenolol ;* ▩ *nebivolol* $^{*}p < 0.05$, $^{**}p < 0.01$ *(atenolol-placebo).*

During maximal exercise testing, no significant differences in perceived exertion rating (RPE) (Fig 3.14) curves were seen between placebo, atenolol and nebivolol. During endurance exercise RPE curves did not differ between placebo and nebivolol, but RPE was significantly ($p < 0.02$) increased with atenolol.

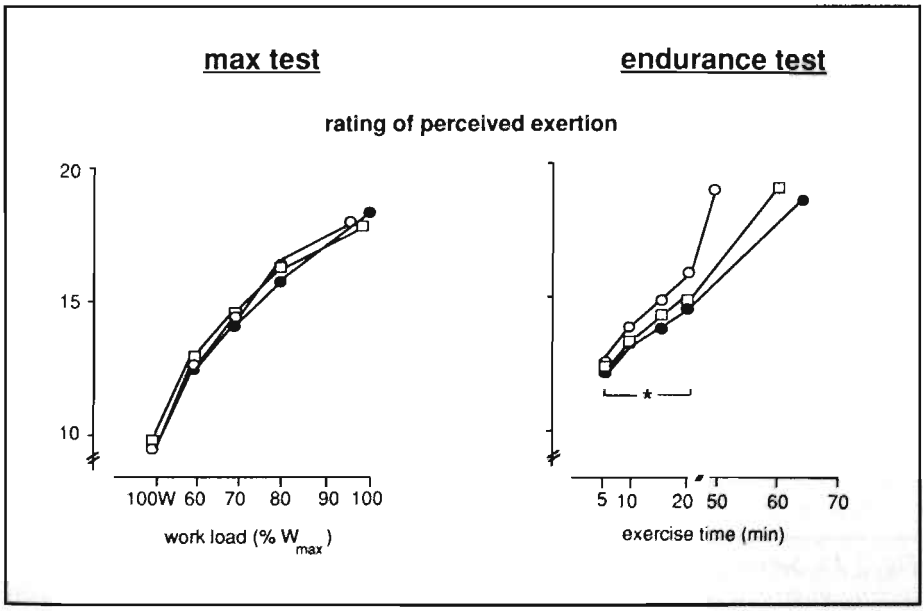

Fig. 3.14. Rating of perceived exertion measured with the 20-point Borg scale during maximal and endurance exercise tests. ● *placebo ;* ○ *atenolol ;* □ *nebivolol. Significant difference between:* **atenolol-placebo. SEM did not exceed 0.5 for placebo, atenolol and nebivolol.*

Serum NEFA and glycerol concentration curves are shown in Fig 3.15. During recovery of endurance exercise, NEFA and glycerol concentrations were reduced during atenolol and nebivolol as compared to placebo. These reductions tended to be more pronounced during atenolol than during nebivolol. Plasma potassium concentrations (Fig 3.16) during endurance exercise were significantly higher during atenolol than during placebo and nebivolol ($p < 0.02$). Although lactate concentration curves did not differ during exercise, lactate concentrations at maximal exercise were lower during atenolol (10.0 ± 0.6 mmol/l; $p < 0.05$) and nebivolol (10.3 ± 0.7 mmol/l; n.s.) than during placebo (11.6 ± 0.8 mmol/l). Changes in plasma volume during exercise and plasma concentrations of sodium and glucose did not differ between the 3 groups.

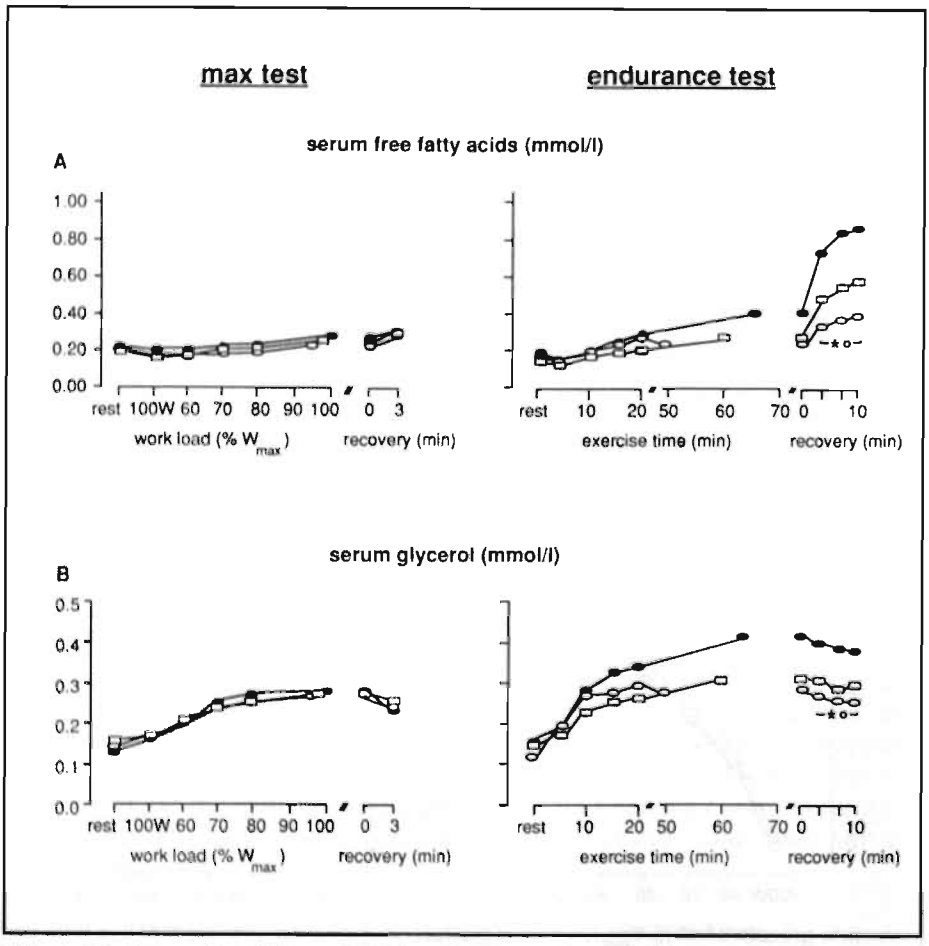

Fig. 3.15. Serum free fatty acid (A) and serum glycerol (B) concentration curves during maximal and endurance exercise tests. ● *placebo ;* ○ *atenolol ;* □ *nebivolol. Significant difference between:* **atenolol-placebo,* °*nebivolol-placebo. Fig. A: SEM did not exceed 0.08, 0.03 and 0.07 mmol/l for placebo, atenolol and nebivolol respectively. Fig. B: SEM did not exceed 0.03, 0.04 and 0.02 mmol/l for placebo, atenolol and nebivolol respectively.*

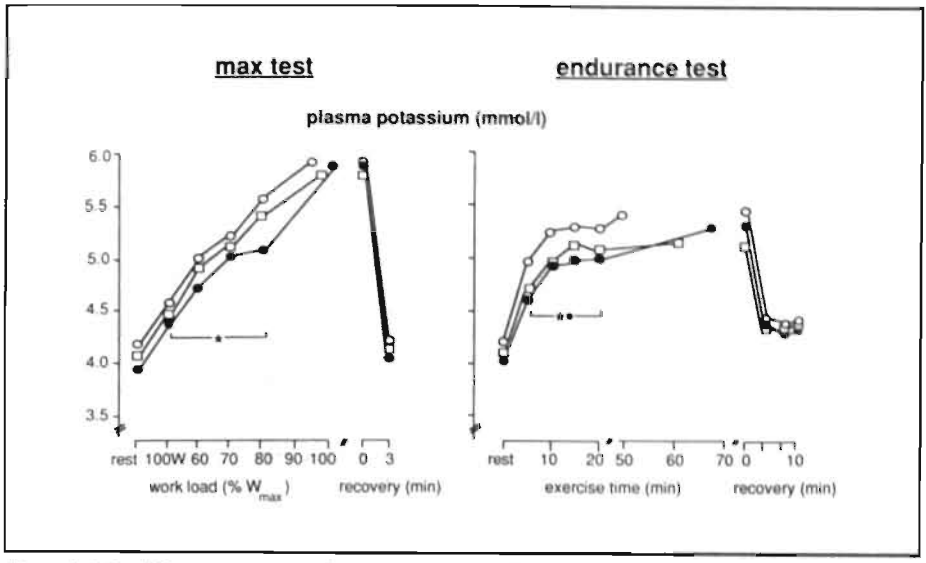

*Fig. 3.16. Plasma potassium concentration curves during maximal and endurance exercise tests. ● placebo ; ○ atenolol ; □ nebivolol. Significant difference between: *atenolol-placebo, *atenolol-nebivolol. SEM did not exceed 0.1 mmol/l for placebo, atenolol and nebivolol.*

discussion

As stated in the introduction, the aim of this study was to investigate the reduction in exercise capacity, a well-known and - for physically active patients - disturbing side-effect of classical beta-blocking drugs. This study did not investigate the - for patients with angina pectoris - beneficial effect of beta-blocking drugs on exercise time by delaying pain and other symptoms of heart ischaemia.

Volunteers' heart rate at rest was relatively high during placebo. This might at least in part be explained, on the one hand, by the position of the volunteer and timing of the measurement - immediately before starting the exercise test with the volunteer already sitting on the bicycle ergometer - and, on the other hand, by the volunteer study population - all volunteers were familiar with physical exercise, but the majority were not well-trained athletes. Based on plasma levels of nebivolol, 2 volunteers are probably poor metabolizers for nebivolol while 1 might be an intermediate metabolizer. This is in accordance with the incidence of poor metabolizers for debrisoquine in the general population (362).

This study shows that in apparently healthy subjects nebivolol 5 mg once daily and atenolol 100 mg once daily cause an equivalent decrease in resting blood pressure. In contrast, atenolol tended to reduce heart rate at rest more than nebivolol.

Maximal exercise capacity is reduced during beta-adrenoceptor blockade in normotensive as well as in hypertensive subjects (345-349). This reduction ranged from 2-15 % (363). In confirmation of these observations, in this study maximal work capacity was statistically significantly decreased (5 %) during atenolol treatment, but was not reduced during nebivolol.

Since, during normal and recreational physical activity, maximal work capacity will usually not be reached, a small decrease in maximal work capacity does not need

to alter the perception of the quality of life. However, reduced exercise endurance performance at submaximal exercise may alter the quality of life in physically active patients. Reduction in endurance capacity during beta-adrenoceptor blockade has been well documented (314-320). In this study atenolol decreased endurance time significantly (23 %). In contrast to classical beta-adrenoceptor blocking drugs, nebivolol did not decrease (6 %) endurance time significantly in healthy volunteers. Since in previous studies with classical beta-blockers no difference in effect on exercise capacity has been found between normotensive and hypertensive subjects (363), for nebivolol similar results might be expected in hypertensive patients. The effect of different antihypertensive drugs on exercise endurance performance is summarized in Fig. 3.17. In 8 studies (314-315, 317-319, 364-366) with non-selective ß-blockers (propranolol, pindolol, nadolol), the decrease in endurance time ranged from 25 to 51 % and was on average 40 %. During selective ß-blockade (315-317,319-320,365 and present study) with atenolol, metoprolol, or epanolol, decrease in endurance time was 26 % (14-39 %). Two studies are published on the calcium-antagonist verapamil. One study mentioned a 16 % reduction (364), the other (320) a reduction in endurance time of 7 % (mean of the 2 studies: 11 %). Endurance time reduction was 3 and 12 % with enalapril and 9 % with captopril (320,367-368); mean of the 3 studies with ACE-inhibitors: 8 %. The reduction in endurance time during nebivolol was comparable with that during antihypertensive treatment with calcium-antagonists and ACE-inhibitors. Complaints related to a small decrease in endurance exercise capacity are not common during treatment with calcium-antagonists and ACE-inhibitors. This suggests that during nebivolol, quality of life might also be pre-

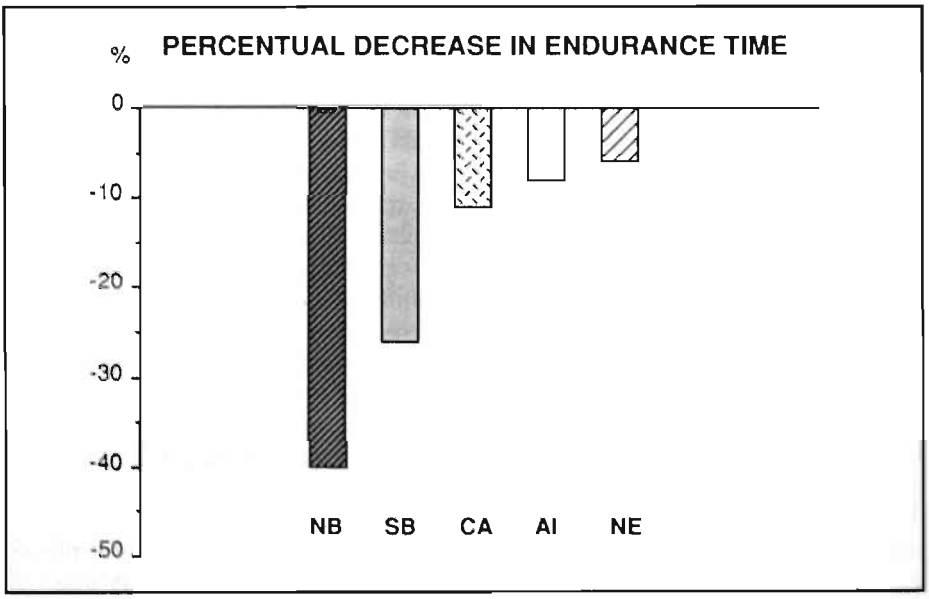

Fig 3.17. Decrease in endurance time during treatment with different antihypertensive drugs. Data are means of different studies. NB, non-selective ß-blockers; SB, selective $ß_1$-blockers; CA, calcium-antagonists; AI, ACE-inhibitors; NE, nebivolol.

served in this respect. This possible difference in effect on quality of life between nebivolol and classical beta-blockers is supported by the results obtained with the Borg scale. Classical beta-blockers increase perceived exertion (347). In the present study atenolol also increased perceived exertion during endurance exercise performance, while nebivolol did not significantly.

In this study, both at rest and at 100 W exercise, mean arterial pressure decreased similarly during atenolol and nebivolol, though heart rate decreased more during atenolol. Stroke volume was similarly increased during atenolol and nebivolol at 100 W exercise. During exercise cardiac output is usually decreased by beta-blocking agents (363). In contrast to our findings in a previous study (349), in the present study, no significant decrease in cardiac output was seen during atenolol at 100 W exercise. However, cardiac output tended to be higher during nebivolol than during atenolol. Total peripheral resistance decreased during nebivolol at 100 W exercise. It is not clear whether this effect was due to less $beta_2$-blockade or to some slight vasodilating properties of nebivolol which might explain why, despite less cardiac beta-blockade, in healthy subjects nebivolol 5 mg daily shows a similar antihypertensive effect as atenolol 100 mg daily.

During endurance exercise at 70 % of the predetermined maximal work capacity (which is a work load > 100 W), not only heart rate but also systolic blood pressure was lower with atenolol than with nebivolol, suggesting a larger degree of beta-blockade with atenolol.

The haemodynamic effects of beta-blockers are thought to play a major role in the alterations of maximal exercise capacity. A positive relationship between % reduction in maximal heart rate and in maximal work capacity has been shown with a threshold at 15-20 % reduction. A maximal heart rate reduction below this threshold did not decrease maximal work capacity (369). In this study maximal heart rate reduction with nebivolol was below the threshold (14 %), while that with atenolol was above the threshold (25 %). This might explain why nebivolol did not change maximal exercise capacity.

During endurance performance metabolic effects play an important role (350). With regard to metabolic aspects, plasma glucose levels during beta-blockade were decreased during exercise in fasted subjects and also during maximal exercise with $beta_2$-blockade (363). In this study, no change in plasma glucose levels was seen. Decreased glucose levels were not expected, since subjects were not fasting and since atenolol and nebivolol are $beta_1$-selective drugs (302).

The literature data on the influence of beta-blockade on plasma lactate during maximal and during endurance exercise are inconsistent. In the present study plasma lactate concentration curves did not differ between placebo, atenolol and nebivolol.

NEFA are an important energy source for skeletal muscle, especially during prolonged exercise (363). Serum levels of NEFA and glycerol are a result of formation by lipolysis and utilization for energy supply and gluconeogenesis. During recovery from exercise, NEFA utilization decreases abruptly, while NEFA production continues for some minutes. Therefore, the increase in serum NEFA concentration during recovery is a measure of lipolysis. Lipolysis is inhibited by beta-blocking drugs. This inhibition was more pronounced during atenolol than during nebivolol. During and after maximal exercise, serum glycerol and NEFA concentrations did not differ between placebo, atenolol and nebivolol. The lack

of increased NEFA levels after maximal exercise suggests that during maximal exercise lipolysis is not important for energy supply.

During beta-blockade, plasma potassium increases during exercise due to a reduced uptake of K^+ in inactive tissues (370). The increase in K^+ concentration appears similar after $beta_1$ and non-selective beta-adrenoceptor blockade (317, 371-372). The loss of potassium during muscle contractions might affect muscle membrane excitability, reduce contractility and increase fatigue (373). In this study plasma potassium was increased during atenolol but not during nebivolol.

This study shows that, at dosages of atenolol and nebivolol which produce a similar blood pressure reduction at rest and at 100 W exercise, nebivolol does not alter maximal work capacity nor endurance performance, nor perceived exertion. These objective (endurance time) and subjective (perceived exertion) findings are unexpected for a beta-blocking drug and suggest that during nebivolol treatment quality of life perception in physically active patients might be preserved. Two explanations for these surprising findings may be considered: a smaller degree of beta-blockade during nebivolol or an ancillary property, as also suggested by previous studies (302). The haemodynamic (heart rate and systolic blood pressure) and metabolic (glycerol and NEFA) effects, and the change in plasma potassium during exercise indicate that, at the dosages used, atenolol has a more pronounced beta-blocking effect than nebivolol. In confirmation of literature data (370), this different degree of beta-blockade might explain the difference in maximal work capacity between nebivolol and atenolol. Although not fully established, such a relationship between the degree of beta-blockade and endurance performance is very likely. This might explain why the well-documented reduction in endurance capacity during beta-blocker treatment does not seem present during treatment with nebivolol because full beta-blockade is not achieved with nebivolol 5 mg once daily. However, an ancillary property, which might influence endurance capacity favorably cannot be excluded. Further investigation is needed to determine the equipotent beta-blocking dosages for atenolol and nebivolol and to investigate the nature of a possible ancillary antihypertensive property of nebivolol.

So far all antihypertensive drugs induced a decrease in endurance performance, albeit not always statistically significant. A small decrease up to 16 % (364) obviously did not result in more complaints of fatigue.

conclusions

The Inventory of Subjective Health

The 2 studies (chapter 1 and 2) showed a good association between the scores of the Inventory of Subjective Health on the one hand and perceived health rates, side effects, dropouts and patients' drug choices on the other hand. This relationship supports the validity of the Inventory of Subjective Health as a measure of general well-being, also during antihypertensive treatment.

The placebo controlled study with nebivolol showed a statistically significant improvement of the ISH-score versus baseline for both nebivolol and placebo. As a consequence this study underlines that an absolute change in quality of life perception cannot be claimed by comparison with baseline, since participation in a trial already influences quality of life perception.

quality of life during antihypertensive treatment

At the dosages used, nebivolol, bisoprolol and enalapril were effective antihypertensive drugs. Nebivolol, a $ß_1$-blocker with vasodilating properties, did not alter quality of life perception. The well-being score during the highly selective $ß_1$-blocker bisoprolol tended to be better than during the ACE-inhibitor enalapril and more patients preferred to be treated with bisoprolol than with enalapril. These studies do not confirm the assumption that all ß-blockers decrease quality of life and that ACE-inhibitors may preserve quality of life more than ß-blocking agents, certainly not more than selective $ß_1$-blockers.

exercise tolerance during antihypertensive treatment

The reduction in endurance performance can influence quality of life of physically active patients. So far all antihypertensive drugs studied, reduce endurance exercise time. However, a reduction of 8-12 % - like with ACE-inhibitors and calcium-antagonists - in general does not result in increased complaints of fatigue. In contrast the complaints of fatigue during ß-blockade are very well known. The reduction in endurance performance depends on the selectivity of the ß-blocker and the dosage used. Regarding nebivolol, a favorable effect of an ancillary property cannot be excluded.

PART IV
GENERAL DISCUSSION: CURRENT ANTIHYPERTENSIVE THERAPY AND ISSUES FOR FUTURE RESEARCH

The goal of antihypertensive treatment is prevention of the ill effects of the elevated blood pressure without impairing quality of life or inducing other cause morbidity and mortality.
Since target-organ damage is associated with marked increases in risk for people with hypertension and since evidence indicates that these aggravated risks are only partially reversible by treatment, a key task is the early detection of high blood pressure - before target-organ damage has occurred - and sustained, intensive, and comprehensive treatment with the objective to prevent the development of target-organ damage (19). Apart from treatment of the elevated blood pressure, management of other risk factors for ill effects of hypertension, like smoking, dyslipidaemia, insulin resistance and emotional stress is helpful. In atherosclerotic disease also antithrombotic agents like aspirin can be useful.
In this part of the thesis current antihypertensive therapy is discussed.

1. which blood pressure to treat?

There is still a lot of debate about which level of raised blood pressure should be treated. On the one hand, studies such as the Australian National Blood Pressure Study (ANBPS; 374) did not provide convincing evidence to treat diastolic blood pressures lower than 100 mmHg. An explanation could be some noxious effect of the drugs, or a lower than expected complication rate in mild hypertension. On the other hand, meta-analysis of nine major trials relating to mild hypertension has demonstrated a 34-40 % lesser incidence of stroke in treated than in control hypertensive patients, while reductions in nonfatal events averaged 10 % and fatal events 8 %, neither change being statistically significant (375).

2. how far should blood pressure be lowered?

There is no consensus that the aim of treatment in patients with hypertension is maximal lowering of blood pressure (376), either because little may be gained beyond a certain level in terms of risk reduction or, more seriously, because risk may increase at lower levels of treated blood pressure (171,377-382). Due to the increased mortality risk of treated diastolic blood pressure below 85 mmHg observed in different studies (171,377-382), the treated blood pressure-risk relation forms a J-shaped curve. However, such a J-shaped curve is not seen in other studies, especially when elderly patients are excluded (177,376). But, in patients with coronary heart disease cardiovascular events were increased at treated diastolic blood pressures below 85 mmHg (383). Since diastolic pressure determines coronary perfusion pressure, a low diastolic pressure might be critical for the oxygen supply in patients with cardiac ischaemia. The strongest evidence against a treatment-induced causal relation comes from the Hypertension in Elderly Patients trial, in which an increased incidence of coronary heart disease was associated with the lowest diastolic pressures (< 80 mmHg). But this increased

risk at the lowest pressures was found in both patients given active treatment and in the untreated controls (383). Thus, it seems that the J-shaped curve exists especially in elderly patients and the increased risk at the lowest blood pressures is not due to the antihypertensive therapy.
There is strong evidence from analysis of large trials in the elderly that J curves are due to the fact that preceding illness lowers blood pressure rather than that lowering the blood pressure precipitates death from coronary heart disease (376). For example, [1] a decrease in blood pressure after myocardial infarction is associated with poor survival (384). Also [2] the high pulse pressure - due to stiff large arteries - is a plausible explanation; subjects with a high systolic pressure and low diastolic pressure are at greater risk for cardiovascular events than the general population (385). A third of the patients in the Systolic Hypertension in the Elderly Program trial had levels of treated blood pressure in this category (isolated systolic hypertension). A reduction in pressure by active treatment reduced the risk (376).
On balance, blood pressure can be decreased without danger to levels of 125/85 mmHg (376). A further decrease might be beneficial. Although many observations indicate that most of the increased risk of the J curve is due to the confounding effect of concomitant illness which lowers blood pressure, it cannot be ruled out that a low diastolic blood pressure might compromise coronary flow in some patients with advanced coronary heart disease.

3. which antihypertensive drug to choose?

3.1. rationale.

3.1.1. effect on risk factors as a discriminating criterion?

Regularly the choice of antihypertensive drugs is argued on the basis of their effects on risk factors for coronary heart disease. A recent extensive report on this issue has been published by Houston (386). In this article the influence of different antihypertensive drugs on 18 risk factors (Table 4.1) was mentioned. In addition, the author calculated a relative risk ratio for each antihypertensive drug by adding the number of known negative influences.

Table 4.1. Cardiovascular risk factors as published by Houston (386)

hypertension	dyslipidaemia	glucose intolerance
exercise	potassium	insulin resistance
magnesium	uric acid	left ventricular hypertrophy
blood viscosity	blood velocity	catecholamines
angiotensin II	antiatherogenic	arrhythmia potential
platelet function	fibrinogen	thrombogenic potential

Apart from the fact that influences mentioned in this article are not always in accordance with other literature data and that no difference has been made between selective and nonselective ß-blockers and calcium-antagonists, also several methodological critiques can be made. [1] It is very unlikely that each listed risk factor should represent a same "risk weight" for coronary heart disease, which is an obligatory condition for simple addition of different risk factors. [2] Risk factors are often not independent. For example, blood viscosity is largely determined by the serum

fibrinogen level. [3] The calculation of the risk ratio did not account for positive or unknown influences. [4] Our knowledge of risk factors is not likely to be complete. For example, little is known about why some patients with high cholesterol levels, or smokers develop less atherosclerosis than others. As a consequence, a risk ratio from an incomplete list might result in completely aberrant results. [5] The clinical significance of drug-induced changes still remains unclear (387).
Different risk calculation formulae have been proposed. For example, the ischaemic heart disease risk formula of Gordon (see appendix; 388), which has been applied to the TAIM study (389), was recently published. Such formulae are clearly more valid than a simple addition of risk factors, since they are derived from large epidemiological studies, such as the Framingham Study (388). But, also these formulae do not face all of the aforementioned critiques, and certainly not the question whether the risk calculation also can be applied to drug-induced changes in risk factors.

Appendix: risk for ischaemic heart disease over the next 8 years.

risk = $(1 + e^{x})^{-1}$
for men: x = 22.41 - 0.49(age) + 0.0032(age^2) - 0.027(SC) - 0.013(SBP) - 0.49(cigs) -0.75(LVH) - 0.25(GI) + 0.0004(SC)(age).
for women: x = 19.31 - 0.35(age) + 0.0021(age^2) - 0.015(SC) - 0.013(SBP) - 0.035(cigs) - 0.43(LVH) - 0.56(GI) + 0.00018(SC)(age).

SC: serum cholesterol (mg/dl); SBP: systolic blood pressure (mmHg), cigs: cigarettes (enter 1 for a smoker, else 0); LVH: left ventricular hypertrophy (enter 1 if diagnosed by electrocardiogram, else 0), GI: glucose intolerance (enter 1 if diabetic, casual blood sugar is over 6.7 mmol/l [120mg/dl], or trace or more sugar in the urine, else 0).

Indeed, there might be substantial doubt about the clinical significance in terms of morbidity and mortality of the observed drug-induced changes. For example, ß-blockers (especially nonselective) may induce an unfavorable lipid profile. Total cholesterol does not change significantly, but triglycerides increase and, maybe more important, in several studies HDL was significantly decreased with nonselective ß-blockers (390). In contrast, the nonselective ß-blockers with intrinsic sympathomimetic activity appear to have less effect on the lipid profile than those without ISA. Paradoxically, despite the potentially adverse changes in the lipid profile, the ß-blockers without ISA, and not those with ISA, provide a persistent reduction in mortality after myocardial infarction (391). Therefore, I have to conclude with Cruickshank (392) that the use of surrogates for coronary heart disease, e.g. coronary risk factors such as plasma lipids, blood sugar and insulin resistance can be dangerously misleading.

3.1.2. major criteria to make a choice.

[1] Most important is the effect of antihypertensive therapy on morbidity and mortality, the so-called hard endpoints. Since in hypertension heart disease is much more common (30,177) and less decreased than stroke by antihypertensive treatment (177), drugs preventing heart disease might bring more progress. In addition, results from interventions with lipid lowering drugs - as discussed in part I -

have taught that drug interventions have to be judged on all cause morbidity and mortality and not on cardiovascular morbidity and mortality alone (239). [2] The effect on quality of life is also very important because it cannot be the aim of therapy to impair quality of life for years and decades in a whole population of asymptomatic patients, while only a part of them might benefit from therapy. The cure should never be worse than the disease. In addition, poor patient compliance with therapy can substantially influence hard endpoints. Compliance may be substantially influenced by drug-induced changes in quality of life (187). [3] Concomitant conditions and diseases may also determine the choice of drug. [4] In the absence of hard endpoints beneficial effects remain speculative. Very careful consideration of the influence on some risk factors might reduce the speculative error of the choice. Cardiac hypertrophy [1] seems to be a key risk factor (part I chapter 2). Other important risk factors might be: progressive atherosclerosis (part I chapter 2), especially when [2] rupture prone weak cholesterol-rich plaques are present, [3] physical stress on large arteries (part II chapter 1) - including stress frequency - and [4] a thrombogenic state (part I chapter 2). Serum cholesterol, glucose intolerance and smoking might increase the risk for these atherosclerosis-associated conditions.

3.2. effect of antihypertensive drugs on criteria for drug choice.

3.2.1. diuretics

effect on hard endpoints. Diuretics are effective against stroke, as shown by different studies such as the Australian National Blood Pressure Study (ANBPS; 393) and the Veterans Administration Cooperative Study (394).

In middle-aged males diuretics had a higher mortality from coronary heart disease than the untreated group (Oslo Study;395) and ß-blocker therapy (MRC and IPPSH, Maphy; 396,397). Also the ANBPS study did not provide evidence for CHD prevention.

hard endpoints in subgroup. In contrast, in elderly hypertensive patients diuretics decreased not only stroke but also incidence and mortality from coronary heart disease (EWPHE study, SHEP study; 398,399). The MRC trial of treatment in older adults confirmed that diuretics, significantly reduced the frequency of myocardial infarction (400). In this trial they were even better than ß-blocker therapy.

quality of life. A meta-analysis on the effect of antihypertensive drugs on quality of life (401) showed that average score on general well-being with diuretics was worse than with ACE-inhibitors, calcium-antagonists and ß-blockers. But diuretics were better than centrally acting α_2-agonists.

3.2.2. ACE-inhibitors

hard endpoints. To date, no morbidity or mortality data are available for hypertensives treated with ACE-inhibitors.

hard endpoints in subgroup. In patients with systolic cardiac dysfunction and overt heart failure ACE-inhibitors lower mortality (CONSENSUS I, SOLVD, V Heft II, SAVE; 67-68,193-194).

speculative beneficial effects.

ACE-inhibitors are also more powerful than other antihypertensive drugs in reducing left ventricular hypertrophy (191). It is not clear whether they are superior to other antihypertensive drugs in primary prevention of cardiac hypertrophy and heart failure in hypertension.

They have potential anti-arrhythmic effects (ischaemic and postinfarction anti-arrhythmic effects have been shown in animal models) and may reduce infarct size (402-405). They might however disturb the cardiac repair process after myocardial infarction (197). In man the lower mortality in patients with cardiac dysfunction during ACE-inhibitor therapy was related to a reduction in the number of sudden deaths (CONSENSUS). This anti-arrhythmic effect might be due to an improved cardiac function, correction of hypokalaemia and hypomagnesiaemia and of the increased levels of catecholamines.
ACE-inhibitors also reduce insulin resistance (406). Diabetics might benefit from ACE-inhibitors, since they improve insulin sensitivity and possibly renal function (406-407).
quality of life. ACE-inhibitors are, in general, well tolerated. But, in contrast to what is generally assumed, they are not superior to selective $ß_1$-blocking agents in preserving quality of life (part III chapter 2, 341,401,408).

3.2.3. calcium-antagonists

hard endpoints. To date no data on primary prevention of morbidity or mortality are available for hypertensives treated with calcium-antagonists. Non-dihydropyridine calcium-antagonists like verapamil and diltiazem, probably reduce mortality after myocardial infarction. But unlike ß-blockers, this effect is only present in patients with a good left ventricular function (DAVIT II, Diltiazem Postinfarcton Trial; 217-218).
The INTACT study (207) showed a significant reduction in new coronary lesions as compared with placebo, in postmyocardial infarction patients. But mortality with nifedipine [n = 12] was higher than with placebo [n = 2]. Dihydropyridine calcium-antagonists are associated with a significant excess of myocardial reinfarction and also with death in the peri-infarction period or in chronic angina (409). A study on chronic angina, published by the United States Food and Drug Administration mentioned a significant 63 % excess of cardiovascular events in the calcium-antagonist studies in comparison with a 24 % decrease in events in ß-blocker studies (410). Among the possible reasons for this finding are increased heart rates and increased levels of angiotensin II and catecholamines (392). This hypothesis has been supported by the results of the HINT trial (411). This trial indicates that the dihydropyridine calcium-antagonist nifedipine, added to a cardioselective ß-blocker, may have a beneficial effect on cardiac ischaemia, while nifedipine alone increased the risk of myocardial infarction.
quality of life. Calcium-antagonists were, on average, somewhat less positive in the preservation of general well-being (401). However, in this meta-analysis no difference has been made between selective and nonselective calcium-antagonists. Dihydropyridines like nifedipine, as monotherapy, are not very well tolerated (412). A recent quality of life study showed that nifedipine retard was associated with more symptomatic complaints and higher discontinuation rate than the ACE-inhibitor cilazapril and the ß-blocker atenolol (408). Side effects of dihydropyridines are vasodilation-related side effects like tachycardia, headache, flushing and oedema (125). Most of these side effects are most predominant at peak plasma level. They can be diminished by decreasing the rate of change in plasma level (413). In this respect calcium-antagonists with a long half-life or controlled release preparations (414) might be of interest.

3.2.4. α-blockers

hard endpoints. There are no data on hard endpoints.

speculative beneficial effects.

They improve the blood lipid patterns, insulin resistance and the calculated risk for CHD (228,415). In hypertensive patients doxazosin reduced platelet aggregation (416), improved fibrinolytic activity and increased tissue plasminogen activity (417). Therefore, they are expected to retard atherogenesis and they might help to prevent acute coronary syndromes.

quality of life. No controlled quality of life studies with α-blockers are available. The main disadvantage is a tendency for postural hypotension. Apart from first dose hypotension and syncope, also during chronic therapy orthostatic hypotension may occur. Orthostatic hypotension is reported in up to 20% of patients, while syncope occurs in less than 2% (168). Orthostatic side effects are less frequent in second generation α-blockers like doxazosin and terazosin than during prazosin (168). Elderly patients are more susceptible to this side effect (125). Since elderly have more osteoporotic bones, a syncope or dizziness might result in life threatening events such as a hip fracture.

3.2.5. ß-blockers

hard endpoints. ß-blockers with ISA are not effective in reducing mortality after myocardial infarction (391). But, ß-blockers without ISA are very effective in preventing stroke in both young and middle-aged patients with mild-to-moderate hypertension (MRC, MAPHY/HAPPHY, IPPPSH; 323,397,418) and elderly patients (Coope; 419).

In middle-aged men with severe hypertension atenolol-based treatment reduced mortality from myocardial infarction (420). Not only in hypertensives but also in normotensive patients, several ß-blockers including propranolol, timolol, and metoprolol have been shown to reduce total and CHD mortality significantly after myocardial infarction (421-424). ß-blockers were more effective than diuretics in preventing sudden death (MRC; 425) and myocardial reinfarction (Wikstrand, MAPHY/HAPPHY, MRC; 396-397,425).

A pooling study by Cruickshank (426) of all ß-blocker trials in hypertension, including retrospective, prospective, controlled and uncontrolled trials suggested that ß-blockers conferred a modest degree of primary prevention from myocardial infarction of 15% when compared with placebo, limited to nonsmoking men. This is due to the fact that nonselective ß-blocking agents were only beneficial for CHD in nonsmokers, while $ß_1$-blockers were effective in both smokers and nonsmokers (397). Not only CHD mortality but also all-cause mortality decreased (323,420).

In addition, ß-blockers reduce the late morning peak incidence of myocardial infarction (81) and also reduce the likelihood of full-thickness myocardial infarction (427). In the peri-infarction period and 28 days after infarction ß-blockers reduce mortality in patients with good and poor left ventricular function (391,428).

hard endpoints in subgroups. The effects in the elderly is not so clear. Two studies did not find a beneficial effect of atenolol on coronary heart disease (MRC, Coope; 400,419), while in the recent SHEP study (399) beneficial effects may have been associated with the presense of atenolol with a low-dose diuretic.

speculative beneficial effects. In animals, ß-blockers have also proved effective in preventing coronary atheroma in spite of ß-blocker induced blood lipid changes

(246). ß-blockers have also a weak antiplatelet action, which might help in the prevention of thrombus formation (429).
ß-blockers are moderately effective in reversing left ventricular hypertrophy (191), although dual acting agents (e.g. nebivolol) that reduce peripheral resistance and increase vascular compliance may be superior (392).
The negative inotropic and chronotropic effect of ß-blockers could be vital components of their life-preserving quality (430). These effects reduce the stress on the coronary arteries, thereby decreasing the risk of plaque rupture, which results in less progression of atherosclerosis and less "acute cardiac events". An association between heart rate and cardiovascular mortality has indeed been found in the Framingham study (431). Recently also clinical evidence of a beneficial effect of ß-blockers in heart failure has been reported (432).
quality of life. The aforementioned meta-analysis indicated that ß-blockers together with ACE-inhibitors were the best in preserving general well-being (401). However, in this analysis no difference has been made between nonselective and selective ß-blockers. Nonselective ß-blockers are not very well tolerated (341,433), while recent studies have shown that $ß_1$-blockers are as well tolerated as ACE-inhibitors (341,401,408) and highly selective ß-blockers like bisoprolol might even be better tolerated (part III chapter 2). Also the selective $ß_1$-blocker with vasodilating properties nebivolol preserved quality of life (part III chapter 1).

3.3. influence of concomitant diseases or conditions on the choice of antihypertensive drugs.

One of the most important determinants for selecting antihypertensive therapy is the presence of concomitant medical conditions and resulting use of medications (434). A concomitant disease can make the use of a drug less suitable or in contrast more appropriate. For example, ß-blocker therapy can enhance bronchospasm in patients with obstructive pulmonary disease. Therefore, a ß-blocker should not be used in this condition (434).
A concomitant disease may favour the choice of drugs, which exert a beneficial effect on the concomitant disease. For example, in hypertensive patients with angina pectoris, ß-adrenoceptor antagonists and calcium channel blockers may be firstline drugs (435). If the hypertensive patient also suffers from supraventricular arrhythmia, non-dihydropyridine calcium-antagonists or ß-blockers might be helpful (436). Diuretics have proven their validity in treatment of congestive heart failure (437). Recently also ACE-inhbitors have shown to reduce mortality in this condition (67,68,194). Studies with other antihypertensive drugs like selective calcium-antagonists and ß-blockers are ongoing.
Concomitant therapy can also influence the choice of the drug. Elderly patients, for example, often suffer from arthritis (438), which can be treated with nonsteroidal anti-inflammatory drugs. However, these drugs can cause sodium retention. As a consequence, in this condition often a diuretic will be required (435).
Apart from concomitant diseases and their therapy, also some conditions of the patient can influence the choice of the antihypertensive agent. For example, in the elderly, diuretics have proven their validity (398-399) and might therefore have some preference above other antihypertensive drugs in these patients. Due to the reduction in exercise tolerance, nonselective ß-adrenoceptor antagonists can better be avoided in physically active patients (part III, chapter 3).

4. monotherapy or low-dose combination therapy?

Controversy exists as whether it will be preferable to increase drug doses or add or substitute other drugs if inadequate antihypertensive effects are not achieved. Since side effects mostly increase with increasing doses of a drug, in general, it may be preferable to add another drug when a partial response with good clinical tolerance to the first drug is achieved. Likewise, the substitution of another drug may be preferable when there is little or no antihypertensive response or if adverse drug effects ensue due to the first agent (439). In this philosophy of low dose therapy and rapid combination of drugs, multiple action drugs gain interest.

5. a personal view on current treatment of hypertension

Most progress in the treatment of hypertension can be made by preventing the ill effects of atherosclerosis. Ideally atherogenesis itself should be prevented or slowed down. However, our knowledge on the pathophysiology and especially the treatment of atherogenesis is still insufficient to justify large and costly detection and intervention programs for early detection and treatment of atherosclerosis. Primary prevention of atherosclerosis and hypertension nowadays should be based on health education programs, dissuading people from smoking and promoting diets with less fat and less saturated fatty acids, a lower sodium/potassium ratio, and maybe also higher content of antioxidants. Also regular moderate physical exercise, alcohol restriction to 2 consumptions per day, and avoidance of overweight and excessive emotional stress (e.g. type A behaviour) should be advised. Early in atherogenesis, calcium-antagonists might become more frequently used to retard atherogenesis, providing they are well-tolerated and do not induce other morbidity or mortality.

Since early prevention of atherogenesis is not yet possible, our efforts should go to the prevention of the ill effects of atherosclerosis, which are mainly due to plaque rupture and thrombus formation. Therefore, if atherosclerotic plaques are present, aspirin (or in some cases a thromboxane synthetase inhibitor/receptor antagonist) could be used to prevent platelet aggregation. Risk factors for plaque rupture are weak (e.g. cholesterol-rich) plaques and physical stress on the vessel wall (systolic blood pressure, pulse pressure, heart rate, cardiac inotropy, and probably also shear stress). Since lipid lowering interventions did not improve all cause mortality and even might induce a more aggressive behaviour, these interventions should be restricted to patients who are at particularly high risk for death from coronary disease: those with substantially elevated serum cholesterol concentrations, history of coronary disease, or several risk factors in addition to hypercholesterolaemia (part I chapter 2).

Which antihypertensive drug to choose? Such a choice has to be made for each individual patient, but a preference drug(s) for the population of hypertensive patients can be considered. Since several drug-induced "speculative beneficial and adverse effects" have not fulfilled expectations on hard endpoints (see 3.1.2), in my opinion, antihypertensive therapy of choice should predominantly be based on the secure hard endpoints and effects on quality of life with a smaller weight for speculative effects. It is clear that the antihypertensive therapy of choice is based on current knowledge and is likely to change as knowledge progresses.

Nowadays, two classes of antihypertensive drugs seem the best in preserving quality of life: selective ß$_1$-blockers and ACE-inhibitors. In addition, ß-blockers have

been shown effective in primary and secondary prevention of coronary heart disease, and also all cause mortality was improved. Therefore, selective $ß_1$-blockers are in general the drugs of choice - certainly in middle-aged hypertensive patients without interfering illness. If ACE-inhibitors prove to have similar favorable effects on mortality, they may develop as alternative first choice drugs.
Further investigation is needed to confirm the beneficial effect of ß-blockers in the elderly. In these patients the beneficial effects on hard endpoints are available for diuretics. It is very likely that, with ongoing research, also other antihypertensive drugs might provide more data on hard endpoints (cardiovascular and all cause morbidity and mortality). However, $ß_1$-blockers also possess several additional speculative beneficial effects (see 3.2.5).
$ß_1$-selective blockers with vasodilating properties are promising since compared with other ß-blockers they reduce the afterload for the heart. This might be an additional beneficial effect in preventing cardiac hypertrophy. In addition, some of these ß-blockers may preserve quality of life and - important in physically active patients - in contrast to other ß-blockers do not substantially alter exercise performance (part III chapters 1 and 3).

6. individualizing therapy

Despite several decades of innovative research that has elucidated behavioral and biological risk factors for coronary heart disease (440), the ability to identify individuals who will eventually suffer acute thrombotic events is incomplete (441). In the United Kingdom Heart Disease Prevention Project (442), for example, high-risk patients identified by hypertension, smoking, and elevated blood cholesterol levels accounted for only 32 % of all future infarctions. In addition, we have to bear in mind that results of trials are means of a population. There are patients doing better, and other patients doing worse. As a consequence, recommendations derived from trials will suit for the majority of patients, but not for each individual patient. Some individualization of therapy can be made by correcting for concomitant risk factors or diseases, but the black box with lack of knowledge about the "patient to treat" remains considerable. Measurement of cardiac mass, vessel wall properties and vessel wall structure might provide more information about the risk of the individual patient. Such measurements might be more helpful for the management of hypertension in the individual patient than current risk calculations.

7. issues for future research

7.1. evaluation of current antihypertensive therapy

Long-term prospective clinical trials are needed to compare morbidity and (all cause) mortality with ACE-inhibitors, calcium-antagonists, and α-blockers to that of diuretics and the different subclasses of ß-blockers (especially the $ß_1$-blockers without ISA and those with vasodilating properties).

7.2. prevention of ill effects

Primary prevention of atherosclerotic complications remains the most important of the unresolved issues in antihypertensive therapy (387). Since atherosclerosis already starts at puberty, prevention has to start early in life. As long as atherogenesis cannot be prevented, much attention should be paid not only to

progression and regression of atherosclerosis but also to prevention of plaque rupture by stabilizing weak plaques and by reducing the stress on these plaques.
As a consequence, much more attention should be paid to the role of physical factors - like circumferential and shear stress - in the pathogenesis of ill effects. Important issues for future research are effects of changes in local wall tension, determination of the relative impact of different stress factors of the pulsatile stress and impact of mean and pulsatile shear stress. Heart rate and pulse pressure are two vessel wall stress factors (part II, chapter 1). These factors might not only be important for large arteries. In a recent study Christensen found that 80 % of the media:lumen ratio of resistance vessels in rats could be explained by the pulse pressure and heart rate, with the mean pressure playing but a small role (443). Long-term prospective studies are needed correlating different aspects of vessel wall stress with morbidity and mortality in hypertension.

7.3. reversal of ill effects

Reduction of blood pressure may result in reduction of some pressure related arterial damage, but until now reversal of hypertension with drugs may not cause reversal of the hypertrophy and collagen content (386). Reversibility potential of organ damage should be further investigated.
Growth factor inhibitors, like ACE-inhibitors and possibly also nonselective HMG co-A reductase inhibitors like simvastatin (444), might be promising not only to prevent but also to reduce hypertrophied structures more rapidly. However, when eutrophy has been reached, do these drugs maintain this eutrophic state or are they inducing (cardiac and/or vascular) atrophy? In other words, can these drugs be used for a long indefinite period or are these drugs only for initial therapy, followed by other therapy when euthrophy has been reached? In addition, there is still little direct evidence that the altered vascular structure in essential hypertension is associated with vascular growth. There is more evidence that it may be associated with remodeling (rearrangement of existing cells), as suggested by Mulvany, Baumbach and Heistad (445-446). This suggests that if antihypertensive treatment is to correct the vascular structure, it is possible that the treatment should be directed not so much at preventing growth, but more at facilitating rearrangement of existing cells (445).

7.4. around the clock protection

The effect of an antihypertensive therapy not only depends on the 'intrinsic efficacy' of a drug, but also on its ability to provide a good around the clock protection. This largely depends on drug adherence which is also influenced by the effect of therapy on quality of life. Investigation of the influence on quality of life should be continued. Not only the effect of different classes of antihypertensive drugs should be compared but also drugs within the same class, e.g. dihydropyridine calcium-antagonists with different half-lives.
Even with satisfactory drug adherence, current antihypertensive therapy often does not protect the early morning hours sufficiently without risk for hypotension during the night. Further development of drug delivery systems might resolve this problem.

7.5. identification of patients at risk

Very important from a socio-economic point of view is the identification of patients at risk. Therefore, considerable efforts should be made to better assess the risk not only in the population but especially in the individual patient. In this respect cardiac hypertrophy, heart rate, vessel wall structure and properties might be key standards. New techniques to detect early stages of atherosclerosis and rupture prone small plaques should be developed. Intravascular echo is a step forward in this respect, but because of its invasive nature, it is not suitable for population screening.

7.6. controlling drug exposure

Poor compliance is a problem of drug therapy in general and not of antihypertensive therapy in particular, but its consequences for outcome of therapy may be very important. Compliance in hypertensive patients and methods to improve it are discussed in part 1, section 1.2.4. Poor compliance may also decrease the power of clinical trials (447). It has been calculated that if 10 % of patients in a trial are noncompliant, the power of the study would be reduced from 0.95 to 0.90, and if 30 % are noncompliant, the number of patients has to be doubled (448,449). In addition, if compliance is different in the 2 limbs of a comparative study, false conclusions about efficacy and side effects can be made (450).

Compliance has been measured by different methods. Patient report reveals only a fraction of the non-compliers (447), since 'patients often lie when they state they have taken certain medicines' (Hippocrates) to please the clinician or to avoid disapproval (451). Pill counts are frequently used in clinical trials since Good Clinical Practice guidelines ask for drug accountability (447). Pill counts are more reliable than patient report (452), but can grossly overestimate compliance (448), and misses some 10 % of overt non-compliers (447). Pill counts only can indicate poor compliers if the amount of pills returned is obviously too large. It never can prove good compliance, since some non-compliers may discard tablets before returning containers (447,451). This "pill dumping" has to be suspected if less pills are returned than expected (453). Drug plasma levels can prove that drug has been taken, but in general cannot detect the 'toothbrush' phenomenon, when non-compliers resume full compliance or more one or a few days before control visits (451,454). Recently, two interesting methods have been developed to monitor drug adherence more adequately: the long half-life, low-dose chemical markers and the micro-electronic medication event monitoring system (MEMS). As low-dose markers phenobarbital (2mg/day) and digoxin (2.2 g/capsule) have been used (448, 452). Phenobarbital has the advantage to give reproducible steady-state plasma levels with little variation between peak and trough levels (455) and without large interindividual variation (456). These markers can monitor drug adherence for the last days to weeks (448), but give no precise information on the time of dosing. With low-dose digoxin monitoring the proportion of good compliers was equal to those who have returned less than 15 % of the capsules. Combination of digoxin monitoring with pill counts improved compliance control (452). The MEMS monitor registers every opening of the container with accurate time registration, but cannot prove drug intake (451). The fact that methods of compliance measurement usually have to be explained to patients prior to the study as a part of informed consent (447), can decrease the validity of pill counts and MEMS devices.

From the results of these newer compliance monitoring methods used in 4 clinical trials, Urquhart estimates that 50 to 70 % of patients will take greater than 80 % of the prescribed doses, 30 to 40 % will take 40 to 80 % of prescribed doses, and a small percentage will take, respectively, 100 to 120 % or less than 40 % of prescribed doses (456). In a subset of the Helsinki Heart Study 31 % of patients were identified as poor compliers (452). With MEMS and low-dose long half-life markers it was also confirmed that compliance with once daily regimens was slightly better than with BID, but markedly better than with TID or QID regimens (457,458). In different short-term trials using once or twice daily regimens compliance averaged more than 80 % of pills taken (457,459), suggesting that noncompliance is also stimulated by chronic treatment.

Altough recently much progress in controlling drug adherence has been made, a gold standard is not yet available. Combination of different methods can improve compliance control (452). Efforts should be made to further improve methods of controlling compliance. Compliance should be considered as a variable in the analysis of trial data. If appropriate, a separate analysis on data of compliers should be made (447).

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SUMMARY

Prevalence of hypertension is high. In most hypertensive patients, the real cause of hypertension is not known (essential hypertension). However, there is much evidence that alterations in small vessels (the microcirculation) play an important role in the onset of most cases of essential hypertension. A minority of hypertensive patients have severe hypertension, which might very quickly lead to death (malignant hypertension). Most patients have mild-to-moderate hypertension, which is, in general, asymptomatic. This class of hypertension can in the long run lead to cardiovascular disease and renal failure. The complications of hypertension are predominantly due to disease of the large vessels (macrocirculation). Therefore, prevention or retardation of these late complications [1] of hypertension has to be the goal of antihypertensive treatment in mild-to-moderate hypertension. This is only in part achieved by treatment of the high blood pressure as such.
The outcome of treatment depends largely on patient compliance to that treatment. Since mild-to-moderate hypertension is asymptomatic, small adverse effects of a drug can easily decrease patient's quality of life [2] and lead to a lower patient compliance.
This thesis pays attention to the above mentioned [1,2] non-antihypertensive aspects of antihypertensive treatment. Part two deals with the influence of physical factors on the vessel wall of large arteries, which might play a role in the appearance of late complications of hypertension. Part three investigates the influence of different antihypertensive treatments on patients' quality of life.
Chapter 1 of part 2 reviews different physical factors and their determinants (such as distensibility and compliance, shear stress and pulse wave reflections). Distensibility and compliance are vessel wall properties. Distensibility reflects the elasticity of the vessel wall, while compliance is a measure for the buffering capacity of the vessel. This chapter also reviews the influence of antihypertensive therapy on physical factors and their determinants. Not all antihypertensive drugs can improve vessel wall properties of large arteries. Calcium-antagonists, ACE-inhibitors and selective $ß_1$-blockers improve vessel wall properties, while nonselective ß-blockers do not. Chapter 2 and 3 investigates the effect on vessel wall properties of the common carotid artery of the calcium-antagonist verapamil and the selective $ß_1$-blocker with vasodilating properties nebivolol, respectively. Both drugs improved distensibility and compliance of the common carotid artery. This improvement might postpone cardiovascular complications of hypertension.
Recently, increasing attention is being paid to the influence of drugs on the quality of life. Several questionnaires have been developed to measure quality of life more adequately. One of these questionnaires, the Inventory of Subjective Health (ISH), has been developed in The Netherlands and is presented in the introduction of part 3. Chapter 1 of part 3 investigates the influence of antihypertensive therapy with nebivolol (a selective $ß_1$-blocker with vasodilating properties) on blood pressure and quality of life. Nebivolol 5mg once daily induced a decrease in blood pressure, similar to that of other antihypertensive drugs, given as monotherapy. No drug tolerance was seen during the 8-week treatment period. Nebivolol did not impair quality of life. In addition, the study showed that participation in a trial by itself already improves quality of life. Therefore, comparison of quality of life

during treatment with quality of life before treatment does not allow conclusions about a beneficial effect of a drug on quality of life.

Chapter 2 compares the influence on quality of life of antihypertensive treatment with the ACE-inhibitor enalapril and the selective $ß_1$-blocker bisoprolol. At dosages, which induced a comparable decrease in blood pressure, less adverse effects were mentioned with bisoprolol than with enalapril. Quality of life, measured with the Inventory of Subjective Health, tended to be better with bisoprolol and the large majority of patients preferred continuation of treatment with bisoprolol. These results clearly do NOT support the assumption that ACE-inhibitors induce less complaints than ß-blockers, and certainly not less than selective $ß_1$-blockers.

ß-Blockers may decrease quality of life in physically active patients by decreasing exercise tolerance. Endurance exercise capacity decreases by about 40 % with nonselective ß-blockers, by 20-25 % with selective $ß_1$-blockers, and by 8-12 % with ACE-inhibitors and calcium-antagonists. Chapter 3 investigates the influence on exercise capacity of nebivolol 5 mg once daily compared to atenolol 100 mg once daily and placebo. Decrease in blood pressure was comparable during nebivolol and atenolol, but heart rate decreased less with nebivolol, suggesting less ß-blockade with nebivolol. Endurance time decreased by 23 % with atenolol, while only by 6 % with nebivolol. Decrease in endurance time with nebivolol was similar to that with calcium-antagonists and ACE-inhibitors, and this decrease, in general, does not induce complaints of fatigue.

Part 4 discusses different aspects of current antihypertensive therapy. A preference for treatments with proven beneficial effect on morbidity and mortality is suggested above treatments with (based on their beneficial effects on risk factors) expected, but not proven, beneficial effect on morbidity and mortality. Finally, issues for future research are proposed such as further evaluation of current antihypertensive therapy, exploration of prevention and possible reversibility of ill effects, 24-hour protection, identification of patients at risk, and, although not limited to antihypertensive treatment, control of patient compliance.

SAMENVATTING

Hypertensie is een vaak voorkomende aandoening. In de meerderheid der gevallen is haar oorzaak niet goed bekend. Deze vorm van hypertensie wordt essentiële hypertensie genoemd. Toch zijn er aanwijzingen dat in vele gevallen afwijkingen in de kleine bloedvaten (de microcirculatie) een belangrijke rol spelen bij het ontstaan van essentiële hypertensie. In een kleine minderheid van de patiënten bestaat een sterk verhoogde bloeddruk die snel tot de dood kan leiden (maligne hypertensie). De meeste patiënten hebben echter een licht tot matig verhoogde bloeddruk en ondervinden hiervan in de regel geen hinder. Deze vorm van hypertensie kan op den duur toch leiden tot hart- en vaatziekten en nierfalen. De complicaties van de hypertensie situeren zich vooral in het hart en de grote vaten (macrocirculatie). De behandeling van hoge bloeddruk moet daarom vooral gericht zijn op het voorkomen of vertragen van deze late complicaties. Behandeling van de hoge bloeddruk alleen, blijkt hierin slechts ten dele te slagen.
Het succes van een behandeling hangt in grote mate af van de trouw waarmee de voorgeschreven medicatie werd ingenomen (therapietrouw). Omdat lichte tot matige hypertensie meestal symptoomloos is, kunnen geringe bijwerkingen van een medicijn de levenskwaliteit van een patiënt snel negatief beïnvloeden en tot een lagere therapietrouw leiden.
In dit proefschrift wordt vooral aandacht besteed aan de genoemde niet-antihypertensieve aspecten van de behandeling van de hoge bloeddruk. Deel 2 behandelt de invloed op de vaatwand van grote vaten van fysische factoren, die een rol kunnen spelen bij het ontstaan van de late complicaties van hypertensie. Deel 3 onderzoekt de invloed van verschillende antihypertensieve behandelingen op de levenskwaliteit van de patiënt.
Hoofdstuk 1 van deel 2 geeft een overzicht van de verschillende fysische factoren en hun determinanten, die een invloed kunnen hebben op de vaatwand (zoals distensibiliteit en compliantie, afschuifspanning en polsgolfreflecties). Distensibiliteit en compliantie worden ook vaatwandeigenschappen genoemd. De distensibiliteit is een maat voor de elasticiteit van de vaatwand, terwijl de compliantie het bufferende vermogen van het bloedvat weergeeft. Een overzicht van de invloed van verschillende bloeddrukverlagende medicijnen op de vaatwandeigenschappen toont aan dat niet alle bloeddrukverlagende middelen de vaatwandeigenschappen verbeteren. Een verbetering werd beschreven met calciumantagonisten, ACE-remmers en $ß_1$-selectieve blokkeerders, maar niet met aselectieve ß-blokkeerders. Hoofdstuk 2 en 3 beschrijven het effect op de vaatwandeigenschappen van de arteria carotis van respectievelijk de calciumantagonist verapamil en van nebivolol, een $ß_1$-selectieve blokkeerder met vasodilaterende eigenschappen. Met beide middelen verbeterde de distensibiliteit en compliantie van de halsslagader. Het is mogelijk dat hierdoor cardiovasculaire complicaties van hypertensie worden vertraagd of vermeden.
De laatste jaren is in toenemende mate aandacht besteed aan de invloed van medicijnen op de levenskwalitiet van de patiënt. Diverse vragenlijsten werden ontwikkeld om de levenskwaliteit adequaat te meten. Een van deze vragenlijsten, de VOEGlijst (vragenlijst onderzoek ervaren gezondheid), werd in Nederland ontwikkeld en wordt in de introductie van deel 3 gepresenteerd. Hoofdstuk 1 van deel 3

onderzoekt de invloed van een antihypertensieve behandeling met nebivolol (selectieve $ß_1$-blokkeerder met vasodilaterende eigenschappen) op de bloeddruk en de kwaliteit van leven. Nebivolol 5mg eenmaal daags gaf een goede bloeddrukdaling, vergelijkbaar met die van andere ß blokkeerders in monotherapie. Gedurende de 8 weken durende studie trad geen tolerantie op. Nebivolol had geen negatieve invloed op de kwaliteit van leven. De studie toonde ook aan dat deelname aan een onderzoek op zichzelf de levenskwaliteit al verbetert. Daarom kan de vergelijking van de levenskwaliteit tijdens met die van vóór de behandeling geenszins een positieve invloed van een medicijn op de levenskwaliteit aantonen. Hoofdstuk 2 vergelijkt de invloed op de kwaliteit van leven van een antihypertensieve behandeling met de ACE-remmer enalapril met een behandeling met de $ß_1$-selectieve blokkeerder bisoprolol. Bij een vergelijkbare bloeddrukdaling werden minder bijwerkingen gesignaleerd tijdens behandeling met bisoprolol dan tijdens enalapril. Ook was (niet significant) de levenskwaliteitscore van de VOEG-lijst beter met bisoprolol en gaf een ruime meerderheid van de patiënten de voorkeur aan het verderzetten van de behandeling met bisoprolol. Deze resultaten ondersteunen duidelijk NIET de aanname dat ACE-remmers minder klachten geven dan ß-blokkeerders, en zeker niet minder dan $ß_1$-selectieve blokkeerders.
Het is bekend dat ß-blokkeerders de levenskwaliteit van fysisch actieve patiënten duidelijk kunnen verminderen door vooral het uithoudingsvermogen van de patiënt te beperken. Gemiddeld neemt het uithoudingsvermogen voor lichamelijke inspanning met ongeveer 40 % af bij behandeling met niet-selectieve ß-blokkeerders. Met selectieve ß-blokkeerders werd een vermindering van 20-25 % gevonden, terwijl dit met ACE-remmers en calciumantogonisten 8-12 % bedroeg. In hoofstuk 3 werd het uithoudingsvermogen tijdens een behandeling met nebivolol 5 mg 1x daags vergeleken met dat tijdens een behandeling met atenolol 100mg 1x daags en placebo. De bloeddrukdaling was vergelijkbaar tijdens nebivolol en atenolol, maar de daling in hartfrequentie was minder groot met nebivolol. Dit suggereert minder ß blockade met nebivolol. Tijdens atenolol werd een daling van de volhoutijd van 23 % gevonden, terwijl deze slechts 6 % bedroeg met nebivolol. De daling van de volhoutijd met nebivolol ligt daarmee in dezelfde grootorde van die met calciumantagonisten en ACE-remmers en dit geeft in de regel kennelijk geen aanleiding tot vermoeidheidsklachten.
In deel 4 worden verschillende aspecten van de huidige antihypertensieve therapie bediscuteerd. Hierbij wordt gepleit voor een voorkeur voor behandelingen met een bewezen gunstig effect op morbiditeit en mortaliteit boven behandelingen met (op grond van hun gunstige invloed op risicofactoren) verwacht, maar niet bewezen, gunstig effect op morbiditeit en mortaliteit. Tenslotte worden velden voor verder onderzoek aangegeven zoals verdere evaluatie van de huidige antihypertensieve therapie, onderzoek naar preventie en eventuele omkeerbaarheid van complicaties van hypertensie, 24-uurs protectie, identificatie van risicopatiënten en, alhoewel niet specifiek voor behandeling van hypertensie, het meten van de therapietrouw van de patiënt.

CURRICULUM VITAE

1949, 18 november	geboren te Kalmthout, België.
1961-1967	Grieks-Latijnse humaniora aan het Sint-Michielscollege te Brasschaat, België.
1967-1970	Kandidaatsjaren geneeskundige wetenschappen Rijksuniversitair Centrum Antwerpen, België.
1970-1974	Geneeskunde studie Rijksuniversiteit Gent, België.
1974	diploma doctor in genees-, heel-, en verloskunde (Rijksuniversiteit Gent).
1974-1976	Assistent interne geneeskunde in het AZ Stuivenberg te Antwerpen, België.
1976-1977	postgraduaat cursus Tropische Geneeskunde aan het Instituut voor Tropische Geneeskunde te Antwerpen, België.
1977-1978	assistent chirurgie-gynaecologie en verloskunde in het Sint-Jansgasthuis te Weert, Nederland.
1978-1980	assistent van het Instituut voor Tropische Geneeskunde Antwerpen met opdracht in Kasongo, Zaire.
1980-1985	assistent in opleiding Interne Geneeskunde in het De Wever-ziekenhuis te Heerlen, Nederland.
1985	erkenning als internist.
1985-1988	assistent klinische farmacologie, vakgroep Farmacologie (Prof. dr. K.H. Rahn en Prof. dr. H.A.J. Struijker Boudier) Rijksuniversiteit Limburg, Maastricht, Nederland.
1986-heden	20% gedetacheerd als internist aan het De Wever ziekenhuis Heerlen, afdeling Interne Geneeskunde.
1989-heden	werkleider sectie klinische farmacologie, vakgroep farmacologie (Prof. dr. H.A.J. Struijker Boudier) Rijksuniversiteit Limburg, Maastricht.
1993	erkenning als internist met aandachtsgebied klinische farmacologie.

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