Beyond blood pressure monitoring
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Chapter 1

Introduction
In the second half of the twentieth century cardiovascular mortality decreased progressively in the industrialized countries\(^1\). Improved control of hypertension has considerably contributed to this decline. For example, in the United States of America, the Health Examination Surveys have demonstrated that while 10% of hypertensive persons had their blood pressure lowered below 140/90 mmHg in the period 1976 till 1980, this proportion had risen to 27%\(^2\) by 1988 till 1991. Still, this leaves over 70% of hypertensive persons with imperfect control, as has been reported in many countries\(^3,4\). This majority of imperfectly controlled hypertensive persons reflect the inherent problem of maintaining long-term therapy for an as yet asymptomatic condition, particularly when therapy may interfere with the patient’s quality of life and its immediate benefits are not obvious to all patients.

Given the aging of the population and the increased prevalence of obesity, strokes and coronary heart disease events are expected to increase or remain stable even if primary and secondary prevention of cardiovascular disease is tightened further. Given the central role of elevated blood pressure in the pathogenesis of both coronary heart disease and stroke, it is clear that one of the biggest challenges public health authorities and medical practitioners face, is the worldwide control of hypertension.

Cardiovascular risk rises linearly with blood pressure and the definition of hypertension is therefore, arbitrary. Most of the evidence about the benefits and risks of lowering blood pressure comes from studies in patients selected on the basis of high blood pressure. It is therefore not clear whether estimates of treatment effect obtained from trials in hypertensives can be extrapolated to individuals with lower blood pressure levels\(^5\).

**Guidelines for the management of hypertension (WHO-ISH 1999 and JNC VI)**

As seen in table 1, hypertension is defined as a systolic blood pressure of 140 mmHg or greater and/or a diastolic blood pressure of 90 mmHg or greater. Like the previous guidelines, issued in 1993, the 1999 guidelines concentrate on the management of patients with mild to moderate hypertension since there often is uncertainty among clinicians and policy makers on how to manage this condition.

**CLINICAL END POINTS**

**Stroke**

Blood pressure levels, both systolic (SBP) and diastolic (DBP), relate positively and continuously to the risk of stroke across a wide range of levels in Western countries.
Among individuals of mostly middle age, a prolonged 5 mmHg lower level of usual DBP was associated with a 35-40% lower risk of stroke. The slope of this association declines somewhat with increasing age, because the incidence of stroke increases rapidly with age. Elderly people still suffer the large majority of blood pressure-related cerebrovascular disease. Blood pressure levels are positively related to both cerebral hemorrhage and cerebral infarction, but the association appears to be somewhat steeper for hemorrhage than infarction. Atrial fibrillation enhances stroke risk significantly. Stroke risk increases fourfold in all age groups once atrial fibrillation develops.

### Sudden death
Hypertensive patients with LVH have a significantly greater prevalence of premature ventricular contractions and complex ventricular arrhythmias than patients without LVH and/or normotensive patients. A study from the Framingham cohort showed that the presence of asymptomatic ventricular arrhythmias was associated with a nearly twofold increase in mortality.

### Atrial fibrillation
Atrial fibrillation may be paroxysmal, persistent or chronic, and a number of attacks are asymptomatic. Suspicion or confirmation of atrial fibrillation necessitates investigation and, as far as possible, appropriate treatment of associated cardiovascular diseases such as hypertension, diabetes mellitus, hypoxemia, hyperthyroidism and...
congestive heart failure. Hypertension is one of the major underlying conditions in atrial fibrillation. In Framingham, 8% of all patients with hypertension developed atrial fibrillation in 7 years time.

**Coronary heart disease**

Blood pressure levels have also been shown to be positively and continuously related to the risk of death due to coronary heart disease or of nonfatal myocardial infarction. The increase in coronary heart disease with elevated blood pressure is about two-thirds as steep as that for stroke, and appears to be similar across a broad range of blood pressure levels, that includes both hypertensive and normotensive persons.

**Heart failure and renal disease**

The risk of heart failure and of renal disease relates to blood pressure levels, but the relationships are less tight than for stroke and coronary heart disease. Nevertheless, patients with a history of hypertension have at least a six times greater risk of heart failure than individuals without such a history.

Among patients with mild hypertension, not only blood pressure is important, also the presence of other factors determine the risks of cardiovascular disease. For example, a man aged 65 years with diabetes, a history of transient ischemic attacks and a blood pressure of 145/90 will have an annual risk of a major cardiovascular event that is more than 20 times greater than in a man aged 40 years with the same blood pressure but without either diabetes or a history of cardiovascular disease. In contrast, a man aged 40 years with a blood pressure of 170/105 mmHg will have a risk of a major cardiovascular event that is about two or three times greater than that of a man of the same age with a blood pressure of 145/90 mmHg and similar other risk factor levels. Therefore, differences in the absolute level of cardiovascular risk between patients with hypertension is determined to a greater extent by other risk factors than by the level of blood pressure.

**MAJOR AND INDEPENDENT RISK FACTORS FOR CHD BESIDES HYPERTENSION**

**Smoking**

Cigarette smoking increases the risk of CHD and ischemic stroke at all ages, but it is of particular importance in younger people. In men under 65 years, smoking increases the risk of cardiovascular death twofold, while in men aged 85 years or older, the risk was observed to be increased by only 20%. In addition to causing cardiovascular disease, smoking also increases the risks of a wide variety of noncardiovascular
Introduction

diseases, in particular respiratory and neoplastic diseases 14.

**Lipids**
Increasing levels of both total and low-density lipoprotein (LDL) cholesterol are associated with increases in the risk of CHD 15. The relative risk appears to decline with increasing age, although the absolute risk typically increases. A lower level of total cholesterol of 0.6 mmol/l in men aged 40 years is associated with a 54% lower risk of CHD, whereas the same difference in cholesterol in men aged 70 years only gives a 20% lower risk. The effect of high-density lipoprotein cholesterol on CHD risk does not appear to be age-dependent; every 0.03 mmol/l increase in HDL cholesterol appears to be associated with at least a 3% reduction in the risk of CHD16. It is still debatable whether there is any independent effect of triglyceride levels on the risk of cardiovascular disease 17.

**Diabetes Mellitus**
Both type 1 and type 2 diabetes mellitus confer a heightened risk for CHD. Type 2 diabetes is of particular concern because it is so common and usually occurs in persons of advancing age, when multiple other risk factors coexist. Once patients with diabetes mellitus develop CHD, they have a poor prognosis. Therefore, there is need to intensify the management of coexisting risk factors in patients with diabetes, in particular hypertension.

**Gender**
At most ages, the risk of cardiovascular diseases is greater in men than women, although this difference declines with increasing age and is greater for coronary heart disease than for stroke. In the United States, the risk of death from stroke is 30% higher in men than in women aged 34 to 74 years, whereas the risk of death from coronary heart disease is two- to threefold greater in men 18. After the age of 75 years, the risk of death from stroke and from coronary heart disease is similar in men and women.

**Age**
Increase in blood pressure, particularly in SBP, is now recognized as a pathophysiologic manifestation of changes in cardiovascular physiology and structure. Aging is not only a continuous chronological process but also a functional process. A distinction must be made between actual age and “biological” age. The latter is often governed by comorbid disease states. Clinical trial data are limited in populations aged 65 or greater, and even more so in the geriatric group aged 75 years or greater.
PREDISPOSING RISK FACTORS

Obesity
Increased body mass index is associated with increased risks of CHD. Compared to lean men, men with BMI of 25-29 kg/m² have a 70% greater risk of CHD whereas men with BMI of 29-33 kg/m² had almost a threefold greater risk of CHD 19. The strength of this association with obesity is likely to be due in part to blood pressure elevation, but reduced HDL cholesterol and increased insulin and glucose levels may also be involved 19,20. Obesity is also a strong risk factor for heart failure 21.

Physical inactivity
Physical inactivity confers an increased risk for CHD. The extent to which physical inactivity raises coronary risk independently of the major risk factors is uncertain, but physical inactivity has an adverse effect on several known risk factors. It is associated with a lower concentration of HDL cholesterol and an increased body weight 22.

Psychosocial factors, ethnic characteristics and family history of premature CHD
A low socioeconomic status is associated with CHD. Socioeconomic differences can be partially explained by difference in prevalence of established risk factors, particularly smoking, hypercholesterolemia, hypertension and overweight. Family history of premature CHD is associated with CHD, due to genetic constitution.

CONDITIONAL RISK FACTORS FOR CHD

In addition to the major risk factors, conditional risk factors are associated with an increased risk of CHD, although their causal, independent and quantitative contributions are less well documented. See table 2.

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
</tr>
<tr>
<td>Small LDL particles</td>
</tr>
<tr>
<td>Lipoprotein (a)</td>
</tr>
<tr>
<td>Prothrombotic factors (fibrinogen)</td>
</tr>
<tr>
<td>Inflammatory markers (e.g. CRP)</td>
</tr>
</tbody>
</table>

Table 2. Conditional risk factors
Subclinical manifestations of cardiovascular disease in asymptomatic patients can be important predictors of events. High rates of major clinical events (a few percent per year) occur among patients with significant left ventricular dysfunction, electrocardiographic signs of infarction, myocardial ischemia or left ventricular hypertrophy. Ultrasonographic evidence of left ventricular hypertrophy or carotid atherosclerosis is also associated with increased risk of cardiovascular disease events.

This thesis will focus on these cardiovascular risk factors and subclinical end organ damage (EOD) by high blood pressure and other cardiovascular risk factors, drawing special attention to their relationship. This thesis has received impetus from the general adoption of the principle of risk stratification in treatment guidelines. This will be discussed further below.

**STRATIFICATION OF PATIENTS BY CARDIOVASCULAR RISK**

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also on the presence of other risk factors, concomitant morbidity and target organ damage, as proposed by the recently published guidelines for the management of hypertension, provided by the World Health Organization. These guidelines define four categories of absolute cardiovascular disease risk (low, medium, high and very high risk), as seen in table 3. Each category represents a range of absolute disease risks. Within each range, the risk of any individual will be determined by the severity and number of cardiovascular risk factors present. In the low-risk group, the risk of a major cardiovascular event in the next 10 years is calculated as less than 15%. This low-risk group consists of men below 55 and women below 65 years of age with grade 1 hypertension without any other cardiovascular risk factors. In the medium-risk group, the risk of a major cardiovascular event in the next 10 years is calculated as 15-20%. This medium-risk group consists of patients with a wide range of blood pressures and cardiovascular risk factors. Some have low blood pressure and multiple risk factors, whereas others have high blood pressures and few other risk factors. In the high-risk group, the risk of a major cardiovascular event in the next 10 years is calculated as 20-30%. This group includes patients with grade 1 or 2 hypertension who have at least 3 additional risk factors, diabetes mellitus or target-organ damage and patients with grade 3 hypertension without other cardiovascular risk factors. In the very-high-risk group, the highest risk of a major cardiovascular event in the next 10 years is calculated as 30% or more. The major advantage of the WHO guidelines above other risk assessment
scores is the fact that in the WHO guidelines counting risk factors is simple.

Several risk scores have been developed. The Framingham Heart Study 17, including age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and use of antihypertensive therapy; the PROCAM München Heart Study 27, including age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history, diabetes mellitus and triglyceride. Using these risk score measurements, the absolute risk for cardiovascular morbidity or mortality in the next 10 years can be calculated.

Table 3. Stratification of risk to quantify prognosis.

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Other risk factors and disease</th>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I No other risk factors</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>II 1-2 risk factors</td>
<td>Medium</td>
<td>Medium</td>
<td>Very High</td>
<td></td>
</tr>
<tr>
<td>III 3 or more risk factors or target organ damage or diabetes</td>
<td>High</td>
<td>High</td>
<td>Very High</td>
<td></td>
</tr>
<tr>
<td>IV Associated clinical conditions</td>
<td>Very High</td>
<td>Very High</td>
<td>Very High</td>
<td></td>
</tr>
</tbody>
</table>

Grade 1,2,3: table 1
Risk factors: men aged > 55 or women aged > 65 years, smoking, total cholesterol > 6.5 mmol/l, diabetes mellitus, family history of premature cardiovascular disease (< 60 years of age).
Target organ damage: Left ventricular hypertrophy (electrocardiogram, echocardiogram or radiogram), Proteinuria and/or slight elevation of plasma creatinine concentration (1.2-2.0 mg/dl), Ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta), General or focal narrowing of the retinal arteries.
Associated clinical conditions: Cerebrovascular disease (ischemic stroke, cerebral hemorrhage, transient ischaemic attack), Heart disease (myocardial infarction, angina pectoris, coronary revascularization, congestive heart failure), Renal disease (diabetic nephropathy, renal failure), Vascular disease (dissecting aneurysm, symptomatic arterial disease), Advanced hypertensive retinopathy (hemorrhages or exudates, papilloedema).
Whether or not the Framingham Heart Study score can be extrapolated for Europe is unknown, and probably this score overestimates the risk for cardiovascular morbidity in Europe as the prevalence of heart disease is significantly different in the south compared to the north of Europe \(^{28,29}\). Other risk assessment scores include the West of Scotland Cardiovascular Event Reduction Tool (CERT) \(^{30}\), the British Regional Heart Study (BRHS) Risk score \(^{31}\), the Dundee Coronary Risk Disc \(^{32}\), the Sheffield table \(^{33,34}\), the National Heart Foundation of New Zealand Guidelines \(^{35}\) and the Copenhagen Risk Score \(^{36}\).

**END ORGAN DAMAGE AND CARDIOVASCULAR RISK**

As stated above, the presence of end organ damage plays an important role in the stratification of cardiovascular risk. Development of hypertension can be associated with the presence of vascular structural changes. The heart, the brain, the kidney and the peripheral arteries comprise the target organs for hypertensive disease, as shown in table 4.

**Left ventricular hypertrophy**

Left ventricular hypertrophy represents an adaptive mechanism, which is initially useful and well tolerated, as it tends to reduce ventricular wall stress, but later may lead to impairment of cardiac function, and eventually cardiac failure. Among all target organ complications of hypertension, left ventricular hypertrophy represents a powerful and independent risk factor for cardiovascular morbidity and mortality. Subjects with left ventricular hypertrophy consistently have an incidence of cardiovascular events ranging from 1-15 events per 100 patients years. This is 2-4 times the rate of cardiovascular complications in subjects without left ventricular hypertrophy. The variable geometry of the left ventricle is also associated with different absolute risks of cardiovascular events \(^{37}\).

**Table 4. Target organ damage**

- Left ventricular hypertrophy (electrocardiogram or echocardiogram)
- Proteinuria and/or slight elevation of plasma creatinine concentration (1.2 – 2.0 mg/dl)
- Evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta)
- Generalized or focal narrowing of the retinal arteries
- Silent myocardial ischemia
**Vascular changes**

Vascular structural alterations are represented by a reduction in compliance and by presence of atherosclerotic lesions in the large arteries, as well as by hypertrophy or remodeling of vascular wall in the smaller resistance arteries. Such alterations are involved in the onset of hypertensive damage in the kidney, in the brain and in the eye. Vascular alterations in the large vessels predict cardiovascular risk. The severity of carotid atherosclerotic changes correlates with angiographic evidence of coronary lesions and predicts subsequent cardiovascular events\(^{38,39}\). Therefore, measurements of vascular wall characteristics are important in the stratification of cardiovascular risk.

Unfortunately, ultrasound imaging cannot discriminate between the intimal layer and the medial layer of the vessel wall to distinguish true atherosclerosis viewed as a disorder restricted to the intimal layer versus the adaptive response of the medial layer to changes in tensile stress such as during hypertension.

**Retinopathy**

It is of course well known that diabetes mellitus affects the retina. Apart from high blood pressure and diabetes mellitus, no such effects have been reported for other cardiovascular risk factors.

**Endothelial dysfunction**

A great deal of attention has been given during the last decade to endothelial dysfunction in cardiovascular risk factors and established cardiovascular disease. Endothelial function can be defined by a series of processes like vessel wall motion, permeability, cell adhesion etc. This has also resulted in an array of markers of endothelial dysfunction, ranging from increased levels of endothelial cell adhesion molecules, markers for increased permeability like TERalbumin or microalbuminuria, to function tests like flow-mediated dilation or the response to intraarterial acetylcholine. Endothelial activation or dysfunction has been reported to exist in the presence of many risk factors, including hypercholesterolemia, smoking, hypertension, diabetes mellitus, both type I and II, and hyperhomocysteinemic. Scarce evidence exists that endothelial dysfunction in specific conditions has a prognostic value. Thus, endothelial function, despite its importance as a research tool, has not (yet) a defined place in risk stratification.

**Silent ischemia**

Silent myocardial ischemia is defined as transient myocardial ischemia in the absence of angina pectoris or other cardiac symptoms. It is frequent among hypertensive
patients with and without atherosclerotic coronary disease, even in the absence of epicardial coronary artery disease or left ventricular hypertrophy \(^{40,41}\).

Important vascular factors contributing to the occurrence of myocardial ischemia in hypertensive patients include atherosclerotic obstruction of the large coronary arteries and a reduced vasodilatory capacity of the coronary microcirculation due to arteriolar hypertrophy and endothelial dysfunction. Also external compression of coronary arteries by the hypertrophic myocardium plays a role. Another factor contributing to the occurrence of myocardial ischemia is the increased myocardial oxygen demand of the hyperthrophic myocardium as it is seen in hypertension. Systolic wall stress is directly correlated with LV myocardial oxygen consumption. In hypertensive hypertrophy there is, even with normal coronary arteries, a significant reduction in coronary reserve. Reduction in coronary reserve and diastolic dysfunction already may occur in the prehypertrophic state of hypertensive heart disease. Taken together, silent or transient ischemia can be considered as a composite marker of end organ damage encompassing both ventricular hypertrophy and vascular abnormalities.

In conclusion, primary prevention measures are available, effective and relatively safe. Emphasis has shifted substantially in the past few years from the question whether to treat patients in the primary prevention setting to the matter of selection of the highest risk patients to maximize the benefit/cost ratio of treatment \(^{42}\). Several noninvasive tests are available, which should be considered as a means of further stratifying risk in a large group of apparently low- and intermediate-risk patients.

REFERENCES

Chapter 1


