TURUN YLIOPISTON JULKAISUJA
ANNALES UNIVERSITATIS TURKUENSIS

SARJA - SER. D OSA - TOM. 871

MEDICA - ODONTOLOGICA

ASSESSMENT OF TOTAL CARDIOVASCULAR RISK IN HYPERTENSIVE SUBJECTS

by

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TURUN YLIOPISTO
UNIVERSITY OF TURKU
Turku 2009

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ISBN 978-951-29-4058-5 (PRINT)
ISBN 978-951-29-4059-2 (PDF)
ISNN 0355-9483
Painosalama Oy – Turku, Finland 2009

Markukselle ja Laurille

Ja toivokaamme, että viimein kaikki on kulkeva hyvän toivon mukaan!
Niin, kaikkihan vihdoin hyvin, jos vaan järkevyys ja oikea taju aina
on johdattavana tähtenämme täällä, polkeissamme elämän tietä.

Aleksis Kivi
Seitsemän veljestä

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Assessment of total cardiovascular risk in hypertensive subjects
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Turku 2009

ABSTRACT

Cardiovascular diseases are the leading cause of death in the world, and still increasing due to changing life habits and ageing population.

The Harmonica Project was created to identify 45–70-year-old persons at risk for cardiovascular diseases in the general population. Using two-stage screening method we could target the nurse-given lifestyle counselling to risk persons, and limit the number of physician's appointments for those who might benefit from preventive medication. Finnish Diabetes Risk Score and nurse-measured blood pressure were practical primary screening methods in the general population. The expertise of nurses could be utilized more in primary care to identify the high risk subjects in communities.

Among the 4 450 participants of the Harmonica project in Harjavalta and Kokemäki, a total of 1 106 subjects with hypertension were identified, when patients with known cardiovascular disease and previously diagnosed diabetes were excluded. In this way, the impact of hypertension *per se* on glucose homeostasis and target organ damage could be estimated.

Glucose disorders are more common in hypertensive subjects than in the general population. Using the criteria of the metabolic syndrome as the criteria for performing an oral glucose tolerance test, the number of tests can be reduced by one third and still find almost all the cases of type 2 diabetes and prediabetes.

Moderately decreased renal function is as common as newly detected diabetes in hypertensive subjects. Especially hypertensive women with the metabolic syndrome are at risk for renal insufficiency. If renal function of the hypertensive subjects is estimated by plasma creatinine alone, three-fourth of the patients with renal insufficiency would be overlooked compared to using estimated glomerular filtration rate as the screening method.

Peripheral arterial disease or borderline peripheral arterial disease can be detected in every third of the hypertensive subjects, more often in those with widened pulse pressure over 65 mmHg. Hypertension is an independent risk factor associated with peripheral arterial disease. Measuring ankle-brachial index using the lower of either one of the ankle pressures might be practical in primary care practice to identify the persons at high cardiovascular risk.

Commonly used cardiovascular risk stratification methods, or the novel risk factor high-sensitivity C-reactive protein, can not replace the estimation of subclinical target organ damage in assessing the total cardiovascular risk of hypertensive subjects.

Keywords: cardiovascular disease, hypertension, target organ damage, glucose homeostasis, epidemiology

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Valtimotautiriskin arviointi verenpainepotilailla
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Annales Universitatis Turkuensis
Turku 2009

TIIVISTELMÄ

Valtimotaudit ovat yleisin kuolinsyy koko maailmassa. Väestön elintapojen muuttuminen ja ikääntyminen uhkaavat edelleen lisätä valtimotautien esiintyvyyttä.

Kokemäenjokilaakson valtimotautien ehkäisyprojektin tavoitteena oli löytää 45–70-vuotiaasta väestöstä henkilöt, joilla on kohonnut riski sairastua valtimotauteihin. Kaksivaiheisen seulontamenetelmän avulla voitiin terveydenhoitajan antama elintapaneuvonta kohdistaa riskihenkilöihin ja rajoittaa lääkärin vastaanoton tarve niihin potilaisiin, jotka todennäköisesti hyötyvät ennaltaehkäisevästä lääkityksestä.

Suomalainen tyypin 2 diabeteksen sairastumisriskin arviointikaavake ja hoitajan toteama kohonnut verenpaine osoittautuivat käytännöllisiksi menetelmiksi seuloa väestöstä riskihenkilöitä.

Valtimotautien ehkäisyprojektissa Harjavallassa ja Kokemäellä todettiin verenpainetauti 1 106 henkilöllä, jotka eivät sairastaneet valtimotautia tai aiemmin todettua diabetesta. Heidän tutkimustulostensa avulla voidaan arvioida kohonneen verenpaineen vaikutusta sokeriaineenvaihduntaan ja verenpaineen aiheuttamiin kohde-elinvaurioihin.

Sokeriaineenvaihdunnan häiriöt ovat verenpainetautia sairastavilla yleisempiä kuin väestössä muutoin. Käyttämällä metabolisen oireyhtymän kriteerejä sokerirasitus-kokeen suorittamisen edellytyksenä voidaan tutkimusten määrää vähentää kolmanneksella ja silti löytää lähes kaikki diabetesta tai sen esiastetta sairastavat verenpainepotilaat.

Verenpainepotilaista etenkin metabolista oireyhtymää sairastavilla naisilla on suurentunut munuaisten vajaatoiminnan riski. Jos verenpainepotilaan munuaisten toimintaa arvioidaan pelkästään plasman kreatiniini -arvon perusteella, kolme neljästä munuaisten vajaatoimintaa potevasta jää toteamatta verrattuna laskennallisen glomerulusten suodattumisnopeuden määritykseen seulontamenetelmänä.

Joka kolmannella verenpainetautia sairastavalla voidaan todeta alaraajavaltimoiden kovettumista; useammin niillä, joiden ylä- ja alaverenpaineen erotus, pulssipaine on yli 65 mmHg. Verenpainetauti on itsenäinen perifeerisen valtimotaudin vaaratekijä. Tutkimuksessa käytetty menetelmä nilkka-olkavarsipainesuhteen määrittämiseksi soveltunee hyvin perusterveydenhuollon käyttöön riskihenkilöiden löytämiseksi.

Valtimotautien kokonaisriskin arviointimenetelmät tai uuden riskitekijän, herkän C-reaktiivisen proteiinin määritys eivät voi korvata kohde-elinvaurioiden mittaamista verenpainepotilaan valtimotautiriskin huolellisessa arvioinnissa.

Avainsanat: valtimotaudit, verenpainetauti, kohde-elinvauriot, sokeriaineenvaihdunta, epidemiologia

TABLE OF CONTENTS

ABBREVIATIONS

ABI	Ankle-brachial index
ACE	Angiotensin converting enzyme
ADP	Dorsalis pedis artery
ATP	Tibial posterior artery
ATP III	Third Adult Treatment Panel
ATR	Angiotensin receptor
CHD	Coronary heart disease
CI	Confidence interval
DBP	Diastolic blood pressure
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
EASD	The European Association for the Study of Diabetes
ESC	The European Society of Cardiology
ESH	The European Society of Hypertension
FINDRISC	Finnish Diabetes Risk Score
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
IDF	The International Diabetes Federation
IDMS	Isotope dilution mass spectrometry
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
JNC	United States Joint National Committee
LDL-C	Low-density lipoprotein cholesterol
LVH	Left ventricular hypertrophy
MDRD	Modification of Diet in Renal Disease
MetS	Metabolic syndrome
NSAIDs	Non-steroidal anti-inflammatory drugs
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAD	Peripheral arterial disease
PARs	Population attributable fractions
PP	Pulse pressure
RR	Relative risk
SCORE	Systematic Coronary Risk Evaluation
SBP	Systolic blood pressure
SD	Standard deviation
TASC II	The Trans-Atlantic Inter-Society Consensus
TC	Total cholesterol
WC	Waist circumference
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in text by their Roman numerals:

I **Korhonen PE, Jaatinen P, Aarnio P, Kantola I, Saaresranta T.** Waist circumference home measurement – a device to find out patients in cardiovascular risk. Eur J Pub Health 2009; 19:95-99.

II **Korhonen P, Aarnio P, Saaresranta T, Jaatinen P, Kantola I.** Glucose homeostasis in hypertensive subjects. Hypertension 2008; 51:945-949.

III **Korhonen P, Aarnio P, Vesalainen R, Saaresranta T, Kautiainen H, Järvenpää S, Kantola I.** Hypertensive women with the metabolic syndrome are at risk of renal insufficiency more than men in general population. J Hum Hypertens 2009; 23:97-104.

IV **Korhonen PE, Syvänen K, Vesalainen R, Kantola I, Kautiainen H, Järvenpää S, Aarnio P.** Ankle-brachial index is lower in hypertensive than in normotensive subjects in a cardiovascular risk population. J Hypertension 2009; 27:2036-2043.

V **Korhonen PE, Vesalainen R, Aarnio P, Saaresranta T, Kautiainen H, Järvenpää S, Kantola I.** The assessment of total cardiovascular risk in hypertensive subjects in the general population. *Submitted.*

In addition, some previously unpublished data are presented.

1 INTRODUCTION

Cardiovascular diseases are the leading cause of death in the world, representing almost 32 % of all deaths in women and 27 % in men in 2004 [1]. Nearly half of all deaths in Europe are due to cardiovascular diseases [2], coronary heart disease being the leading cause of mortality in men over 45 years, and in women over 65 years [3]. Stroke is the main cause of long-term disability in the Western society [4]. Patients diagnosed with atherothrombosis in one arterial bed have a 35 % chance of disease in one or more other arterial beds. This multivessel disease is most likely in patients with peripheral arterial disease (PAD) with one in two having also coronary heart disease and one in two cerebrovascular disease [5]. Among patients with established cardiovascular disease, the one-year incidences of cardiovascular death, myocardial infarction, stroke or hospitalization for atherothrombotic event are 15 % for coronary heart disease, 14 % for cerebrovascular disease, and 21 % for PAD patients [6].

The major causes of cardiovascular diseases are well established and well known: elevated blood pressure, raised plasma lipids, raised plasma glucose, and smoking. "The causes of the causes" – more often than not – are unhealthy diet, physical inactivity and central obesity. In clinical practice, physicians do not treat individual risk factors but people as a whole, whose cardiovascular risk usually reflects the combined effects of several risk factors. Patients with established cardiovascular or renal disease or type 2 diabetes mellitus are considered to be at the highest risk of major cardiovascular events, calling for intense cardiovascular risk reduction often with multidrug therapy. However, most patients in primary care do not belong to this category and identification of those at high risk requires the use of models to estimate total cardiovascular risk in order to adjust the intensity of the therapeutic approach accordingly. The European model for estimating individual's total cardiovascular risk in primary prevention of cardiovascular diseases is based on the large data-base provided by the Systematic Coronary Risk Evaluation (SCORE) project [7]. The SCORE model estimates the risk of dying from cardiovascular diseases over ten years, based on the knowledge of age, gender, smoking status, systolic blood pressure and cholesterol level.

Sometimes patients may also benefit from medical therapy directed toward a single risk factor. This is often the case with high blood pressure which is the leading risk factor to mortality throughout the world [1]. The complications of hypertension can be considered as hypertensive – caused more directly by the increased level of the blood pressure *per se* – or atherosclerotic which have multiple causes, with hypertension playing a variable role. With modern medical technology it is possible to detect hypertension-related structural and functional alterations in several organs before clinical symptoms occur. These target organ damages can be considered as intermediate

endpoints for cardiovascular events, and they markedly increase the patient's total cardiovascular risk beyond that caused by the simple presence of risk factors [8].

In Finland, blood pressure level of the population has declined since 1982, but this favourable trend has stopped between 2002 and 2007, most likely due to increasing obesity and alcohol consumption [9]. When concomitantly present, high blood pressure and obesity-related metabolic risk factors potentiate each other, leading to a total cardiovascular risk which is greater than the sum of its individual components [10, 11]. Changing life habits and ageing population are going to increase the prevalence of cardiovascular diseases worldwide as well as in Finland in the near future. To stem the rising tide of cardiovascular diseases, it will be necessary to strengthen primary care and attack the causes of these diseases. Determination of total cardiovascular risk is critical to the effective and efficient management and control of cardiovascular risk at both population and individual levels [12]. Although the SCORE system takes into account the multifactorial nature of cardiovascular diseases, it does not consider glucose homeostasis or hypertensive target organ damage like left ventricular hypertrophy, decreased renal function or ankle-brachial index, which can easily be measured in clinical practice also in primary care.

The aim of this thesis was to create a targeted screening method for primary care to identify persons at risk for cardiovascular diseases, and to assist clinicians in estimating absolute cardiovascular risk of their hypertensive patients. In doing so, primary care could govern the best use of limited resources to prevent cardiovascular diseases.

2 REVIEW OF THE LITERATURE

2.1 Cardiovascular disease prevention

Cardiovascular prevention aims to reduce mortality and morbidity in those at high risk and to assist those at low risk to maintain this stage lifelong [13]. Individuals at highest risk, such as patients with established cardiovascular or renal disease or diabetes mellitus, gain most from preventive efforts, but most deaths in a community come from those at lower levels of risk, simply because they are more numerous [13].

In the United Kingdom, it has been estimated that reductions in population total cholesterol, mean blood pressure and prevalence of smoking in apparently healthy people (primary prevention) achieved a fourfold larger reduction in coronary heart disease deaths between 1981 and 2000 than risk factor reduction in patients with coronary heart disease (secondary prevention) [14]. In Finland, based on the results of the FINRISK 2007 study it can be estimated that the mortality from cardiovascular diseases has declined 80 % since the North Karelia Project started in 1972 [15]. Between 1982 and 1997, coronary heart disease mortality rates in Finland decreased by 63 %, which can be attributed by 53 % to reductions in risk factors (population mean cholesterol 37 %, smoking 9 %, mean blood pressure 7 %), and by 24 % to improvements of medical treatments [16]. These findings emphasize the importance of a comprehensive strategy that promotes primary prevention programmes and also supports secondary prevention programmes [16].

Since the 1990s there has been an explosive increase in the number of people with diabetes globally. Type 2 diabetes is positioned to be one of the largest epidemics in human history and, certainly, it is one of the major threats to human health in the 21st century [17]. It has been shown that type 2 diabetics have as high a risk of myocardial infarction as non-diabetic patients with prior myocardial infarction [18]. Up to 50 % of all patients with type 2 diabetes are undiagnosed since they remain asymptomatic for many years [19].

The Interheart study confirmed in 2004 that nine common and potentially modified risk factors account for over 90 % of the risk of an initial acute myocardial infarction: dyslipidemia, hypertension, smoking, diabetes, abdominal obesity, lack of daily consumption of fruits and vegetables, lack of exercise, alcohol consumption and psychosocial factors [20]. The Finnish Diabetes Prevention Study was the first to demonstrate that type 2 diabetes can be prevented by changes in the lifestyles of high risk subjects [21]. However, there is no evidence that mass screening for detection of early stages of cardiovascular disease is a cost-effective way to prevent disease. The International Diabetes Federation (IDF) recommends the use of brief questionnaires to help health-care professionals to quickly identify people who may be at a higher risk of

developing type 2 diabetes and who need to have their level of risk further investigated [22]. Such a questionnaire is the Finnish Type 2 Diabetes Risk Assessment Form developed in 2001 based on highly representative random cohorts of the Finnish population [23]. Variables clearly correlated with the risk of developing diabetes were chosen for the test: age, body mass index, waist circumference, use of anti-hypertensive medication, history of elevated blood glucose, daily physical activity, daily consumption of fruit and vegetables, and history of diabetes in the family. The variables were assigned scores according to the relative risk they conferred. The higher the respondent's likelihood of developing diabetes, the more points they receive in the test (Figure 1).

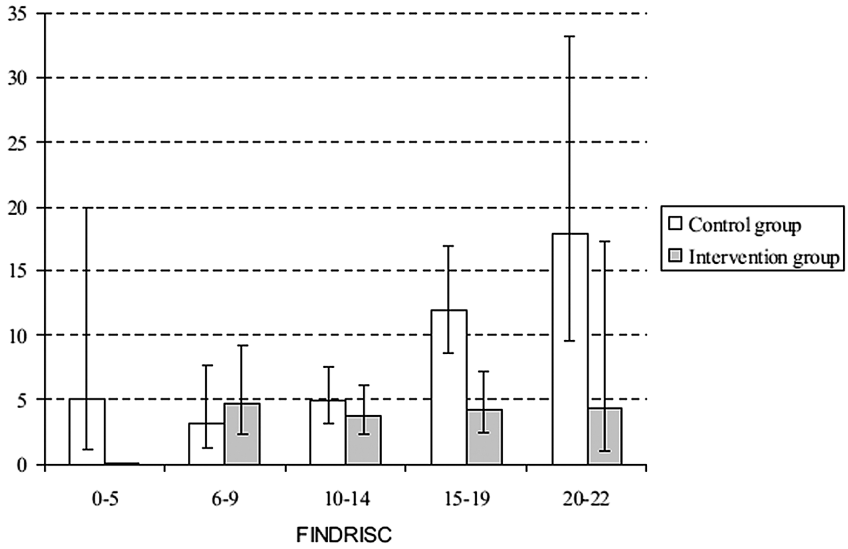


Figure 1. Incidence rate of diabetes (cases per 100 person-years ± 95 % CI) during the Finnish Diabetes Prevention Study intervention period by baseline Finnish Diabetes Risk Score (FINDRISC). In the intervention group, the intensive lifestyle intervention abolished the diabetes risk associated with baseline risk factors [24]. Reprinted with permission from National Institute for Health and Welfare.

FINDRISC value ≥9 has the sensitivity of 0.81 and the specificity of 0.76 to predict new cases of drug-treated type 2 diabetes [23].

2.2 Estimation of total cardiovascular risk

The combined effects of all risk factors determine total cardiovascular risk, and often, modest increases in multiple risk factors have a greater impact on the risk than a significant increase in just one risk factor [10, 12]. Total cardiovascular risk is a measure of the number of cardiovascular disease events in a defined population per unit of time. In effect, a total risk compares a person's or population's risk with a zero risk [12].

The principle of assessing the total cardiovascular risk associated with multiple risk factors was first introduced in New Zealand in 1993, in relation to the management of blood pressure [25]. Since then, a number of tools for estimating risk of coronary heart disease have been developed the most famous being models published by the Framingham Study investigators in the United States. The Framingham general cardiovascular risk profile for use in primary care [26] was introduced recently. Ideally though, cardiovascular risk prediction should be based on a prospective population cohort study undertaken in the population to which the risk score is to be applied [12].

The SCORE system for total cardiovascular risk estimation for clinical practice in Europe was introduced in 2003 [7]. It is based on data from 12 European cohort studies, and includes 205 178 subjects examined at baseline between 1970 and 1988 with 2.7 million years of follow-up and 7 934 cardiovascular deaths. The participating studies include the FINRISK Study with 37 296 Finnish 24–64-year-old participants [27]. The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, whether a heart attack, a stroke, an aneurysm of the aorta, or other. All International Classification of Diseases codes that could reasonably be assumed to be atherosclerotic are included. The cardiovascular risk factors entered into the SCORE model are total cholesterol or cholesterol/HDL cholesterol ratio, age, sex, smoking status, and systolic blood pressure. In the SCORE risk charts (Figure 2) information is provided in the age group 40 to 65. Persons aged 30 are essentially risk free within the next ten years, and on the other hand, the vast majority of persons over 65 years will have estimated cardiovascular disease death risks exceeding the 5 % threshold based on age only [13]. Risk estimates for clinical decisions in subjects younger than 60 years of age are made by projecting the risk to the age of 60 years. In this way, individuals with low cardiovascular risk today, but who will become high risk in the long term unless there is a risk reduction, can be identified and treated earlier. Separate charts for high risk and low risk countries are available based on national mortality statistics and estimates of the prevalence of major cardiovascular risk factors [7]. The high risk model (Figure 2) should be used in estimating the total cardiovascular risk of Finns.

The sensitivity of SCORE risk chart in predicting cardiovascular mortality in Finnish men and women has been shown to be 64 % (95 % CI 60.5 to 66.7) and 24 % (95 % CI 19.8 to 29.8), respectively. The corresponding figures regarding specificity are 66 % (95 % CI 65.0 to 66.7) and 94 % (95 % CI 93.5 to 94.3). [24].

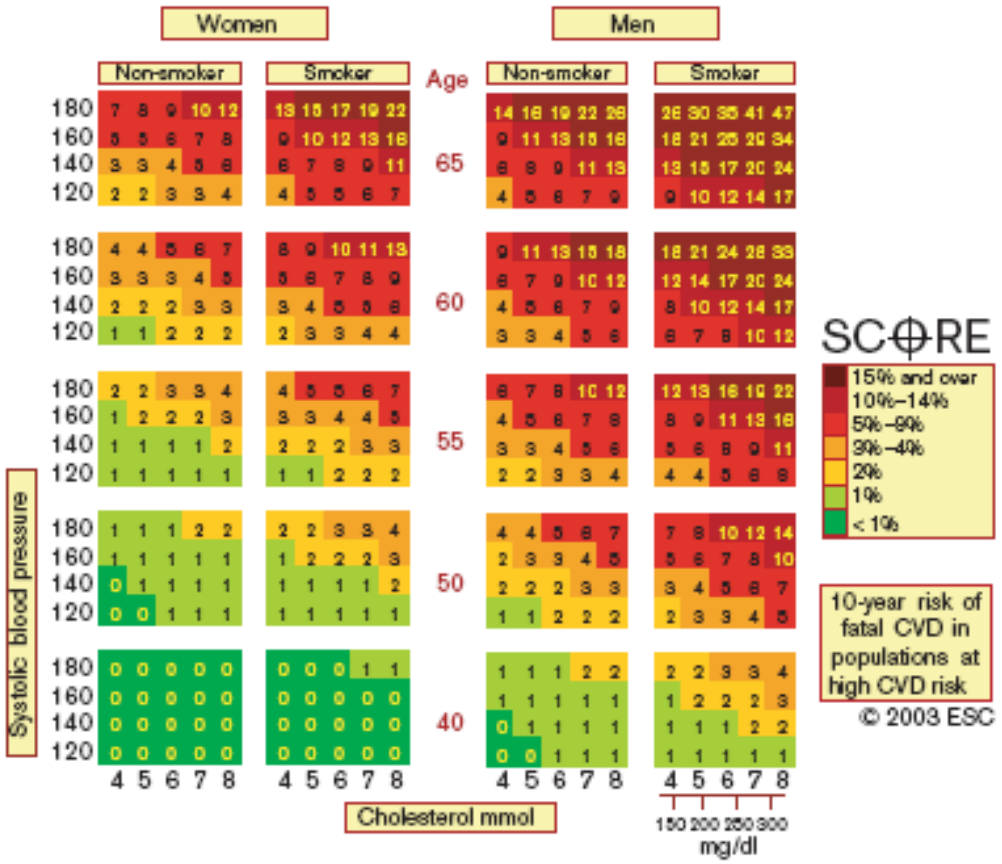


Figure 2. SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in population at high CVD risk based on age, gender, smoking, systolic blood pressure, and total cholesterol. Reproduced with permission from the European Society of Cardiology.

A 10-year risk of cardiovascular disease death of 5 % or more is arbitrarily considered high risk calling for preventive actions [7]. Besides fatal cardiovascular disease events, clinicians often wish for quantification of non-fatal events. FINRISK study has data on non-fatal events suggesting that at the level of fatal events of 5 %, total cardiovascular event risk is about 10 % [27]. Since 2008, clinicians in Finland have been able to estimate the risk of coronary events and stroke of their patients with the FINRISK function, which also takes into account the FINRISK survey 1992 not incorporated into the SCORE system [28].

The European Guidelines on cardiovascular disease prevention in clinical practice [13] categorizes patients as high risk according to concomitant cardiovascular disease or diabetes mellitus, the SCORE chart, markedly increased blood pressure or cholesterol level, and family history of premature cardiovascular disease (Table 1).

Table 1. Individuals at high risk for cardiovascular disease events

1. Patients with established atherosclerotic cardiovascular disease
2. Asymptomatic individuals who are at increased risk of cardiovascular diseases because of
   2.1. Multiple risk factors resulting in raised total cardiovascular risk (≥5 % 10-year risk of cardiovascular death)
   2.2. Diabetes mellitus type 2 and type 1 with microalbuminuria
   2.3. Markedly increased single risk factors (especially if associated with end-organ damage)
   - blood pressure ≥180/110 mmHg
   - total cholesterol ≥8.0 mmol/l or LDL-C ≥6.0 mmol/l
3. Close relatives of subjects with premature atherosclerotic cardiovascular disease or of those at particularly high risk: men at age <55 years, women at age <65 years

Risk calculation itself is based on evidence. However, using risk calculation in managing patients relies on consensus about when does a "risk" become a "high risk" justifying a lifelong drug treatment [29]. When the European Guidelines [13] were implemented to Norwegians, nearly all men aged 60 years and older and all women aged 65 years and older were classified as at "high risk" – in a population with one of the highest life expectancies in the world [30]. Overestimation of a person's risk of cardiovascular disease can cause unnecessary concern, it undermines the patient's informed choice for intervention, and it is likely to increase prescribing costs [31]. It may be necessary to add more specific secondary biomarkers or imaging methods to truly identify high-risk individuals [32]. This opinion is highlighted by the fact that up to 20 % of all coronary events - the most common and most lethal cardiovascular disease – occur in the absence of any major risk factors incorporated to the SCORE system [16, 33, 34].

Many biomarkers have been related to identify persons who are at increased risk for the development of cardiovascular disease. One of the most promising of these is a component of the acute-phase response, C-reactive protein, when measured in blood with high-sensitivity assay (hs-CRP). Several epidemiological studies have consistently observed an association between elevated plasma hs-CRP levels and cardiovascular events [35, 36, 37], and provided evidence for the hypothesis that manifestations of atherosclerosis may be an inflammatory disorder [38]. However, the association of hs-CRP and cardiovascular events is susceptible to confounding, since multiple cardiovascular risk factors, including smoking, hypertension, obesity, and lack of physical activity, all relate independently to elevated plasma levels of hs-CRP [39, 40]. Genetic variations in the CRP gene are associated with marked increases in hs-CRP levels, but these polymorphisms are not in themselves associated with an increased risk of ischemic vascular disease [41, 42]. For established risk factors, causality in the development of atherosclerosis has been proven by randomized treatment trials showing the clinical benefits of lowering blood pressure, cholesterol levels, and

glucose levels. The causal role of CRP needs to be tested in randomized clinical trials of CRP inhibitors [43].

2.3 Hypertension as a cardiovascular risk factor

Hypertension is the leading global risk factor for mortality and the third most important cause for disability-adjusted life-years, i.e. lost years of healthy life [44]. It has been estimated that every other death from ischemic heart disease or from stroke worldwide are attributable to high blood pressure (Figure 3) [45].

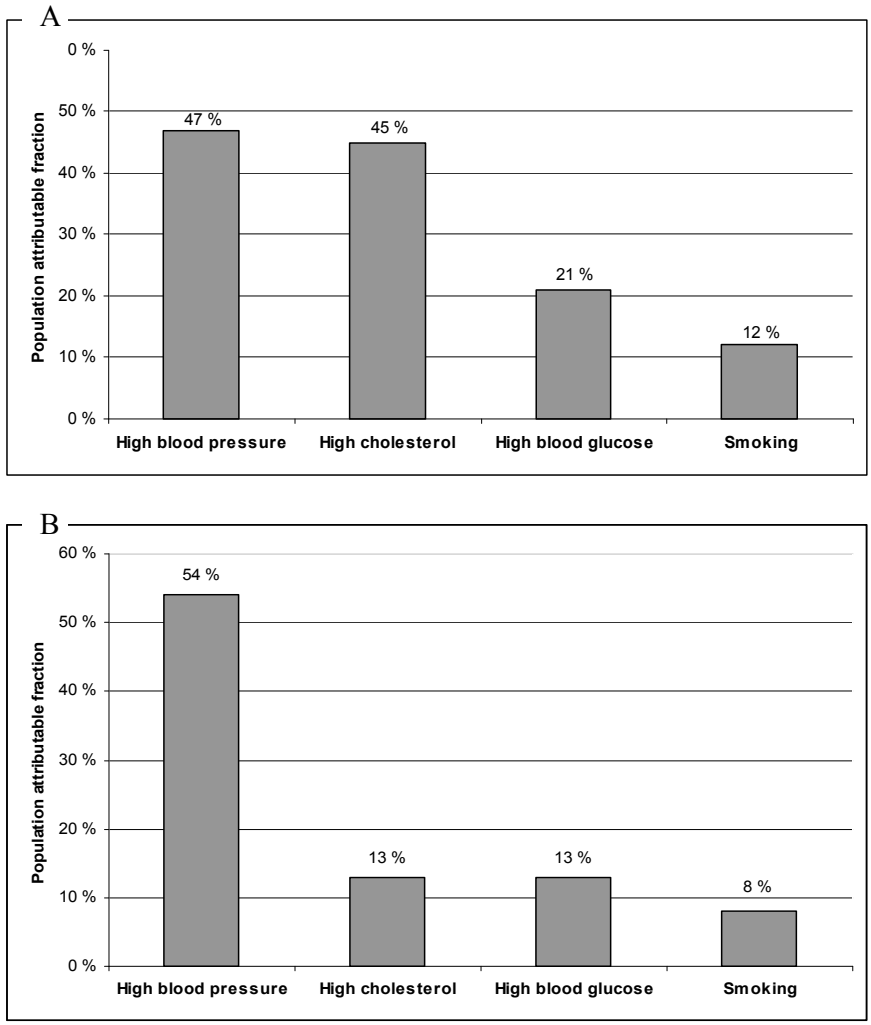


Figure 3. Population attributable fractions (PARs) for major risk factors of ischemic heart disease (A) and stroke (B) mortality. Population attributable fraction is equivalent to the proportional reduction in cardiovascular mortality that would be observed if the population were entirely unexposed compared with the actual exposure pattern [45]. The sum of individual PARs exceeds 100 % since a subject can simultaneously be attributed to more than one risk factor.

In a Finnish population sample of men and women aged 25–59 years, men with diastolic blood pressure >104 mmHg lost 2.7 years of life, of which 2.0 years due to cardiovascular disease, compared to men with diastolic blood pressure <95 mmHg. Among women the corresponding differences were 2.0 and 1.5 years. [46].

More than a quarter of the adult population of the world – totalling nearly one billion – had hypertension in the year 2000, and this proportion is predicted to increase by about 60 % to a total of 1.56 billion by the year 2025 [47].

The prevalence of hypertension increases with advancing age. As the arteries age, the elastic elements degrade with repeated stress and are replaced by inelastic elements such as collagen, leading to less compliance and an elevation of systolic blood pressure. The loss of elastic elements reduces recoil in the smaller vessels, leading to a decrease in diastolic blood pressure. Pulse pressure – the difference between the systolic and diastolic blood pressure – can be used as an indirect measurement of arterial compliance and thus atherosclerotic disease. [48]

The rise in systolic blood pressure continues throughout life, in contrast to diastolic blood pressure, which rises until approximately the age of 50, tends to level off over the next decade, and may remain the same or fall later in life [49]. Diastolic blood pressure is a more potent cardiovascular risk factor than systolic blood pressure until the age of 50; thereafter, systolic blood pressure is more important [50]. There is increasing evidence that pulse pressure predicts the development of coronary heart disease [51, 52], heart failure [53, 54], and stroke [55, 56] better than the other parameters of blood pressure. The Framingham Heart Study has shown that for any given level of pulse pressure 50 mmHg or higher, subjects with a parallel increase in systolic and diastolic blood pressure have only a minimal increase in coronary heart disease risk [51].

Data from observational studies involving more than one million individuals have indicated that death from both ischemic heart disease and stroke increases progressively and linearly from blood pressure levels as low as 115 mmHg systolic and 75 mmHg diastolic upward (Figure 4) [57].

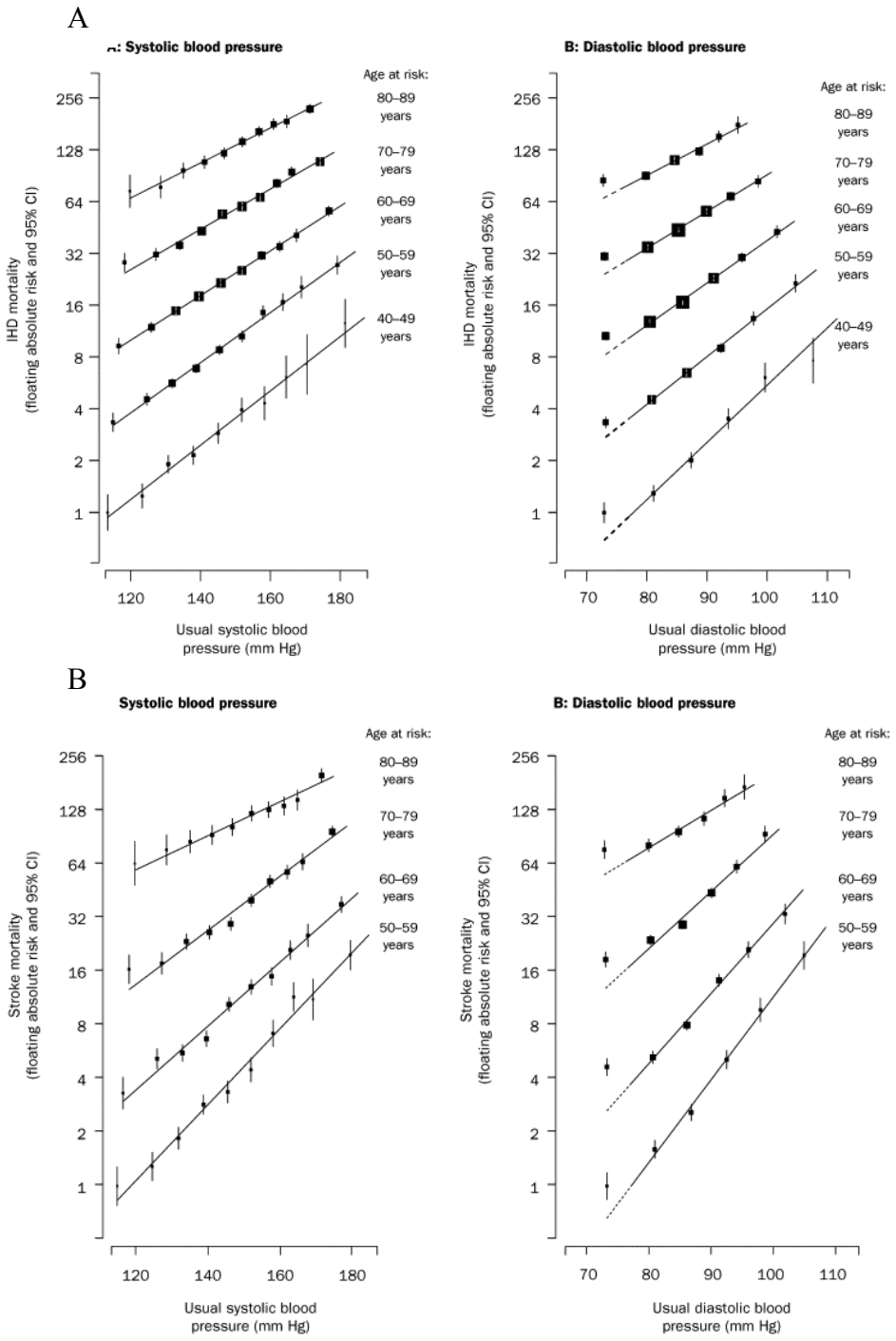


Figure 4. Ischemic heart disease (IHD) mortality rates (A) and stroke mortality rates (B) in each decade of age versus usual blood pressure at the start of that decade. Reprinted with permission from Elsevier [57].

For every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure, there is a doubling of mortality from both ischemic heart disease and stroke [57]. These facts make the classification of hypertension based on cut-off values arbitrary, but in daily practice, cut-off values simplify diagnostic and treatment approaches.

Because of the increased risk of cardiovascular diseases associated with levels of blood pressure previously considered to be normal, the 2003 United States Joint National Committee 7 Guidelines on Hypertension (JNC-7) introduced a new classification that includes the term "prehypertension" [58]. The 2007 Guidelines for the Management of Arterial Hypertension, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), however, kept the definition of high normal, normal and optimal blood pressure (Table 2) [8].

Table 2. Definitions and classification of blood pressure levels (mmHg) for adults according to the 2007 guidelines of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) and the 2003 guidelines of the United States Joint National Committee 7 (JNC-7).

ESH/ESC 2007 category	Systolic blood pressure		Diastolic blood pressure	JNC-7 2003 category
Optimal	<120	and	<80	**Normal**
Normal	120-129	and/or	80-84	**Prehypertension**
High normal	130-139	and/or	85-89	
Grade 1 hypertension	140-159	and/or	90-99	**Stage 1 hypertension**
Grade 2 hypertension	160-179	and/or	100-109	**Stage 2 hypertension**
Grade 3 hypertension	≥180	and/or	≥110	
Isolated systolic hypertension	≥140	and	<90	

The classification of the ESH/ESC guidelines seems more justified according to a recent Danish study in which 1 958 subjects initially free of overt cardiovascular disease or diabetes were followed for a median of 12.8 years. Subjects with high normal blood pressure had a greater risk (hazard ratio 1.8; 95% CI 1.0 to 3.1) for a composite endpoint of cardiovascular death, non-fatal myocardial infarction and stroke than subjects with optimal blood pressure. In contrast, subjects with normal blood pressure did not have a significantly increased risk compared to subjects with optimal blood pressure [59]. Separate consideration of normal and high normal blood pressure category was found reasonable also in the women's health study, in which women with high normal blood pressure had a 64 % higher risk for major cardiovascular event than women with normal blood pressure, and almost doubled compared with women with optimal blood pressure [60].

The ESH/ESC 2007 guidelines classify hypertensive subjects into risk categories "low", "moderate", "high" or "very high" risk to indicate an approximate risk of cardiovascular morbidity and mortality in the coming ten years [8]. The subjects with high or very high risk (Table 3) should be treated with lifestyle changes and medical treatment of cardiovascular risk factors, whereas patients with low to moderate risk are mainly adviced to adhere to healthy lifestyle. The distinction between high and very high risk categories is that very high risk subjects have established cardiovascular disease and multidrug treatment may be necessary throughout the blood pressure range from normal to high [8].

Table 3. Subjects with high or very high risk for cardiovascular diseases according to the 2007 guidelines of the European Society of Hypertension and the European Society of Cardiology [8].

- Established cardiovascular or renal disease
- Diabetes mellitus
- Metabolic syndrome
- SBP ≥180 mmHg and/or DBP ≥110 mmHg
- SBP >160 mmHg with DBP <70 mmHg
- One or more subclinical target organ damage
  - left ventricular hypertrophy
  - ankle-brachial index <0.9
  - estimated glomerular filtration rate <60 ml/min/1.73 m^2
  - slight increase in plasma creatinine: women 107–124 μmol/l
    men 115–133 μmol/l
  - microalbuminuria 30–300 mg/24 h
  - carotid artery wall thickening
  - increased arterial stiffness
- ≥3 cardiovascular risk factors
  - hypertension
  - age: women >65 years, men >55 years
  - smoking
  - dyslipidemia:
    TC >5.0 mmol/l or LDL-C >3.0 mmol/l or TG >1.7 mmol/l
    or HDL-C women <1.2 mmol/l, men <1.0 mmol/l
  - fasting plasma glucose 5.6–6.9 mmol/l
  - abnormal glucose tolerance test
  - abdominal obesity:
    waist circumference >88 cm in women, >102 cm in men
  - family history of premature cardiovascular disease:
    women at age <65 years, men at age <55 years

2.4 Subclinical target organ damage

The occurrence of major cardiovascular disease events, myocardial infarction and stroke, is usually the result of long-term exposure to risk factors and, in most hypertensive subjects, is preceded by the development of asymptomatic structural and functional

abnormalities at the vascular and cardiac level [61]. Detection of one of these target organ damages (Table 3) in hypertensive subjects initially considered to have low cardiovascular risk, should lead to shifting these patients to the high-risk category [8].

2.4.1 Arteries

The arterial system can be seen as a tube between the heart and the periphery. Left ventricular ejection is intermittent, but the elastic properties of the arterial tree permit generation of continuous forward pressure wave which travels along the tube and carries blood to the organs. Numerous branch points of the arterial tree and resistant arteries at the end of the tube generate retrograde waves towards the heart. In normal young adults, pressure wave velocity in the aorta is low and the reflected wave returns to the heart in diastole, boosting coronary perfusion [62].

Ageing, high blood pressure, chronic kidney disease, dyslipidemia, hyperglycaemia, and obesity are well-established promoters of arterial stiffening [63]. These risk factors can cause various alterations in arterial wall: breaks in elastic fibers, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, calcifications, and diffusion of macromolecules within the arterial wall [64]. With arterial stiffening, pulse wave velocity is increased, so that the reflected wave causes an augmentation to late systolic pressure, a greater fall in pressure in diastole, and increased pulse pressure [62]. In essential hypertension, endothelial dysfunction has been shown to occur at the level of both resistance and conduit arteries, and the relative vasoconstriction adversely affects wave reflection and systolic pressure augmentation, and may contribute to hypertensive target organ damage [65, 66].

Several screening tests are available for identifying the structural and functional abnormalities of arteries. Ultrasound examination of the carotid arteries with measurement of intima-media thickness and the presence of atherosclerotic plaques can be used for precise risk stratification in hypertensive patients [67]. Available data indicate that intima-media thickness >0.9 mm represents a risk of clinical cardiovascular events [68]. Measurement of carotid-femoral pulse wave velocity provides a non-invasive assessment of arterial stiffness, which has been shown to have an independent predictive value for cardiovascular mortality, coronary events and strokes in patients with uncomplicated essential hypertension [69-71]. Measurements of the wall to lumen ratio of small arteries by tissue biopsy and the endothelial responsiveness to various stimuli are invasive and laborious techniques. The availability and high cost of these procedures limit their use mainly to research centres.

In contrast to the other cardiovascular diseases, peripheral arterial disease (PAD) is easily detectable with determination of the ankle-brachial index (ABI), the ratio between the systolic blood pressures in the arm and the ankle, using a continuous wave Doppler

unit and a blood pressure manometer. ABI level ≤0.90 is 95 % sensitive in detecting angiogram-positive PAD and almost 100 % specific in identifying apparently healthy individuals [72]. PAD is rarely an isolated disease of the lower limb arteries; patients with PAD frequently also have coronary heart disease or cerebrovascular disease [5, 73, 74]. The prevalence of PAD in general adult population aged ≥40 years has varied between 3.6 % and 6.9 % in published studies [75-78]. Longitudinal follow-up studies among general white population have revealed that PAD increases the risk of cardiovascular mortality and morbidity by twofold compared with subjects without PAD [79, 80]. Lamina et al. also observed an inverse linear relationship between ABI and cardiovascular disease outcomes which even included ABI values between 0.9 and 1.1 [80]. This is in concordance with a recent meta-analysis of 16 cohort studies, in which participants aged 47 to 78 years were derived from general population [81]. It was shown that in men with ABI 0.91–1.00, compared to reference ABI 1.11–1.20, the hazard ratios for total mortality, cardiovascular mortality and major coronary events were 1.61 (95 % CI 1.47 to 1.77), 1.68 (95 % CI 1.40 to 2.00) and 1.43 (95 % CI 1.23 to 1.66), respectively. The corresponding figures in women were 1.52 (95 % CI 1.38 to 1.67), 1.84 (95 % CI 1.53 to 2.22) and 1.53 (95 % CI 1.30 to 1.79) [81]. The prevalence of borderline PAD in unselected samples of United States adults has been reported to be 7.1 % – 8.7 % depending on the definition [76, 82]. Different methods for calculating ABI, and different cut-off values for the ABI to define PAD have often resulted in non-comparable prevalence of PAD between published studies. International cooperation between medical and surgical vascular, cardiovascular, vascular radiology and cardiology societies provided a new consensus statement about diagnosis and management of PAD in 2007. This 2007 Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) defines cut-off value of ABI ≤0.90 for diagnosing PAD by using the higher of the two ankle pressures in calculating ABI [83]. This method has been recently shown to underestimate the true prevalence of PAD. With regard to cardiovascular prognosis, more patients at risk could be identified using the lower instead of the higher ankle pressure in calculating ABI [84].

2.4.2 Heart

Hazardous effects of arterial stiffening are attributable to greater systolic pressure, which increases cardiac metabolic requirements, causes hypertrophy, and predisposes to both systolic and diastolic heart failure. On the other hand, the lower pressure throughout diastole impairs coronary perfusion and predisposes to myocardial ischemia and coronary events [62]. Left ventricular hypertrophy (LVH) significantly increases the risk of coronary artery disease, congestive heart failure, cerebrovascular accidents, arrhythmia, and sudden death [85-87]. Echocardiographically determined LVH increases the relative risk of mortality by twofold in subjects with coronary artery disease and by fourfold in those with normal epicardial coronary arteries [88]. Increased left ventricular mass and

enlarged left atrium are independent determinants of new onset atrial fibrillation [89], which is the major risk factor for embolic stroke [90]. On a population basis, hypertension is the most important risk factor for atrial fibrillation [91].

Electrocardiography (ECG) is a part of routine assessment of subjects with hypertension in order to detect LVH, patterns of strain, ischaemia and arrhythmias. The 2007 ESH/ESC Guidelines define ECG-LVH by the Sokolow-Lyon index (SV_1 + RV_{5-6}) >38 mm or by the Cornell product [Cornell voltage (RaVL + SV_3 plus 6 mm for women) x QRS duration] >2440 mm x ms [8]. These criteria for ECG-LVH are independent predictors of cardiovascular disease events and in addition, regression of the Cornell product by 1 050 mm x ms and the Sokolow-Lyon index by 10.5 mm is associated with 14.5 % and 16.6 % reductions in the incidence of cardiovascular morbidity and mortality in hypertensive patients aged 55 to 80 years within five years [92]. However, the sensitivity of the Cornell product in detecting LVH is only 51 % and that of Sokolow-Lyon index 31 % when examined at a matched specificity of 95 % [93]. Hence, ECG is a poor screening tool to exclude LVH in hypertensive patients. The 2007 ESH/ESC Guidelines recommend echocardiography when a more sensitive detection of LVH is considered useful [8]. Echocardiography may be more informative than ECG in hypertensive patients who, on the basis of age, sex, smoking history, and blood lipids, are at low or intermediate risk of cardiovascular events. In patients known to be at high risk, echocardiographically detected LVH will often not affect clinical management, because interventions to reduce cardiovascular disease risk are already indicated [94].

In a recent study of hypertensive patients without criteria for ECG-LVH, R-voltage in lead aVL correlated significantly with echocardiographically measured left ventricular mass [95]. More importantly, R in aVL correlated with cardiovascular events during the 7.7 years of follow-up: each 0.1 mV (1.0 mm) higher value of the R wave voltage was associated with a 9 % higher risk of cardiovascular events. A voltage value of 0.57 mV (5.7 mm) in R-aVL marked the crossing point between sensitivity and specificity, and might be considered as a diagnostic threshold [95].

The sensitivity of ECG voltages for a diagnosis of LVH tends to decrease in obese subjects due to the accumulation of subcutaneous adipose tissue in the chest wall [96, 97]. On the other hand, obesity has been shown to be associated with increased left ventricular mass estimated by echocardiography [98, 99]. In a study of 1 840 lean and 3 555 overweight (BMI ≥25 kg/m^2) subjects with hypertension, LVH determined as Sokolow-Lyon criterion ≥3.5 mV (≥35 mm) was detected in 16 % of lean and 12 % in overweight women, and in 35 % in lean and 20 % in overweight men [100]. For each of 0.1 mV (1.0 mm) increase in ECG voltage, the age and sex adjusted risk of stroke, ischemic heart disease and cardiovascular disease mortality increased significantly by 3.0, 1.5 and 1.8 % in overweight subjects and by 2.8, 1.8 and 2.4 %

in lean subjects [100]. Even though the sensitivity of ECG-LVH is lower in obese than in lean subjects, the Sokolow-Lyon voltage criterion of ≥3.5 mV (≥35 mm) is a good predictor of mortality also in overweight subjects [100].

To date, the most accurate estimation of left ventricular mass can be obtained using cardiac magnetic resonance imaging [101], the cost of which, however, prevents large scale use. The same applies to coronary angiography and high resolution cardiac computer tomography, which can demonstrate atherosclerosis in coronary arteries, but are usually not available in primary care.

2.4.3 Brain

By increasing arterial stiffness, hypertension can increase the risk of stroke through several mechanisms, including an increase in central pulse pressure, influencing arterial remodelling both at the site of the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and plaques, the likelihood of plaque rupture, and the prevalence and severity of cerebral white matter lesions [102-106]. Hypertension and older age increase the prevalence of small silent brain infarcts, microbleeds and white matter lesions, which are associated with an increased risk of stroke, cognitive decline and dementia [107, 108]. Silent brain infarcts are five times as prevalent as symptomatic brain infarcts in the general population aged 60 to 90 years [109], and the presence of silent brain infarcts more than double the risk of dementia during four years follow-up time [110]. Hypertension is strongly associated with silent brain infarcts (age- and gender-adjusted Odds ratio (OR) 2.4; 95 % CI 1.7 to 3.3), but diabetes mellitus and smoking are not [109]. Cranial magnetic resonance imaging is superior to computed tomography to identify cranial small vessel disease, but availability and cost considerations do not allow a widespread use of magnetic resonance imaging in the evaluation of hypertensive subjects before clinical symptoms occur [8].

2.4.4 Eye

Only in the optic fundi can small blood vessels be seen with ease, either by fundoscopy or by retinal photography. In response to hypertension, but also to other processes, retinal arterioles narrow, their intima and media thicken and show sclerotic changes [111]. These changes of hypertensive retinopathy manifest as diffuse and focal areas of arterial narrowing, and compression of the venules by arterioles at their common adventitial locations (arteriovenous nipping) [112]. With more pronounced hypertension, the blood-retinal barrier breaks down, resulting in exudation of blood (haemorrhages), lipids (hard exudates), and subsequent ischemia of nerve-fibre layers (cotton-wool spots) [112]. In the setting of hypertensive crisis, raised intracranial pressure and concomitant optic nerve ischemia can lead to disc swelling (papilloedema)[112].

Retinal arteriolar narrowing is associated with increased risk of incident coronary heart disease (relative risk 1.37 adjusted for cardiovascular risk factors) in women but not in men, suggesting a more prominent microvascular role in the development of coronary heart disease in women than in men [113]. In a 3-year population-based cohort study, incident stroke events were more common in participants with signs of hypertensive retinopathy than in participants without retinopathy (Figure 5) [114].

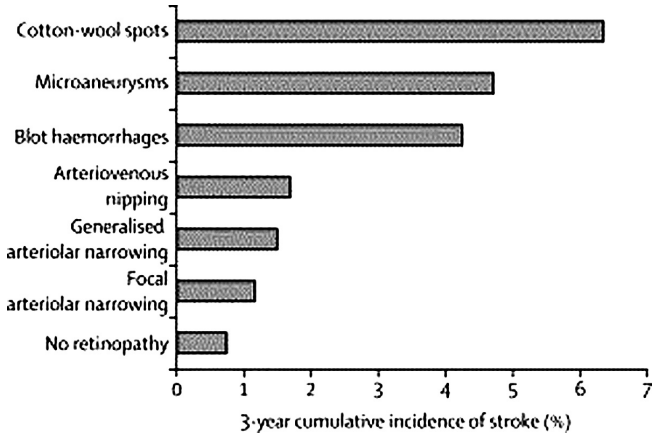


Figure 5. Relation between signs of hypertensive retinopathy and 3-year incidence of stroke. Reprinted with permission of Elsevier [114].

The ESH/ESC 2007 guidelines classify advanced retinopathy (haemorrhages, exudates, papilloedema) into established cardiovascular disease [8].

2.4.5 Kidney

Chronic kidney disease is a worldwide public health problem with rising incidence, poor outcomes and high cost. Chronic kidney disease is also an independent risk factor for cardiovascular diseases; individuals with GFR <60 ml/min/1.73 m^2 have an approximate 16 % increase, and individuals with GFR <30 ml/min/1.73 m^2, a 30 % increase in cardiovascular mortality [115]. In fact, patients with chronic kidney disease are 100 times more likely to die, principally of cardiovascular disease, than to develop kidney failure [116].

Hypertension can both initiate kidney damage and cause faster decline in kidney function after initiation of kidney damage [117]. Pathological changes in renal biopsy of non-diabetic hypertensive subjects with glomerular filtration rate (GFR) between 25 to 70 ml/min/1.73 m^2 and without marked proteinuria show hyalinization and sclerosis of the afferent arterioles, referred to as hypertensive nephrosclerosis [118]. Brenner et al. hypothesized that the reduction of nephron mass – due to any cause – elicits preglomerular vasodilatation in the remaining nephrons, leading to enhanced transmission of systemic blood pressure to the glomerular capillaries [119]. The ensuing

glomerular hypertension and hyperfiltration in the remaining nephrons serve to maintain overall glomerular filtration rate and sodium balance in the short term, but also lead to progressive hypertensive glomerular damage, glomerular protein leakage, and renal function loss in the long term [119]. It has been demonstrated in autopsy studies that women have fewer glomeruli than men [120, 121] and that the number of nephrons is reduced in white patients with primary hypertension [122].

Renal excretory function, as represented by GFR, deteriorates with age beginning in the third or fourth decade of life, and by the sixth decade, GFR commonly declines by 1 to 2 ml/min per year [123]. This age-related loss of renal function is proportional to blood pressure level, and the rate of GFR deterioration can accelerate to 4 to 8 ml/min per year if systolic blood pressure remains uncontrolled [123]. GFR <60 ml/min/1.73 m^2 is selected as the cut-off value for definition of chronic kidney disease because it represents a reduction by more than half of the normal value of 125 ml/min/1.73 m^2 in young adults, and this level of GFR is associated with the onset of laboratory abnormalities characteristic of kidney failure, including increased prevalence of several cardiovascular risk factors [124].

Diagnosis and staging of chronic renal insufficiency has for decades been based on serum creatinine concentration, which is an inexpensive, common test in clinical practice. However, serum or plasma creatinine is quite an inaccurate test for estimating kidney function: it begins to rise only when GFR has diminished by one half and thereafter the rise is exponential, not linear to GRF deterioration (Figure 6).

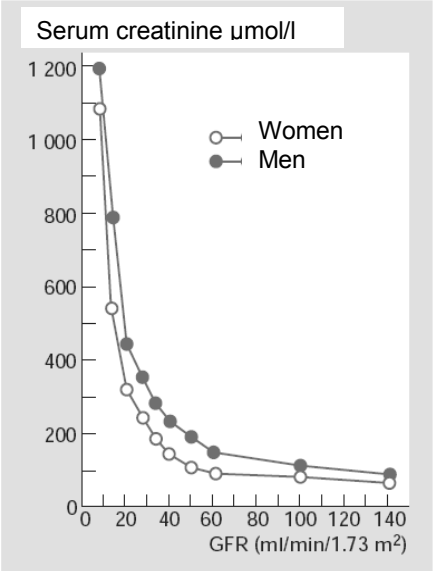


Figure 6. The relationship between serum creatinine concentration and glomerular filtration rate (GFR). Reproduced with permission from Lääketieteellinen Aikakauskirja Duodecim [125].

Estimation of GFR (eGFR) with prediction equations, such as the Cockcroft-Gault formula [126] or Modification of Diet in Renal Disease (MDRD) Study equation [127] including serum creatinine, age, gender, race, and body size, can help to avoid the misclassification of individuals on the basis of serum creatinine alone.

A new definition and classification system of chronic kidney disease was published in the year 2005 in order to identify an earlier, often asymptomatic stage where interventions may prevent the progression to end-stage renal disease [128]. Kidney disease severity is classified into five stages according to the level of GRF (Table 4). Chronic kidney disease is defined as kidney damage or GFR <60ml/min/1.73m^2 for three months or more, irrespective of cause. Kidney damage can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio in two of three spot urine specimens [128].

Table 4. Classification of chronic kidney disease

Stage	Description	GFR ml/min/1.73m^2	Marker of kidney damage
I	Kidney damage with normal or increased GFR	≥90	Proteinuria, hematuria
II	Kidney damage with mildly decreased GFR	60 − 89	Proteinuria, hematuria
III	Moderately decreased GFR	30 − 59	Chronic renal insufficiency, early renal insufficiency
IV	Severely decreased GFR	15 − 29	Chronic renal insufficiency, late renal insufficiency
V	Kidney failure	<15 or dialysis	End-stage renal disease, uremia

Subclinical increase of the albumin excretion in the urine, i.e. microalbuminuria, has been related to subclinical atherosclerosis [129, 130] or endothelial dysfunction and perhaps an augmented atherogenic susceptibility to other risk factors, including arterial hypertension [131]. Microalbuminuria has been shown to confer a 4-fold increased risk of ischemic heart disease among hypertensive or borderline hypertensive subjects [132]. However, the prevalence of microalbuminuria ranges from 5 % to 40 % among non-diabetic subjects with essential hypertension [132]. The reason for this high variability relates to severity and duration of hypertension, other cardiovascular risk factors, and day-to-day variability of albumin excretion which lays in the range of 31–52 % [133].

The European 2007 guidelines for the management of arterial hypertension list an eGFR level <60 ml/min per 1.73 m^2, slight increase in plasma creatinine (women: 107 to 124 μmol/l, men: 115 to 133 μmol/l), and microalbuminuria among evidence of subclinical organ damage (Table 2) [8].

The problem with the estimation of GFR on the basis of equations depending on serum creatinine is that mildly elevated creatinine, and thus mildly decreased eGFR, is both a marker of fitness (increased muscle mass) and a marker of disease. Thus, the diagnosis of chronic kidney disease, especially with stage 3, requires clinician input that considers additional evidence of kidney damage such as hypertension, diabetes, proteinuria, hematuria, renal ultrasound and metabolic abnormalities [134].

2.5 Hypertension and metabolic risk factors of cardiovascular disease

2.5.1 Dyslipidemia

Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein(a), and in women but not men, fasting plasma triglycerides are all independent predictors of coronary heart disease with no threshold values [135]. Elevated nonfasting triglyceride levels are associated with increased risk of coronary events also in men [136]. In middle-aged subjects free of cardiovascular disease, risk of coronary events is elevated approximately 40 % for every 1 mmol/l increment in LDL-C, the optimal LCL-C value being <2.6 mmol/l [135]. However, in epidemiological studies, there is little evidence for any important association between circulating cholesterol and incident stroke [137, 138].

The magnitude of the risk of total mortality and coronary heart disease mortality associated with hypercholesterolemia is similar to the magnitude of risk associated with hypertension [139]. To determine the joint relevance of cholesterol and blood pressure with cardiovascular mortality, a meta-analysis of 61 prospective studies was carried out, consisting of almost 900 000 adults without previous cardiovascular disease and with baseline measurements of total cholesterol and blood pressure [140]. In both men and women, a 1 mmol/l lower total cholesterol was associated with an ischemic heart disease mortality that was about a half lower in early middle age (40–49 years), about a third lower in later middle age (50–69 years), and about a sixth lower in old age (70–89 years). These findings were only slightly attenuated by adjustment for systolic blood pressure and were unaltered by adjustment for smoking. The absolute effects of cholesterol and blood pressure on ischemic heart disease mortality were approximately additive (Figure 7). [140].

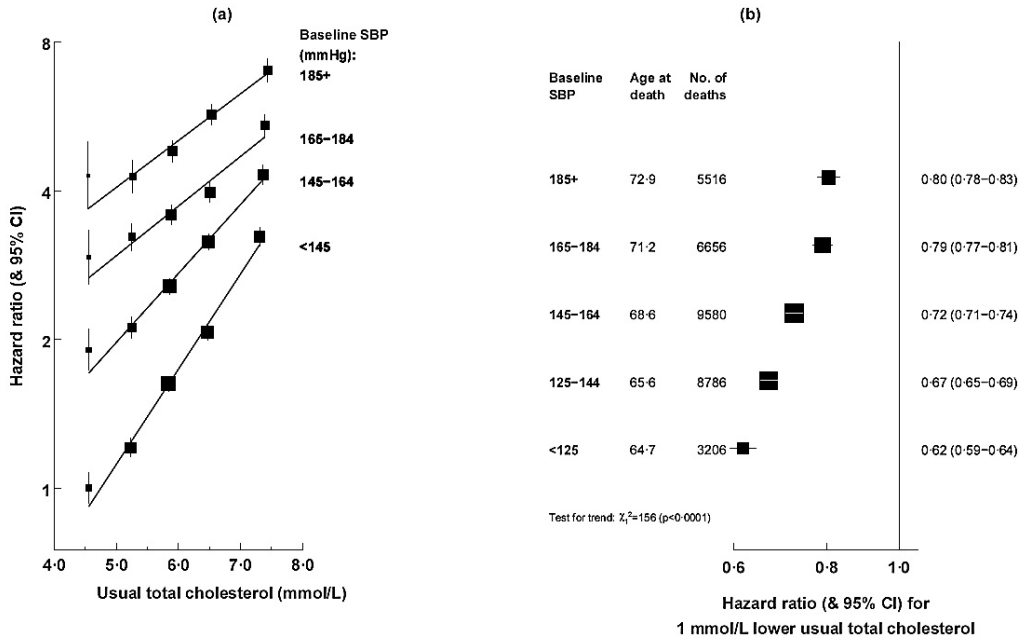


Figure 7. Ischemic heart disease mortality versus usual total cholesterol: (a) systolic blood pressure (SBP) associations (b) SBP-specific hazard ratios for 1 mmol/l lower usual total cholesterol. Reprinted with permission from Elsevier [140].

The role of hypercholesterolemia and tobacco smoking in cardiovascular mortality is significantly higher in younger than in older hypertensive subjects. In a French population-based study of 29 640 normotensive men without associated risk factors (reference group) and 60 343 hypertensive men with and without associated risk factors, relative risk of cardiovascular mortality in hypertensive men <55 years with hypercholesterolemia was 1.80 (95 % CI 1.50 to 2.16) and in hypertensive men ≥55 years 1.18 (95 % CI 1.02 to1.38) compared to the reference group [141]. Thus, in younger hypertensive subjects, evaluation of cardiovascular risk and therapeutic strategies should target associated risk factors, and in older subjects, the presence of high blood pressure levels seems to be the major determinant of cardiovascular risk [141].

Although epidemiological data do not show serum cholesterol concentration to be closely associated with stroke, lipid lowering agents, statins, have been shown to be effective in preventing both coronary and cerebrovascular events. Administration of a statin in hypertensive patients with at least three other cardiovascular risk factors and a serum cholesterol <6.5 mmol/l reduced coronary events by 36 % and stroke by 27 % [142]. In comparison, several randomized placebo controlled trials and meta-analyses investigating the benefit of blood pressure lowering have shown that antihypertensive treatment is associated with a reduction in the risk of stroke by 30-40 % and in the risk of coronary events by approximately 20 % [8].

2.5.2 Obesity

Being overweight or obese has become highly prevalent throughout the world in the 21st century. In Finnish adult population, there has been a steady increase in the waist circumference both in men and women during the years 1987–2007 [9]. In a recent population survey among 4 500 randomly selected Finns aged 45 to 74 years, the prevalence of obesity, defined as body mass index ≥30 kg/m^2, was 24 % in men and 29 % in women [143]. In addition, 50 % of men and 38 % of women were overweight (body mass index 25–29.9). The prevalence of central obesity, defined as waist circumference ≥94 cm in men and ≥80 cm in women, was 69 % in men and 76 % in women [143].

Data from almost 900 000 adults in 57 prospective studies showed that overall mortality is lowest at body mass index 22.5–25 kg/m^2 in both sexes and at all ages [144]. Above this range, each 5 kg/m^2 higher body mass index is associated with about 40 % higher vascular mortality (HR 1.41; 95 % CI 1.37 to 1.45), 120 % higher diabetic mortality (HR 2.16; 95 % CI 1.89 to 2.46), 60 % higher renal mortality (HR 1.59; 95 % CI 1.27 to 1.99), 80 % hepatic mortality (HR 1.82; 95 % CI 1.59 to 2.09), and 30 % higher overall mortality (HR 1.29; 95 % CI 1.27 to 1.32). Median survival is reduced by 2–4 years at body mass index 30–35 kg/m^2, and by 8–10 years at body mass index 40–45 kg/m^2 compared to the apparent optimum of 22.5–25 kg/m^2 [144].

According to data from a United States population survey, hypertension is the most common condition related to overweight and obesity that shows a marked increase with increasing categories of body mass index. Prevalence of hypertension rose from 15 % for the normal weight category (body mass index 18.5–24.9) to 42 % among obese men and 38 % among obese women [145].

Although body mass index provides a useful measure of obesity, it does not take into account where the excess fat is located in the body. Abdominal or visceral obesity with accumulation of fat within liver, pancreas and muscle, and estimated with waist circumference measurement, is also strongly associated with risk of death even after adjustment with body mass index [146]. Relative risk (RR) of death among Europid men with waist circumference 96.5–102.6 cm was 1.63 (95 % CI 1.46 to 1.83), and with waist circumference ≥102.7 cm 2.05 (95 % CI 1.80 to 2.33) compared to men with waist circumference <86.0 cm [146]. In Europid women with waist circumference 81.0–88.9 cm, RR was 1.46 (95 % CI: 1.30 to 1.64), and with waist circumference ≥89.0 cm RR was 1.78 (95 % CI 1.56 to 2.04) compared to waist circumference <70.1 cm [146].

There is increasing evidence that adipose tissue is a source of inflammatory cytokines like C-reactive protein, interleukin-6, and tumor necrosis factor-α which may create a pro-inflammatory and pro-thrombotic vascular milieu in obesity [147]. However,

a direct relationship between the cytokines released from adipose tissue and hypertension or target organ damage or both has not yet been clearly established.

2.5.3 The metabolic syndrome

Arterial hypertension is often part of a constellation of metabolic disturbances including abdominal obesity, dyslipidemia, and impaired glucose homeostasis. These cardiovascular risk factors occur simultaneously more often than would be expected by chance alone, supporting the existence of a discrete disorder, the metabolic syndrome. A meta-analysis of longitudinal studies that included 172 573 people, indicated that subjects with three or more cardiovascular risk factors (regardless of whether this was termed the metabolic syndrome) had 1.78 (95 % CI 1.58 to 2.00) relative risk of cardiovascular disease events and death [148]. The association remained after adjusting for traditional cardiovascular risk factors, RR 1.54 (95 % CI 1.32 to 1.79). Among subjects without prevalent cardiovascular disease, RR 1.49 (95 % CI 1.37 to 1.61) was detected in subjects with the three or more cardiovascular risk factors compared with those without [148].

Several criteria for the metabolic syndrome have been developed to improve identification of individuals at risk for type 2 diabetes and cardiovascular disease [149]. The most clinically oriented definitions of the metabolic syndrome are the United States National Cholesterol Education Program Third Adult Treatment Panel (ATP III) definition [150] and the International Diabetes Federation (IDF) definition [151] (Table 5).

Table 5. Diagnostic criteria of the metabolic syndrome

Clinical measure	**ATP III (2005)** [150] any three of the following	**IDF (2005)** [151] WC + any two of the following
Waist circumference	>88 cm in women >102 cm in men	≥80 cm in women ≥94 cm in men
Blood pressure	≥130/85 mmHg or drug therapy	≥130/85 mmHg or drug therapy
Fasting plasma glucose	≥5.6 mmol/l * or drug therapy	≥5.6 mmol/l or type 2 diabetes
Triglycerides	≥1.7 mmol/l or drug therapy	≥1.7 mmol/l or drug therapy
HDL-C	<1.29 mmol/l in women <1.03 mmol/l in men or drug therapy	<1.29 mmol/l in women <1.03 mmol/l in men or drug therapy

* Before the year 2005 the cut-off value of fasting plasma glucose was 6.1 mmol/l

The Hoorn Study showed that in a Dutch population-based cohort of 50–75 years old men and women, the metabolic syndrome – defined as the ATP III criteria – is associated with a twofold increased risk of incident cardiovascular morbidity and mortality [152]. The Kuopio Ischaemic Heart Disease Risk Factor Study followed 1 209 Finnish men

aged 42 to 60 years at baseline and initially free of cardiovascular disease or diabetes, for 12 years [153]. Men with the metabolic syndrome as defined by the ATP III, were 2.9 to 4.2 times more likely to die of coronary heart disease after adjustment for conventional cardiovascular risk factors. However, the risk of death from any cardiovascular cause did not reach statistical significance. [153].

In an Italian population study, 80 % of the 2 013 individuals aged 25–74 years fulfilled the blood pressure criteria ≥130/85 of the metabolic syndrome [154]. Patients with the metabolic syndrome according to the ATP III criteria had greater left ventricular mass index than the patients without the metabolic syndrome. Over the follow-up period of 12 years, the incidence of cardiovascular and all-cause death in subjects with the metabolic syndrome was 7.3 % and 20.2 %, respectively. The corresponding figures in subjects without the metabolic syndrome were 2.4 % and 9.2 % ($p < 0.0001$ for both) [154].

A limited number of studies have examined the prognostic importance of the metabolic syndrome in hypertensive populations. An Italian study followed up 1 742 hypertensive subjects (age 50 ± 12 years) without cardiovascular disease for a mean of 4.1 years [155]. Patients with the metabolic syndrome (34 %) according to the ATP III criteria had an almost double cardiovascular disease event rate than those without. In patients without diabetes, the hazard ratio was 1.43 (95 % CI 1.02 to 2.08) [155]. Different results were obtained in another Italian study of 2 334 hypertensive subjects aged 45–75 years, of whom 33 % had the metabolic syndrome according to the ATP III criteria at baseline [156]. During the four years of follow-up, there was no significant difference in the incidence of new cardiovascular disease events between patients with or without the metabolic syndrome. However, new-onset diabetes occurred in 5.5 % of the study subjects, and was three times higher among patients with than those without the metabolic syndrome (10.3 % versus 3.4 %, $p < 0.0001$) [156].

There is controversy over the ability of the metabolic syndrome to improve the prediction of cardiovascular disease beyond what is achievable by the conventional risk prediction tools. In fact, in two prospective studies of middle-aged subjects, the diagnosis of the metabolic syndrome defined as the ATP III, did not predict cardiovascular events as well as the Framingham risk score [157, 158]. However, the metabolic syndrome was shown to be a strong predictor of incident type 2 diabetes [158]. Also in elderly populations up to 82 years, the metabolic syndrome and its components had weak or no association with cardiovascular disease risk but were associated with increased risk of type 2 diabetes [159]. A recent collaborative data analysis of 4 041 men and 3 812 women of Finnish and Swedish population-based cohorts showed that hazard ratios for ischemic stroke in men were 1.16 (95 % CI 0.77 to 1.74) and 1.27 (95 % CI 0.87 to 1.86), respectively for the ATP III and the IDF definitions of the metabolic

syndrome, and in women 2.31 (95 % CI 1.27 to 4.20), and 1.91 (95 % CI 1.05 to 3.49), respectively [160]. The corresponding hazard ratios for coronary heart disease were 1.63 (95 % CI 1.25 to 2.13), and 1.46 (95 % CI 1.12 to 1.89) in men, and 1.81 (95 % CI 1.02 to 3.21), and 2.47 (95 % CI 1.37 to 4.45) in women. Both a full definition of the metabolic syndrome and its single individual components predicted the development of ischemic stroke and coronary heart disease equally well. [160].

The most obvious weakness of the metabolic syndrome criteria is the lack of inclusion of major risk factors for cardiovascular disease such as age, total or low-density lipoprotein cholesterol and smoking status. Instead, the criteria include insulin resistance-related factors and it has been shown to be more strongly associated with incident type 2 diabetes than cardiovascular events [156, 158, 169]. Furthermore, fasting serum triglyceride has a particularly high within-subject biological variability of 20 % [161], which might easily label a subject as having or not having metabolic syndrome depending simply on the day of sampling.

2.5.4 Impaired glucose homeostasis

Defects of insulin secretion, insulin action or a combination of both lead to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. In type 2 diabetes and its pre-states – impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) – the rising blood glucose results from a combination of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight with a central fat distribution, resulting in complex pathophysiological processes that predispose to cardiovascular diseases [162].

People with type 2 diabetes have a two to four times higher risk of coronary heart disease than people without diabetes, and 75–80 % of people with diabetes eventually die of cardiovascular disease [163]. Among Finnish men aged 25–74 years with diabetes, with previous myocardial infarction or with both diseases, hazard ratios for coronary mortality, adjusted for other risk factors, were 2.1, 4.0, and 6.4, respectively, compared to men without either disease [164]. The corresponding hazard ratios for Finnish women were 4.9, 2.5, and 9.4 during an average follow-up time of 17 years [164]. Data from 9 European cohorts comprising 18 360 individuals between 25 to 90 years of age showed that type 2 diabetes, both previously diagnosed and screen-detected, was associated with a double risk of ischemic stroke, but no relationship between hyperglycemia and the risk of hemorrhagic stroke was found [165]. Premature mortality caused by diabetes results in an estimated 12-14 years of life lost [166].

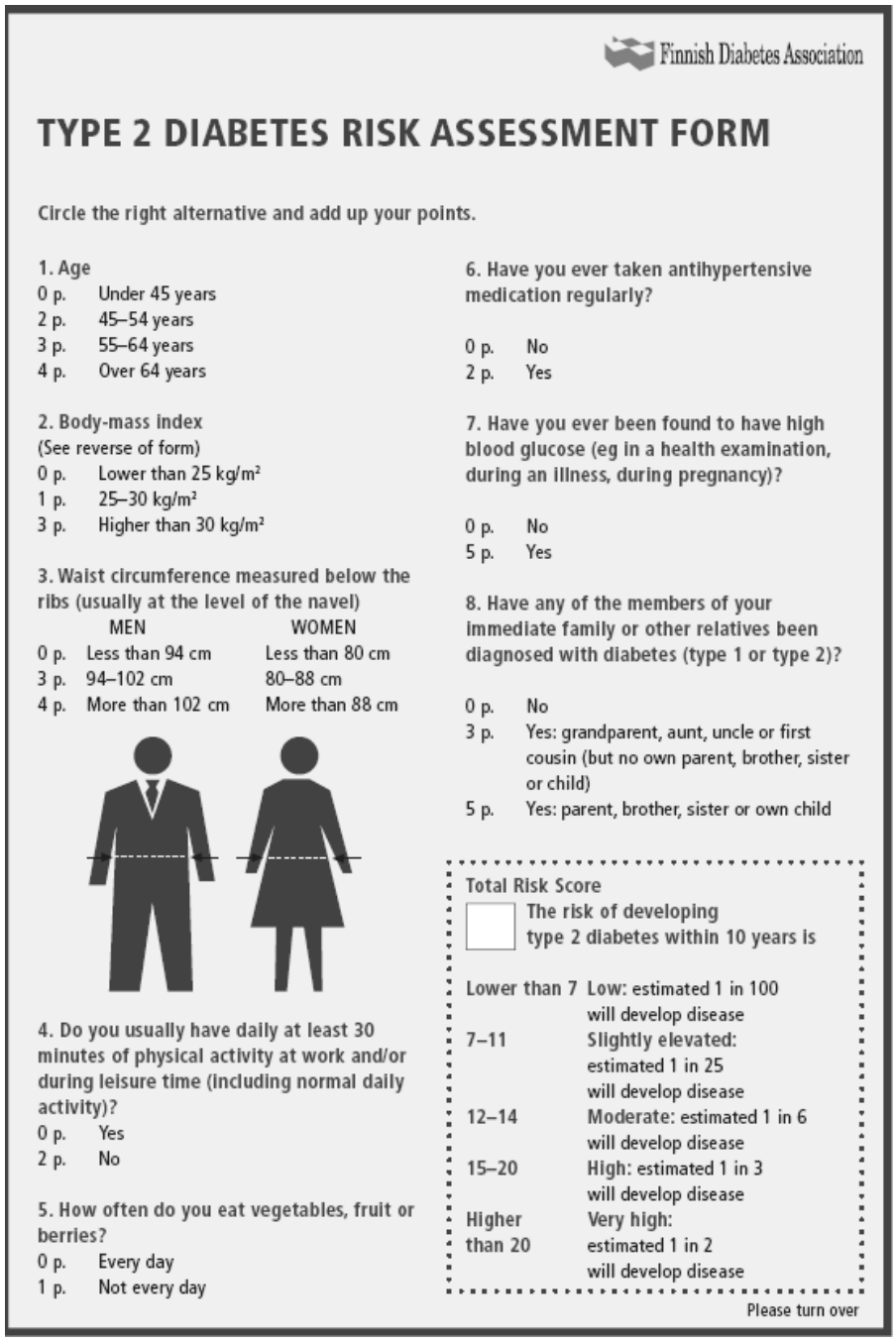
Significantly increased mortality from all-causes and cardiovascular diseases has been observed also in subjects with IGT, whereas increased mortality in people with IFG is largely related to simultaneous elevation of postprandial glucose [167]. However,

IFG is a better predictor of stroke mortality than IGT in women, whereas the opposite has been shown in men in a large European population-based follow-up study [168]. The pathophysiologies of IFG and IGT are different. IFG is predominantly associated with hepatic insulin resistance and decreased first-phase insulin secretion, whereas IGT is associated with peripheral insulin resistance and impairment of both early- and late phase insulin responses [169]. The Euro Heart Survey showed that in patients with acute or stable coronary heart disease, 31 % had known diabetes, 17 % had previously undetected diabetes, 32 % had IGT and 5 % had IFG [170]. In a Finnish population-based survey of 4 500 randomly selected subjects aged 45–74 years, the prevalence of known type 2 diabetes was 7 %, previously undetected diabetes 8 %, IGT 15 % and IFG 9 % [141]. Up to 70-80 % of patients with type 2 diabetes also have hypertension [171]. Hypertension, *per se,* is associated with a double risk of developing type 2 diabetes [172]. Twenty years of prospective follow-up of nearly 50 000 Finnish subjects aged 25–74 and without history of cardiovascular disease showed that both hypertension and type 2 diabetes increase the risk of coronary heart disease and stroke independently, and in people who have both the risk increases dramatically [173, 174]. Thus, it is possible that the increased risk of cardiovascular disease usually seen in hypertensive subjects may sometimes be related not only to the hypertension itself but also to undiagnosed diabetes or glucose intolerance.

In the 21st century there has been an explosive increase in the number of people with obesity and type 2 diabetes globally. A recent estimate suggests that the number of people with diabetes throughout the world will more than double between the years 2000 and 2030 [175]. In Finland, the prevalence of type 2 diabetes in 1992 among middle-aged population was 10 % in men and 7 % in women [176]. In 2005, the corresponding figures were 16 % in men and 11 % in women [141].

There is growing evidence that early detection of people at high risk for developing diabetes, followed by lifestyle or medical interventions to improve glucose control, can result in clinically important reductions in the incidence of diabetes and co-morbidities [22]. The ESC and the European Association for the Study of Diabetes (EASD) guidelines recommend that an OGTT should be carried out in all high-risk patients, such as patients with cardiovascular disease [177]. The 2007 ESH/ESC guidelines recommend that an OGTT should be carried out in all hypertensive subjects whose fasting plasma glucose is ≥5.6 mmol/l [8]. The IDF, the ESC and the EASD recommend that primary screening for the potential type 2 diabetes in population level can be done most efficiently using a non-invasive risk score, followed by a diagnostic oral glucose tolerance test (OGTT) in people with high score values [22, 177]. The Finnish Diabetes Risk Score (FINDRISC, Figure 8) was developed to identify individuals at increased risk for type 2 diabetes. FINDRISC can be conveniently used in primary care and also by individuals themselves, since it does not require any laboratory tests or other clinical

measurements needing professional skills. The tool predicts the ten year risk of type 2 diabetes with 85 % accuracy [23].



Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age
0 p. Under 45 years
2 p. 45–54 years
3 p. 55–64 years
4 p. Over 64 years

2. Body-mass index
(See reverse of form)
0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm

4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?
0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?
0 p. Every day
1 p. Not every day

6. Have you ever taken antihypertensive medication regularly?
0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?
0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?
0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child

Total Risk Score
The risk of developing type 2 diabetes within 10 years is

Lower than 7	Low: estimated 1 in 100 will develop disease
7–11	Slightly elevated: estimated 1 in 25 will develop disease
12–14	Moderate: estimated 1 in 6 will develop disease
15–20	High: estimated 1 in 3 will develop disease
Higher than 20	Very high: estimated 1 in 2 will develop disease

Please turn over

Figure 8. Finnish Diabetes Risk Score (FINDRISC). Reprinted with permission from the Finnish Diabetes Association [23]

3 AIMS OF THE STUDY

This thesis was planned to assist clinicians in estimating total cardiovascular risk of their hypertensive patients and in doing so to govern the best use of limited resources to prevent cardiovascular diseases. The specific aims were the following:

1. To create a screening strategy for the primary care to find the people at risk for cardiovascular diseases and type 2 diabetes in the general population (I).

2. To assess the prevalence of impaired glucose homeostasis in hypertensive subjects and the most useful screening method for glucose disorders (II).

3. To assess the prevalence and determinants of renal insufficiency in hypertensive subjects (III).

4. To assess the prevalence of peripheral arterial disease and borderline peripheral arterial disease in hypertensive subjects using ankle-brachial index measurement (IV).

5. To assess the ability of multivariable cardiovascular disease risk prediction tools and high-sensitivity C-reactive protein (hs-CRP) to identify hypertensive subjects with target organ damage (V).

4 STUDY POPULATION AND METHODS

4.1 Study population

The study population of this thesis was drawn from a population survey, the Harmonica Project (Harjavalta Risk Monitoring for Cardiovascular Disease), which was carried out in the rural towns of Harjavalta (7 646 inhabitants on 31.12.2007) and Kokemäki (8 217 inhabitants on 31.12.2007) in south-western Finland from August 2005 to September 2007. An invitation to the project, a cardiovascular risk factor survey, tape for the measurement of waist circumference, and type 2 diabetes risk assessment form (FINDRISC, Finnish Diabetes Risk Score) [23] (Figure 8) were mailed to inhabitants aged 45 to 70 years (n = 6 013). In Harjavalta, diabetic subjects (n = 199) and patients with known cardiovascular disease (n = 75) who were already in systematic follow-up in the Harjavalta health center were not invited to the project.

In the risk factor survey (Appendix), subjects were asked to report for waist circumference measured at the level of the navel, latest blood pressure, use of antihypertensive medication, history of gestational diabetes or hypertension, and history of coronary heart disease, myocardial infarction, or stroke of their parents or siblings. The subjects were asked to mail the risk factor survey back to the health center if they were able to participate in the project. Participation and all the tests included were free of charge for the subjects. Participation rate was 74 % (4 450 of 6 013). Respondents with above-mentioned risk factors, or those with FINDRISC ≥12 in Harjavalta [178] or ≥15 in Kokemäki [179], were invited for laboratory tests (OGTT and plasma lipids) and physical examination (measurements of waist circumference, height, weight, body mass index and blood pressure) performed by a trained nurse, who also explained the test results and gave life style information to all subjects personally. Every subject had his/her test results written down in a notebook along with target values.

If the test results revealed hypertension, diabetes, IGT, metabolic syndrome, body mass index ≥30 kg/m^2, or the ten year risk of cardiovascular death yielded 5 % or more based on the SCORE system, an appointment with a physician was scheduled after 2–4 months. At that time plasma lipids and fasting glucose were retested. Such a short interval was chosen so that the participants could better assess the effects of dietary changes made or not made. Laboratory tests were also taken to exclude secondary causes of hypertension, dyslipidemia or glucose intolerance. The physician examined the risk persons, assessed target organ damage, and in Harjavalta measured ABI. The decision about starting preventive medication was made by estimating the total cardiovascular risk by the SCORE system. If the ten year risk for developing a fatal cardiovascular event now or extrapolated to the age of 60 years was ≥5 %, preventive medication – an antihypertensive drug, a lipid lowering agent or low dose aspirin – was started.

Antihypertensive treatment was initiated regardless of SCORE system if systolic blood pressure exceeded 160 mmHg or diastolic blood pressure exceeded 100 mmHg or target organ damage was diagnosed [180].

In order to create a cohort in the primary prevention setting, patients with known cardiovascular disease or previously diagnosed diabetes (n = 381) were excluded from the data analysis of this thesis.

The formation of the study population is illustrated in Figure 9.

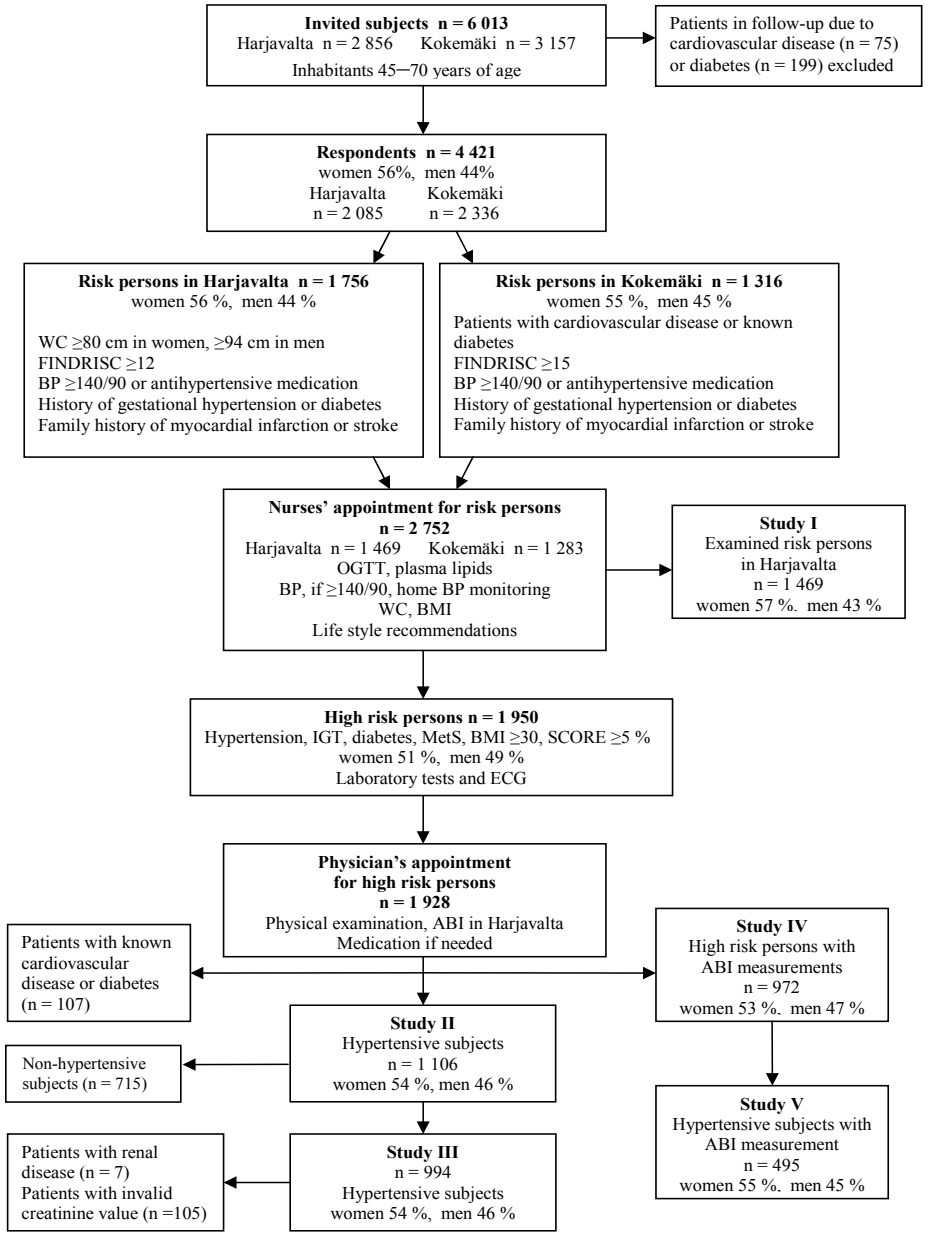


Figure 9. The design of the Harmonica Project and the formation of the study population

4.2 Methods

Subjects were invited to attend laboratory measurements and physical examination after an overnight fasting of at least 12 hours. They were asked to avoid strenuous physical activity on the previous day, or night shifts during the previous 48 hours. They were also asked not to take any medication before the tests were made.

4.2.1 Blood pressure measurement

Blood pressure was measured by a trained nurse with a mercury sphygmomanometer with subjects in a sitting posture, after resting for at least five minutes with the cuff placed on the arm. In obese arms a larger cuff was used. Systolic and diastolic blood pressures were defined according to the Korotkoff sounds I and V. In each subject the mean of two readings taken at intervals of at least two minutes was used in the study. If the mean systolic blood pressure was ≥140 mmHg or the mean diastolic blood pressure ≥90 mmHg, subjects were taught to use an automatic validated blood pressure monitor (Omron® M4-1, the Netherlands) which was lent them for home blood pressure monitoring. In the subjects whose arm circumference was >32 cm a larger cuff was used. The subjects were instructed to take duplicate blood pressure measurements in the seated position after five minutes of rest in the morning and evening for one week. The recorded measurements except those from the first day were used to calculate the mean home blood pressure as recommended by the recent guidelines of ESH [181]. Hypertension was defined as the use of antihypertensive medication, or as the mean of home blood pressure monitoring ≥135 mmHg for systolic or ≥85 mmHg for diastolic blood pressure [181].

4.2.2 Height, weight, and body mass index

Height and weight were measured with the subjects in standing position without shoes and outer garments. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.1 kg. Digital scales (Seca® 861, Germany) were used, and their calibration was monitored regularly. Body mass index was calculated as weight (kilograms) divided by the square of height (meters squared).

4.2.3 Waist circumference

In the invitation letter to the project, people were advised to measure their waist circumference at the level of navel. The nurses were instructed to measure subjects' waist circumference at the level midway between the lower rib margin and the iliac crest, rounded to the nearest 0.1 cm. The subjects were asked to breathe out gently at the time of the measurement, and the tape was held firmly in a horizontal position. The mean difference between self-measured and nurse-measured waist circumference

was -3.76 cm ± 6.59 in women and -2.41 cm ± 4.49 in men (p <0.001). The professionally measured waist circumferences were used in the subsequent screening decisions.

4.2.4 Oral glucose tolerance test

OGTT was performed by measuring a fasting plasma glucose and a two hour plasma glucose after ingestion of a glucose load of 75 g anhydrous glucose dissolved in water. Glucose values were measured from capillary whole blood with HemoCue® Glucose 201+ system (Ängelholm, Sweden) which is based on a glucose dehydrogenase method and consists of a small portable analyzer and a disposable microcuvette. The analyzer converts the result from capillary whole blood to plasma glucose values (conversion factor 1.11) and the result is displayed within 40–240 seconds depending on blood glucose concentration.

Glucose disorders were classified according to the World Health Organization (WHO) 1999 criteria which were updated in 2006 [182]. On the basis of 2-hour plasma glucose alone, individuals were classified into categories of newly diagnosed diabetes, impaired glucose tolerance and normal glucose tolerance if their 2-hour plasma glucose concentrations were ≥12.2, 8.9–12.1, and <8.9 mmol/l, respectively. On the basis of fasting plasma glucose alone, individuals were classified into categories of newly diagnosed diabetes, impaired fasting glucose and normal fasting glucose, using cut-off levels of ≥7.0, 6.1–6.9 and ≤6.0 mmol/l, respectively (Figure 10).

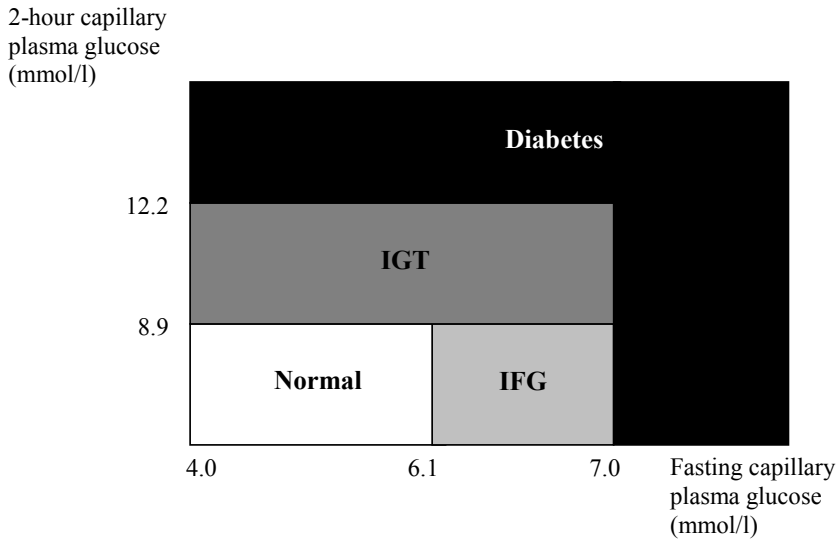


Figure 10. Categories of glucose disorders and diagnostic threshold values

The diagnosis of diabetes was confirmed with a control fasting plasma glucose value on another day if the fasting plasma glucose on OGTT was 7.0 mmol/l or higher but the 2-hour plasma glucose was <12.2 mmol/l.

4.2.5 Other laboratory measurements

Total cholesterol, HDL cholesterol and triglycerides were measured enzymatically (Olympus® AU640, Japan). LDL cholesterol was calculated according to the Friedewald's formula. Plasma creatinine and alaninaminotransferace were measured enzymatically (Olympus® AU640, Japan). Plasma potassium and sodium were measured with indirect ISE method (Olympus® AU640, Japan). Thyroid stimulating hormone was measured with two site sandwich immunoassay using direct chemiluminometric technology (Siemens Medical Solutions®, Germany). High-sensitivity CRP was assayed using a microparticle enhanced turbidometric method on a Konelab® 60i analyzer (Thermo Electron, Finland). The cut-off point of high risk was defined hs-CRP >3 mg/l [183].

4.2.6 The metabolic syndrome

The metabolic syndrome was diagnosed according to the criteria of the ATP III [150] and the IDF [151] (Table 3).

4.2.7 Renal function (III, V)

Renal function was estimated by the plasma creatinine level and eGFR. Because the test method of plasma creatinine has been calibrated to be traceable to isotope dilution mass spectrometry, eGFR was calculated using the recently developed modified 4-variable MDRD Study equation 175 x $(P_{Cr}/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.21 if black), where P_{Cr} = plasma creatinine in μmol/l, and age is expressed in years [184]. Race was not applicable in our study because all patients were white. Because the MDRD formula is based on data from patients with advanced renal failure, the results may not be valid in patients with normal or near normal glomerular filtration rates. Therefore only eGFR levels <60 ml/min/1.73 m^2 are reported as renal insufficiency. To test the agreement of the two eGFR methods, eGFR was also assessed by the Cockroft-Gault formula: 1.23 x (140-age) x weight x (0.85 if female) / P_{Cr}, where weight is expressed in kilograms [126].

4.2.8 Ankle-brachial index (IV, V)

ABI was determined from blood pressure measurements in the arms and ankles with the patient supine. Systolic blood pressure in the brachial artery was measured in both arms using a blood pressure cuff and Doppler instrument (UltraTec® PD1v with a vascular probe of 5 MHz, United Kingdom) in the antecubital fossa. Systolic blood pressure at the left and right dorsalis pedis arteries (if not found, at the left and right posterior tibial arteries) was then measured with Doppler detection with a blood pressure cuff applied to the ankle just proximal to the malleoli. ABI was the lower ankle systolic blood pressure divided by the higher brachial systolic blood pressure.

Participants who had an ABI ≤0.90 in either leg were categorized as having PAD. Subjects with an ABI between 0.91 and 1.00 were considered as borderline PAD cases. Normal ABI was defined as 1.01–1.40. False elevation of the ankle pressure because of non-compressible tibial vessels was considered if ABI was higher than 1.40.

4.2.9 Electrocardiography (IV, V)

Standard resting 12-lead ECGs were digitally recorded and stored as digital data with a Welch Allyn CardioPerfect™ system (Welch Allyn, U.S.). LVH was diagnosed if the Sokolow-Lyon voltage (SV_1 + RV_{5-6}) was >38 mm or the Cornell product [Cornell voltage (RaVL + SV_3 plus 6 mm for women x QRS duration] was >2440 mm x ms [8].

4.2.10 Statistical analyses

The data is presented as the means with standard deviations or as counts with percentages. The 95 per cent confidence intervals (CIs) are given for the most important outcomes. Statistical comparisons between groups were made by using t-test, Chi-Square or Fischer´s exact test, when appropriate. A bootstrapped type t-test was used to analyse differences in continuous variables with skewed distributions. Correlations were estimated by Spearman´s correlation coefficient method. Univariate and multivariate logistic regression analyses were applied to investigate the relationships between important risk factors and eGFR (Study III) and PAD (Study IV). The equality of distributions of ABI (Study IV) was tested by Kolmogorov-Smirnov test. In Study V, the diagnostic characteristics of the test, i.e. accuracy, sensitivity, specificity and positive likelihood ratios were calculated for Framingham risk, SCORE risk and hs-CRP in predicting target organ damage. Receiver operating characteristic curves were used for determination of optimal cut-off point, and the respective areas under the curve were calculated with a bias-corrected bootstrap confidence interval. Differences between the areas under the curves were evaluated using an algorithm by DeLong.

4.2.11 Ethical issues

The study protocol and consent forms of the Harmonica Project were reviewed and approved by the ethics committee of Satakunta hospital district. All participants provided written informed consent for the project and subsequent medical research.

5 RESULTS

5.1 A strategy to find out patients in cardiovascular risk in the general population (I)

The basis of this thesis is the two-stage screening strategy, the Harmonica Project, which was created to identify and inform people at risk for cardiovascular disease and type 2 diabetes in the general population. The design of the screening strategy is illustrated in figure 9.

Participation

In the first stage of the strategy, risk factor questionnaires were mailed to 45–70-year-old inhabitants of the communities. The participation rate was 74 %. In Harjavalta, 2 085 (73 %) of the invited 2 856 persons responded to the invitation and mailed the risk factor survey back to the health center. At least one cardiovascular risk factor, including waist circumference ≥94 cm in men and ≥80 cm in women, was detected in 84 % (1 756/2 085). Of them, 14 % (287/2 085) were not willing to take part in further examinations. Out of the respondents, 16 % (329/2 085) had no cardiovascular risk factors. Of the invited subjects, 27 % (771/2 856) who did not respond were predominantly male but practically of the same age as the respondents. (Table 6)

Table 6. Respondents (n = 2 085) and results of the primary screening methods

	Risk persons		**No risks**
	Examined n = 1 469 (70 %)	**Not examined n = 287 (14 %)**	**n = 329 (16 %)**
Women			
n	833 (57 %)	149 (52 %)	180 (55 %)
Age, years, mean (SD)	58 (7)	58 (8)	57 (7)
Waist circumference, cm, mean (SD)	91 (13)	90 (12)	76 (3)
FINDRISC, mean (SD)	12 (5)	10 (5)	6 (3)
Men			
n	636 (43 %)	138 (48 %)	149 (45 %)
Age, years, mean (SD)	58 (7)	56 (6)	57 (6)
Waist circumference, cm, mean (SD)	101 (11)	100 (13)	89 (4)
FINDRISC, mean (SD)	11 (5)	10 (4)	5 (2)

Risk persons in Harjavalta

Risk persons willing to proceed with the project (n = 1 469) were examined by a nurse and got personal information and guidance to treat the risk factors discovered.

The most common cardiovascular risk factors were hypertension and dyslipidemia (Table 7).

Table 7. Cardiovascular risk factors among the examined risk persons (n = 1 469)

	n (%)
Hypertension	717 (48.8)
LDL-C ≥3.0 mmol/l	851 (57.9)
Metabolic syndrome	
IDF	681 (46.3)
ATP III	475 (32.3)
SCORE ≥5 %	516 (35.1)
Body mass index	
≥30.0 kg/m^2	463 (31.5)
25.0–29.9 kg/m^2	683 (46.5)
New type 2 diabetes	65 (4.4)
Impaired glucose tolerance	193 (13.1)
Impaired fasting glucose	182 (12.4)

Glucose homeostasis

In Harjavalta, an OGTT was performed to all 1 469 respondents who had at least one cardiovascular risk factor including nurse-measured waist circumference ≥80 cm in women and ≥94 cm in men. Table 8 summarizes the results of OGTT by insulin resistance-related factors.

Table 8. Glucose homeostasis amongst different risk categories (Study I). Parenthesis show the proportions of diagnosed glucose homeostasis in various risk categories.

Marker of insulin resistance		**n**	**Normal** n = 1 029	**IFG** n = 182	**IGT** n = 193	**T2D** n = 65
Waist circumference, women	≥80 cm	690	488 (47.4 %)	72 (39.6 %)	97 (50.3 %)	33 (50.8 %)
	>88 cm	437	291 (28.3 %)	51 (28.0 %)	69 (35.8 %)	26 (40.0 %)
Waist circumference, men	≥94 cm	478	303 (29.4 %)	76 (41.8 %)	70 (36.3 %)	29 (44.6 %)
	>102 cm	244	140 (13.6 %)	37 (20.3 %)	43 (22.3 %)	24 (36.9 %)
Metabolic syndrome						
	IDF criteria	681	341 (33.1 %)	128 (70.3 %)	152 (78.8 %)	60 (92.3 %)
	ATP III criteria	475	223 (21.7 %)	85 (46.7 %)	114 (59.1 %)	53 (81.5 %)
FINDRISC ≥12		697	423 (41.1 %)	102 (56.0 %)	131 (67.9 %)	41 (63.1 %)

Central obesity as a screening method for impaired glucose homeostasis

The prevalence of central obesity in risk persons according to the IDF definition was 82.8 % in women and 75.2 % in men, and according to the ATP III definition 52.5 % and 38.4 %, respectively. Nurse-measured waist circumference ≥80 cm in women and ≥94 cm in men (n = 1 168) identified 95 % of the new OGTT diagnosed cases of type 2 diabetes (n = 65) and 84 % of the new OGTT diagnosed cases of prediabetes (n= 375). If those women only whose waist circumference was >88 cm had been examined, 21.2 % (7/33) of the cases of new type 2 diabetes, 35.5 % (38/107) of IGT and 38.6 % (32/83) of IFG would have been missed. Likewise, if those men only whose waist circumference was >102 cm had been examined, 25.0 % (8/32) of the cases of new type 2 diabetes, 50.0 % (43/86) of IGT and 63.6 % (62/99) of IFG would have been missed.

The metabolic syndrome as a screening method for impaired glucose homeostasis

The metabolic syndrome was diagnosed according to the IDF criteria in 46.4 % of the risk persons, 43.5 % (362/833) in women and 50.2 % (319/636) in men. According to the ATP III criteria, the metabolic syndrome was diagnosed in 32.3 % of the risk persons, 32.2 % in women and 32.5 % in men.

The IDF criteria of the metabolic syndrome identified 92.3 % of the subjects with new type 2 diabetes, 78.8 % with IGT and 70.3 % with IFG. The corresponding figures with the ATP III criteria were 81.5 % for type 2 diabetes, 59.1 % for IGT and 46.7 % for IFG.

FINDRISC as a screening method for impaired glucose homeostasis

FINDRISC score value ≥12 was fulfilled in 47.4 % of the risk persons. This criteria for screening identified 63.1 % of the subjects with new type 2 diabetes, 67.9 % with IGT and 56.0 % with IFG.

Nurse-measured blood pressure as a screening method

At the nurses' appointment blood pressure ≥140/90 was measured in 400 study subjects who had no previously detected hypertension. Out of these 400 subjects, 258 (64.5 %) had true hypertension confirmed with home blood pressure measurements, and 142 (35.5 %) had "white coat hypertension" or "isolated office hypertension", i.e. nurse measured blood pressure was ≥140/90 mmHg but the average of home readings was <135/85 mmHg [8].

If only subjects with elevated office blood pressure (n = 400) and the subjects already on antihypertensive medication (n= 459) had been chosen for further examinations, 311/440 (70.7 %) cases of impaired glucose homeostasis and 391/516 (75.8 %) cases of SCORE ≥5 % would have been found. Furthermore, elevated office blood pressure also seems to be quite an accurate screening test for total cardiovascular risk: sensitivity

89 % and specificity 51 % for the high 10-year risk of a fatal cardiovascular event, i.e. SCORE ≥5 %.

Performance of the screening methods to detect glucose disorders

Non-invasive screening tools used in the first phase of the strategy, measurement of waist circumference and FINDRISC form with the cut-off value 12, performed quite well in detecting glucose disorders in the general population. In addition, nurse-detected hypertension showed quite good accuracy in detecting impaired glucose homeostasis (Table 9).

Table 9. Diagnostic tests for glucose disorders with their sensitivity, specificity and positive predictive value (Study I)

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Waist circumference			
≥80 cm in women	91	20	29
≥94 cm in men	81	28	37
Metabolic syndrome IDF	77	67	50
ATP III	57	78	53
FINDRISC ≥12	62	59	39
Nurse-measured BP ≥140/90 mmHg or antihypertensive medication	71	47	36

5.2 Glucose homeostasis in hypertensive subjects (II)

A total of 1 106 hypertensive subjects (46 % men) without cardiovascular disease and previously known diabetes were examined. According to OGTT, 66 of them (6.0 %) had type 2 diabetes, 220 (19.9 %) had IGT, and 167 (15.1 %) had impaired fasting glucose.

Selection criteria for proceeding to OGTT

Fasting plasma glucose was ≥5.6 mmol/l in 545 subjects. Among them, 58 (10.6 %) had type 2 diabetes and 133 (24.4 %) had IGT based on the 2-hour postload plasma glucose. Thus, by using this selection criteria for proceeding to OGTT, 58 (87.9 %) of 66 patients with type 2 diabetes and 133 (60.5 %) of 220 patients with IGT were found.

The IDF criteria of the metabolic syndrome were met by 744 subjects. Among them, 8.5 % had type 2 diabetes and 25.9 % had IGT. OGTT identified 95.5 % of the patients with type 2 diabetes and 87.7 % of the patients with IGT (Figure 11 A).

Among the 636 subjects who met the ATP III criteria of the metabolic syndrome, 9.3 % had type 2 diabetes and 25.3 % had IGT. Thus, with OGTT, 89.4 % of the patients with type 2 diabetes and 73.2 % of the patients with IGT were found (Figure 11 B).

Overweight and obesity in hypertensive subjects

In the cohort of 1 106 hypertensive subjects, 484 (43.8 %) were overweight (body mass index 25 to 29.9 kg/m^2), and 463 (41.9 %) were obese (body mass index ≥30 kg/m^2).

Central obesity defined as waist circumference ≥80 cm in women and ≥94 cm in men was particularly prevalent, in 538 (89.8 %) of 599 women and 413 (81.5 %) of 507 men. Of the women in this study, 395 (65.9 %) of 599 had waist circumference >88 cm, and of the men, 251 (49.5 %) of 507 had waist circumference >102 cm.

The mean waist circumference in subjects with IGT was 97.5 ± 14.1 cm in women and 103.3 ± 11.8 cm in men. The mean waist circumference in women and men with type 2 diabetes was 102.6 ± 15.3 cm and 107.7 ± 9.7 cm, respectively. In hypertensive subjects with normal glucose homeostasis, the mean waist circumference was 93.1 ± 12.2 cm in women and 102.2 ± 10.9 cm in men. There was a statistically significant difference between impaired glucose homeostasis and waist circumference only in women.

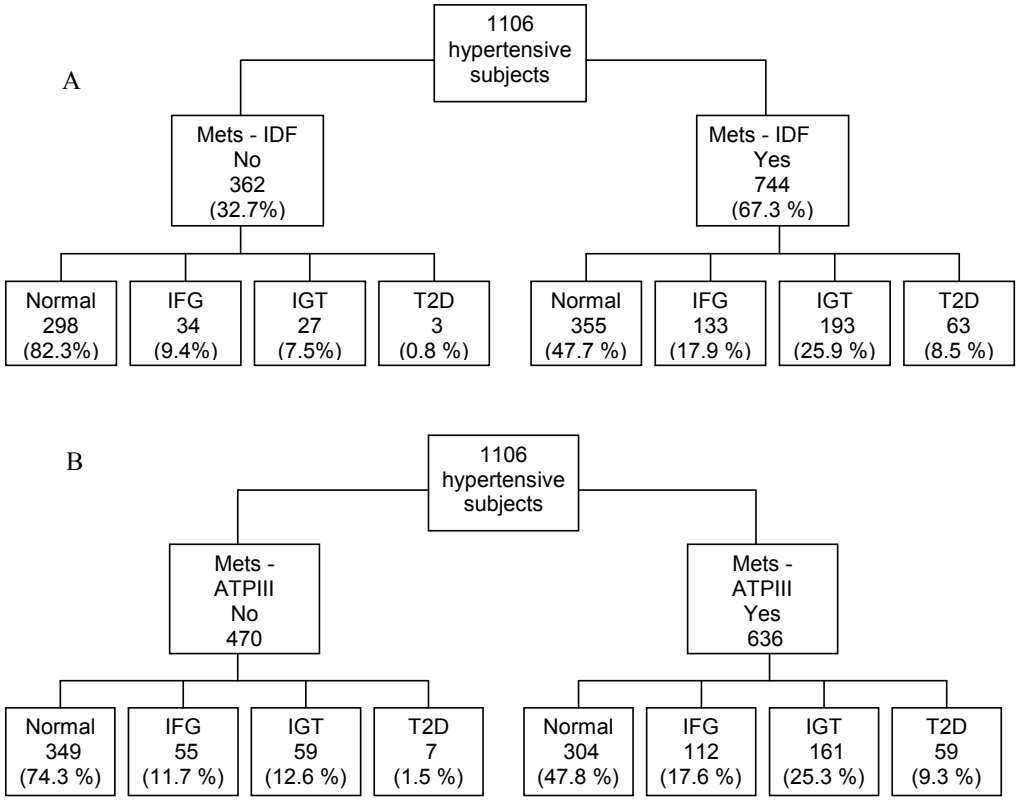


Figure 11. Categories of glucose tolerance in subjects with and without the metabolic syndrome according to the IDF criteria (A) and the ATP III criteria (B) (Study II).

5.3 Hypertensive subjects and the risk of renal insufficiency (III)

In order to minimize the interaction between hypertension, diabetes and cardiovascular disease, 994 hypertensive subjects (46 % men) without previously diagnosed diabetes, cardiovascular or renal disease were studied (Table 10).

Table 10. Baseline characteristics of study participants according to estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula

	eGFR		P value
	<60 ml/min n = 67	**≥60 ml/min** n = 927	
Demographic			
Number of female, (%)	54 (80.6)	484 (52.2)	<0.001
Age, years, mean (SD)	64 (5)	59 (7)	<0.001
Weight, kg, mean (SD)	83.8 (13.1)	85.5 (16.6)	0.40
Body mass index, kg/m², mean (SD)	31.5 (5.7)	29.9 (5.0)	0.01
Waist circumference, cm, mean (SD)			
Women	98.7 (12.6)	95.2 (13.5)	0.07
Men	101.7 (6.5)	103.4 (11.2)	0.57
Clinical			
Blood pressure, mmHg, mean (SD)			
Systolic	150.6 (17.2)	153.0 (17.4)	0.29
Diastolic	87.9 (10.0)	90.5 (8.4)	0.01
Pulse pressure	62.8 (13.8)	62.4 (14.6)	0.87
Metabolic syndrome present (%)			
IDF	58 (86.6)	637 (68.7)	0.002
ATP III	48 (71.6)	552 (59.5)	0.05
Biochemical			
Total cholesterol, mmol/l	5.35 (0.98)	5.30 (0.92)	0.70
LDL-cholesterol, mmol/l, mean (SD)	3.19 (0.81)	3.19 (0.80)	0.98
Triglycerides, mmol/l, mean (SD)	1.48 (0.73)	1.42 (0.73)	0.54
Fasting glucose, mmol/l, mean (SD)	5.72 (0.68)	5.71 (1.08)	0.92
2-hour glucose, mmol/l, mean (SD)	8.19 (2.26)	7.85 (2.48)	0.25
Current medication, (%):			
ACE inhibitor or ATRantagonist	31 (46.3)	333 (35.9)	0.09
Diuretic	20 (29.9)	123 (13.3)	<0.001
Statin	9 (13.4)	127 (13.7)	0.95
NSAIDs	4 (6.0)	27 (2.9)	0.15

According to OGTT, 65 (6.5 %) of the study subjects had new type 2 diabetes, 205 (20.6 %) had IGT, and 158 (15.9 %) had IFG. The prevalence of the metabolic syndrome was 69.9 % (69.5 % in women, 70.4 % in men) according to the IDF criteria and 60.4 % (60.8 % in women, 59.9 % in men) according to the ATP III criteria.

Prevalence of renal insufficiency

According to the MDRD formula, the crude prevalence of renal insufficiency defined as eGFR <60 ml/min per 1.73 m^2 was 6.7 % (95 % CI 5.3 to 8.5), 10.0% (95 % CI 7.6 to 12.9) in women and 2.9 % (95 % CI 1.5 to 4.8) in men (age adjusted p <0.001). None had eGFR <30 ml/min per 1.73 m^2. The MDRD formula mean was 77 (SD 15) ml/min in women and 86 (SD 16) ml/min in men.

According to the Cockcroft-Gault formula, the crude prevalence of renal insufficiency in women was 4.8 % (95 % CI 3.2 to 7.0), and in men 0.9 % (95 % CI 0.2 to 2.2). The mean eGFR by the Cockroft-Gault formula was 97 (SD 28) ml/min in women, and 111 (SD 30) ml/min in men. Correlation between the MDRD formula and the Cockroft-Gault formula was 0.70 (95 % CI 0.67 to 0.73).

Of the 538 women, only 6 (1.1 %) had plasma creatinine ≥107 μmol/l (range 83 to 114 μmol/l). Of the 456 men, 11 (2.4 %) had plasma creatinine ≥115 μmol/l (range 111 to 132 μmol/l).

Risk factors for renal insufficiency

Patients with eGFR<60 ml/min per 1.73 m^2 tended to be more often female, elderly, to have higher body mass index and diastolic blood pressure or present metabolic syndrome and use of diuretics. Neither fasting plasma glucose nor 2-hour postload glucose values showed significant differences in patients with renal insufficiency versus patients with preserved renal function (Table 10).

Subjects with the metabolic syndrome were more likely to have renal insufficiency than subjects without the metabolic syndrome (p = 0.002 for the definition of IDF, p = 0.05 for the definition of ATP III). In patients with the metabolic syndrome according to the IDF criteria, the age adjusted prevalence of renal insufficiency was 10.2 % (95 % CI 7.3 to 14.0) in women and 2.5 % (95 % CI 1.2 to 5.2) in men (age adjusted p <0.001 for the difference between the genders). When the ATP III criteria were used, the age adjusted prevalence of renal insufficiency among those with the metabolic syndrome was 9.8 % (95 % CI 6.8 to13.8) in women and 2.4 % (95 % CI 1.1 to 5.3) in men (age-adjusted p <0.001).

In subjects without the metabolic syndrome, the age adjusted prevalence of renal insufficiency was 3.5 % (95 % CI 1.6 to 7.3) in women and 1.1 % (95 % CI 0.2 to 4.5) in men when the IDF criteria were used. When the ATP III criteria were used, the age adjusted prevalence of renal insufficiency was 5.5 % (95 % CI 3.2 to 9.4) in women and 1.5 % (95 % CI 0.5 to 4.6) in men (Figure 12). There was no significant difference between genders in the prevalence of renal insufficiency among subjects without the metabolic syndrome as defined by either of the criteria used.

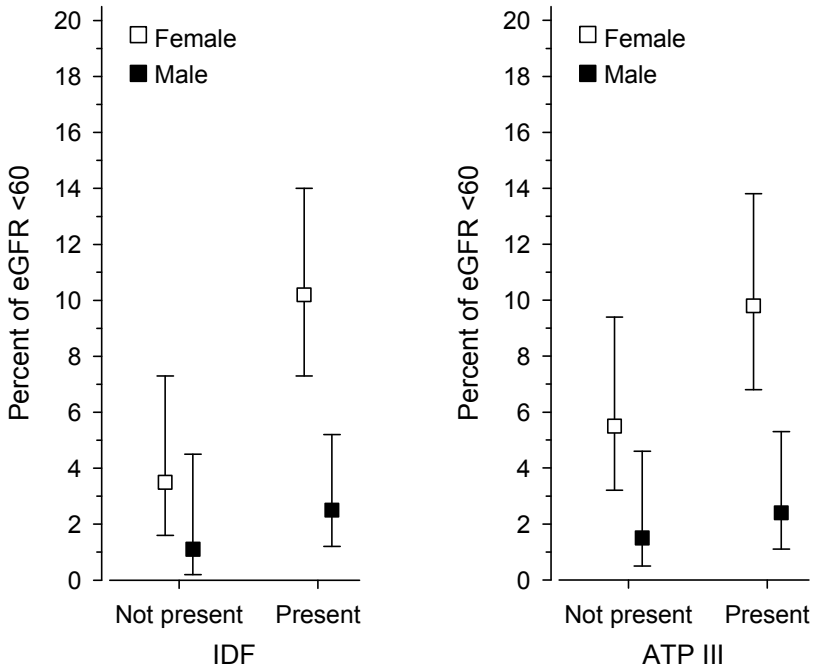


Figure 12. Age adjusted prevalence of low estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula according to the definition of the metabolic syndrome in females and males. Whiskers show 95 % confidence intervals. (Study III)

The use of diuretics was more common in patients with renal insufficiency than in patients with preserved eGFR (29.9 % versus 13.3 %, p <0.001; Table 10), but no difference in the use of diuretics was found by gender (29.6 % in women versus 30.8 % in men with renal insufficiency, and 14.5 % in women versus 12.0 % in men without renal insufficiency). Treatment with loop diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers or statins showed no statistically significant differences among patients with renal insufficiency or preserved renal function. Daily use of non-steroidal anti-inflammatory drugs was rare and was not different in the presence of renal insufficiency.

When adjusted for age and sex, renal insufficiency was associated with body mass index, use of diuretics and the presence of the metabolic syndrome defined by the IDF and ATP III criteria. In multivariate analysis female gender [OR 3.57 (95 % CI 1.90 to 6.72)], age [OR 1.13 (95 % CI 1.07 to 1.18)], use of diuretics [OR 2.13 (95 % CI 1.19 to 3.82)] and the metabolic syndrome [OR 2.79 (95 % CI 1.34 to 5.79)] were entered in logistic regression model with forward selection (Table 11).

Table 11. Univariate and multivariate predictors of low estimated glomerular filtration rate (eGFR <60 ml/min) by the Modification of Diet in Renal Disease formula. (Study III)

Variables	Univariate*		Multivariate†	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Female	3.52 (1.88 to 6.57)	<0.001	3.57 (1.90 to 6.72)	<0.001
Age	1.14 (1.09 to 1.19)	<0.001	1.13 (1.07 to 1.18)	<0.001
BMI	11.05 (1.01 to1.10)	0.02		
SBP	0.99 (0.97 to 1.00)	0.06		
DBP	0.99 (0.96 to 1.02)	0.53		
Total cholesterol	0.99 (0.75 to 1.32)	0.96		
Triglycerides	1.33 (0.94 to 1.88)	0.11		
Glucose homeostasis		0.59		
Normal	1.00 (reference)			
IFG	1.51 (0.75 to 3.07)			
IGT	0.92 (0.48 to 1.75)			
Type 2 diabetes	0.79 (0.26 to 2.37)			
Current medication				
ACE inhibitor or ATR antagonist	1.47 (0.88 to 2.47)	0.14		
Diuretic	2.31 (1.30 to 4.12)	0.004	2.13 (1.19 to 3.82)	0.001
Statin	0.71 (0.34 to 1.50)	0.37		
NSAIDs	1.48 (0.48 to 4.57)	0.49		
Metabolic syndrome				
IDF	2.98 (1.44 to 6.17)	0.003	2.79 (1.34 to 5.79)	0.006
ATP III	1.79 (1.02 to 3.15)	0.04		

* Adjusted for age and sex, as appropriate.

† Forward selection. Only statistically significant variables in univariate analysis were entered in the multivariate model.

5.4 Ankle-brachial index in hypertensive subjects (IV)

ABI was measured in 972 non-claudicant risk subjects (47 % men) who had hypertension, metabolic syndrome, newly detected type 2 diabetes, IGT or whose ten year risk of cardiovascular death was 5 % or more according to SCORE system. None of the study subjects had previously diagnosed cardiovascular or renal disease or diabetes mellitus.

Table 12 shows the demographic and clinical characteristics of the hypertensive and non-hypertensive subjects. The hypertensive patients were slightly older, had more often metabolic syndrome, slightly lower LDL-cholesterol value, higher body mass index, higher fasting glucose and 2-hour postload glucose values than the non-hypertensive subjects. Of the 532 hypertensive subjects, 415 (78.0 %) were under antihypertensive treatment.

Table 12. Characteristics of the subjects according to the presence of hypertension (Study IV)

	Hypertension		**P value**
	Not present n = 440	**Present** n = 532	
Demographic			
Number of female (%)	224 (51)	293 (55)	0.20
Age, years, mean (SD)	57(7)	60 (7)	<0.001
Current smokers (%)	93 (21)	77 (14)	0.0065
Body mass index, kg/m^2, mean (SD)	28.8 (4.6)	29.9 (5.4)	<0.001
Clinical			
ABI, mean (SD)	1.11 (0.11)	1.06 (0.12)	<0.001
SBP, mmHg, mean (SD)	143 (17)	154 (17)	<0.001
DBP, mmHg, mean (SD)	86 (8)	91 (8)	<0.001
Pulse pressure, mmHg, mean (SD)	57 (13)	63 (14)	<0.001
Total cholesterol, mmol/l, mean (SD)	5.36 (0.97)	5.26 (0.91)	0.099
HDL-C, mmol/l, mean (SD)	1.46 (0.40)	1.50 (0.41)	0.18
LDL-C, mmol/l, mean (SD)	3.28 (0.87)	3.12 (0.82)	0.0038
Triglycerides, mmol/l, mean (SD)	1.39 (0.70)	1.41 (0.67)	0.63
Fasting glucose, mmol/l, mean (SD)	5.61 (1.16)	5.77 (1.12)	0.036
2-hour glucose, mmol/l, mean (SD)	7.40 (2.54)	7.94 (2.56)	0.0012
Metabolic syndrome present (%)			
IDF	206 (47)	350 (66)	<0.001
ATP III	152 (35)	296 (56)	<0.001

Prevalence of PAD and borderline PAD

Ten [2.3 % (95 % CI 1.1 to 4.1)] out of 440 non-hypertensive and 39 [7.3 % (95 % CI 5.3 to 9.9] out of 532 hypertensive subjects had PAD defined as ABI ≤0.90. The prevalence of borderline PAD was 23.7 % (95 % CI 20.1 to 27.5) (126/532) in hypertensive and 15.0 % (95 % CI 11.8 to 18.7) (66/440) in non-hypertensive subjects.

The cumulative distribution of ABI in hypertensive and non-hypertensive subjects is illustrated in Figure 13. Although a rather similar shape of distribution was seen, the ABI values of the hypertensive subjects were significantly lower (p <0.001) than those of the non-hypertensive subjects. The mean value (SD) of ABI was 1.06 (0.12) in hypertensive subjects, respectively in non-hypertensive subjects 1.11 (0.11).

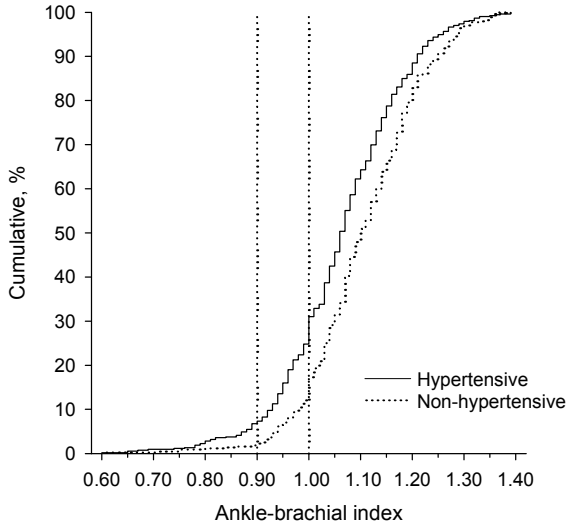


Figure 13. The cumulative distribution of ankle-brachial index in hypertensive and non-hypertensive subjects. (Study IV)

Risk factors for peripheral arterial disease

Hypertension, age, current smoking and higher triglycerides were significantly associated with PAD in univariate analysis. When the same variables were entered into the multivariate forward stepwise logistic regression model (Table 13), hypertension remained an independent factor associated with PAD defined as ABI ≤0.90 (adjusted Odds ratio (OR) 3.20; 95 % CI 1.56 to 6.58).

Table 13. Relationships between peripheral arterial disease and important risk factors. (Study IV)

Variable	Univariate model		Multivariate model*	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Hypertension	3.40 (1.68 to 6.90)	<0.001	3.20 (1.56 to 6.58)	0.001
Gender, male	1.01 (0.57 to 1.79)	0.98		
Age, years	1.07 (1.02 to 1.12)	0.003	1.08 (1.03 to 1.13)	0.002
Current smoker	2.19 (1.16 to 4.11)	0.015	3.15 (1.61 to 6.16)	<0.001
BMI, kg/m^2	1.01 (0.96 to 1.07)	0.61		
HDL-C ≤1.0, mmol/l	1.58 (0.72 to 3.47)	0.25		
LDL-C ≥3.0, mmol/l	1.05 (0.58 to 1.89)	0.87		
Triglycerides ≥1.7, mmol/l	1.89 (1.05 to 3.40)	0.034	1.93 (1.06 to 3.53)	0.033
Fasting glucose, mmol/l	1.03 (0.81 to 1.30)	0.82		

*Forward selection. Only statistically significant variables in univariate model were entered in the multivariate model.

Blood pressure on the arm and ABI subgroups

The means of systolic blood pressure and pulse pressure increased linearly across the three ABI subgroups, normal (ABI 1.01–1.40), borderline (ABI 0.91–1.00) and PAD (ABI ≤0.90) in hypertensive patients (p value of linearity <0.001 adjusted for age and gender), whereas no such linear association was found in the normotensive subgroups (Figure 14). Although higher diastolic blood pressure was significantly associated with dichotomized ABI ≤ 0.90 (Table 13), no linear association of diastolic blood pressure across the three ABI subgroups was found in either hypertensive (p = 0.16 adjusted for age and gender) or non-hypertensive (p = 0.13 adjusted for age and gender) subjects (Figure 14).

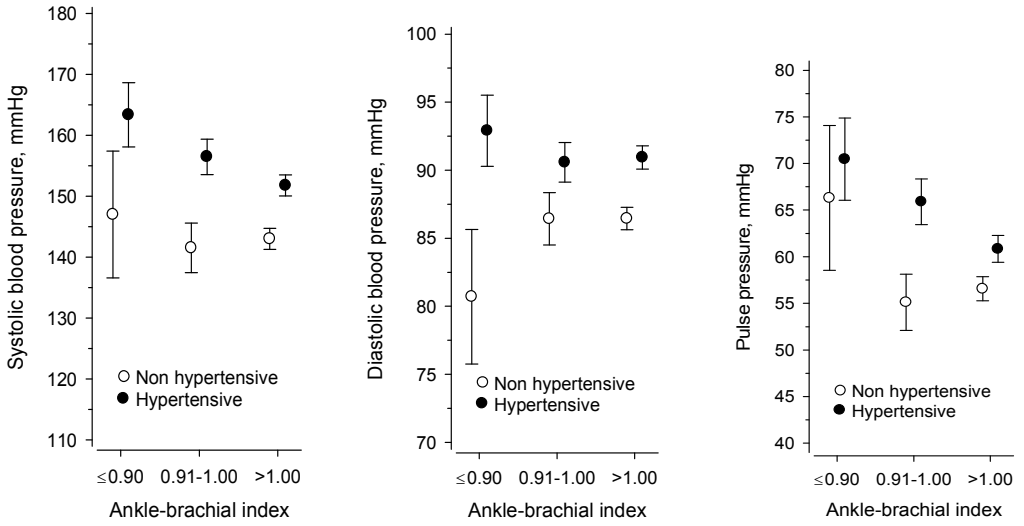


Figure 14. Mean systolic blood pressure, diastolic blood pressure, and pulse pressure according to ankle brachial index group in hypertensive and non-hypertensive subjects. The means of systolic blood pressure and pulse pressure, but not diastolic blood pressure increased linearly across the ABI subgroups, normal (ABI 1.01–1.40), borderline (ABI 0.91–1.00) and PAD (ABI ≤0.90) only in hypertensive patients (p value of linearity <0.00 adjusted for age and gender). Whiskers show 95 % confidence intervals. (Study IV)

Hypertensive subjects and risk factors for PAD

Among the hypertensive subjects, current smoking [OR 2.72 (95 % CI 1.23 to 6.04)] and the presence of LVH [OR 2.26 (95 % CI 1.08 to 4.70)] were associated with dichotomized PAD (defined as ABI ≤0.90) in age and gender adjusted analyses (Table 14). Although the prevalence of new type 2 diabetes was 7 %, impaired glucose tolerance 20 %, and impaired fasting glucose 20 % among the hypertensive subjects, glucose homeostasis was not related to PAD. Increasing pulse pressure [OR 1.04 for each increase of 1 mmHg (95 % CI 1.01 to 1.06)] and systolic blood pressure [OR 1.03 (95 % CI 1.01 to 1.05)] were also associated with PAD when dichotomized ABI ≤0.90 was used as a cut-off. These results were only slightly attenuated after further adjustment with current medication.

Table 14. Relationships between the dichotomized peripheral arterial disease (ABI≤0.90 versus ≥0.91) and important risk factors in subjects with hypertension (Study IV)

Characteristic	Model 1 †		Model 2 ‡	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Gender, male	0.68 (0.34 to 1.33)	0.26	0.70 (0.35 to 1.40)	0.32
Age, years	1.03 (0.98 to 1.09)	0.20	1.03 (0.98 to 1.09)	0.28
Current smoking	2.72 (1.23 to 6.04)	0.014	2.69 (1.20 to 6.03)	0.016
LVH present	2.26 (1.08 to 4.70)	0.030	2.30 (1.09 to 4.83)	0.028
Pulse pressure, mmHg	1.04 (1.01 to 1.06)	0.002	1.04 (1.01 to 1.06)	0.001
SBP, mmHg	1.03 (1.01 to 1.05)	0.001	1.04 (1.02 to 1.06)	<0.001
DBP, mmHg	1.04 (1.00 to 1.08)	0.041	1.05 (1.00 to 1.09)	0.029
Body mass index, kg/m^2	1.02 (0.96 to 1.08)	0.54	1.02 (0.96 to 1.08)	0.50
HDL-C ≤1.0, mmol/l	1.59 (0.57 to 4.39)	0.37	1.58 (0.57 to 4.43)	0.38
LDL-C ≥3.0, mmol/l	1.01 (0.52 to 1.95)	0.98	1.12 (0.55 to 2.30)	0.76
Triglycerides ≥1.7, mmol/l	1.69 (0.86 to 3.34)	0.13	1.71 (0.86 to 3.41)	0.12
Glucose homeostasis				
Normal	1.00 (reference)	0.40†	1.00 (reference)	0.33†
IFG	0.82 (0.32 to 2.13)		0.86 (0.33 to 2.24)	
IGT	1.19 (0.51 to 2.77)		1.19 (0.51 to 2.81)	
T2D	1.86 (0.64 to 5.40)		2.12 (0.71 to 6.31)	
MBO				
IDF	1.00 (0.50 to 2.00)	0.99	0.96 (0.47 to 1.94)	0.90
ATPIII	1.30 (0.65 to 2.49)	0.49	1.26 (0.64 to 2.50)	0.51
Current medications				
Vasodilatators	0.69 (0.36 to 1.34)	0.28		
Betablockers	1.59 (0.81 to 3.12)	0.18		
Diuretics	1.37 (0.62 to 3.01)	0.44		
Statins	1.27 (0.56 to 2.88)	0.58		

† Model 1 was adjusted with age and gender.

‡ Model 2 was adjusted with age, gender and current medication.

5.5 The assessment of total cardiovascular risk in hypertensive subjects in primary care (V)

This study analyzed the results of 495 hypertensive subjects (45 % men) in whom valid measurements of ABI, hs-CRP and renal function were attainable (Table 15). Patients with established cardiovascular disease, hs-CRP values >10 mg/l (n = 59), previously diagnosed diabetes or renal disease were excluded from the study.

Table 15. Baseline characteristics of study participants. SCORE risk estimates of the diabetic subjects have been multiplied by two in men and by four in women [7]. (Study V)

	Female n = 272	**Male** n = 223	**All** n = 495
Demographic, mean (SD)			
Age, years	60 (7)	59 (7)	60 (7)
Weight, kg	78.5 (15.7)	90.4 (14.3)	83.9 (16.2)
Body mass index, kg/m²	29.9 (5.7)	29.2 (4.2)	29.6 (5.1)
Waist circumference, cm	94.1 (13.0)	102.5 (10.7)	97.9 (12.7)
Current smokers, n (%)	30 (11)	37 (17)	67 (14)
Clinical, mean (SD)			
Duration of hypertension, years, median (interquartile range)	5 (0, 11)	4 (0, 11)	4 (0, 11)
LVH, n (%)	51 (19)	30 (13)	81 (16)
Blood pressure, mmHg			
Systolic	153.2 (17.3)	154.0 (15.9)	153.6 (16.7)
Diastolic	89.8 (8.0)	92.2 (8.0)	90.9 (8.1)
Pulse pressure	63.5 (14.6)	61.8 (13.4)	62.7 (14.1)
ABI	1.06 (0.12)	1.07 (0.12)	1.07 (0.12)
eGFR	77.4 (15.3)	83.5 (16.6)	80.2 (16.2)
Framingham score, %	14 (9)	24 (13)	19 (12)
SCORE, %	5 (7)	10 (7)	7 (7)
Biochemical, mean (SD)			
hs-CRP, mg/l	2.75 (2.26)	2.24 (1.92)	2.52 (2.13)
Total cholesterol, mmol/l	5.31 (0.92)	5.14 (0.85)	5.23 (0.90)
LDL-cholesterol, mmol/l	3.14 (0.86)	3.06 (0.75)	3.11 (0.81)
HDL-cholesterol, mmol/l	1.57 (0.38)	1.41 (0.42)	1.50 (0.41)
Triglycerides, mmol/l	1.35 (0.58)	1.47 (0.73)	1.40 (0.65)
Fasting glucose, mmol/l	5.59 (0.85)	5.90 (1.15)	5.73 (1.01)
2-h glucose, mmol/l	8.00 (2.44)	7.80 (2.55)	7.91 (2.49)
Current medication, n (%):			
Vasodilatators	135 (50)	127 (57)	262 (53)
Betablockers	87 (32)	65 (29)	152 (31)
Diuretics	48 (18)	38 (17)	86 (17)
Statins	47 (17)	34 (15)	81 (16)

There were no differences between genders in the prevalence of ECG-LVH ($p = 0.11$) or mean ABI values ($p = 0.19$), but the mean hs-CRP ($p = 0.011$) level was higher in female

subjects and mean eGFR higher in men (p <0.001). According to OGTT, previously unknown diabetes was diagnosed in 34/495 (6.9 %) without significant difference between the genders (p = 0.91).

Prevalence of hypertensive target organ damage

Of the 495 study subjects, 123 [24.8 % (95% CI 21.1 to 28.9)] had ABI <1.00, 81 [16.4 % (95 % CI 13.2 to 19.9)] had ECG-LVH, and 41 [8.3 % (95 % CI 6.0 to 11.1)] had eGFR <60 ml/min/1.73 m^2.

Performance of the risk estimation tools to predict target organ damage

Framingham general cardiovascular disease risk >20 %, SCORE risk ≥5 % and hs-CRP >3 mg/l all showed poor accuracy to detect subclinical target organ damage as assessed by ABI <1.00, eGFR <60 ml/min/1.73 m^2 or presence of ECG-LVH, with a sensitivity of 31–57 %, specificity of 51–70 % and a non-significant positive likelihood ratio varying from 0.90 to 1.19 (Table 16).

Receiver operating characteristic curves for the target organ damage are shown in Figure 15. The Framingham score was slightly, but not significantly (p = 0.06), better discriminator of low eGFR than the other methods. Otherwise, the screening methods we used showed no predictive value for identifying patients with target organ damage.

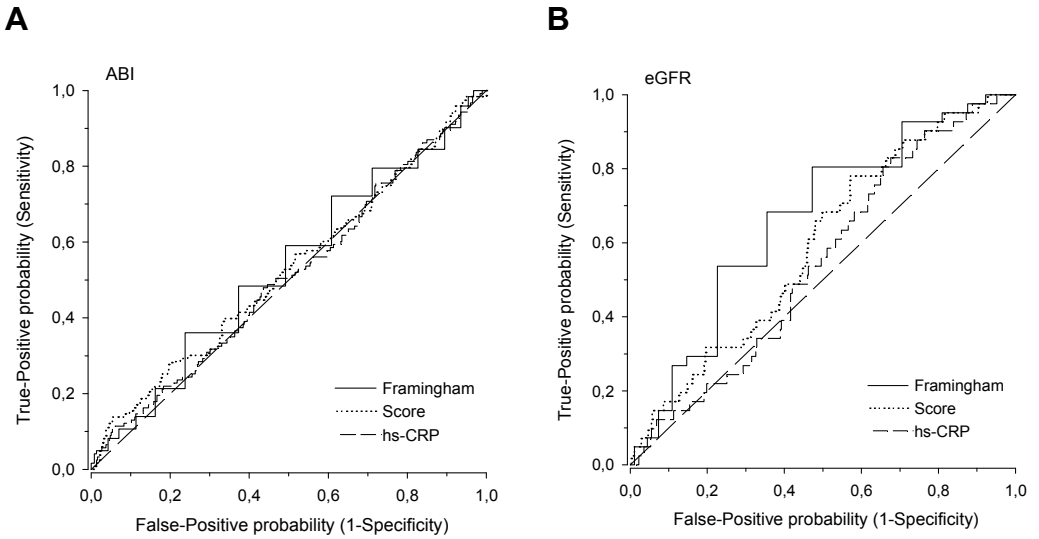


Figure 15. Receiver operating characteristic curves for prediction of ankle-brachial index <1.00 (A) and eGFR <60 ml/min/1.73 m^2 (B).

Table 16. The diagnostic characteristics of the test (Framingham cardiovascular disease risk, SCORE risk and hs-CRP) with a cut-off value of high risks in predicting target organ damage. Parenthesis shows 95 per cent confidence intervals. (Study V)

	Cut-off point	Accuracy	Sensitivity	Specificity	Positive likelihood ratio
ABI <1.0					
Framingham	≥20 %	57 (52 to 61)	0.31 (0.23 to 0.40)	0.65 (0.60 to 0.70)	0.90 (0.66 to 1.20)
SCORE	≥5 %	51 (47 to 56)	0.50 (0.41 to 0.60)	0.51 (0.46 to 0.57)	1.04 (0.84 to 1.26)
hs-CRP	>3	60 (56 to 65)	0.32 (0.24 to 0.41)	0.70 (0.65 to 0.75)	1.05 (0.77 to 1.41)
eGFR <60					
Framingham	≥20 %	64 (60 to 68)	0.37 (0.22 to 0.53)	0.67 (0.62 to 0.71)	1.09 (0.69 to 1.59)
SCORE	≥5 %	52 (47 to 56)	0.54 (0.37 to 0.69)	0.51 (0.47 to 0.56)	1.10 (0.79 to 0.43)
hs-CRP	>3	67 (63 to 71)	0.34 (0.20 to 0.51)	0.70 (0.65 to 0.74)	1.13 (0.70 to 1.70)
LVH					
Framingham	≥20 %	62 (58 to 66)	0.37 (0.27 to 0.49)	0.67 (0.62 to 0.72)	1.14 (0.82 to 1.53)
SCORE	≥5 %	53 (49 to 58)	0.57 (0.45 to 0.68)	0.52 (0.47 to 0.57)	1.19 (0.95 to 1.46)
hs-CRP	>3	64 (59 to 68)	0.32 (0.22 to 0.43)	0.70 (0.65 to 0.74)	1.06 (0.74 to 1.48)

Number of the study subjects classified as high risk (test positive) or non-high risk (test negative) subjects according to the risk estimation tests and the number of patients with target organ damage within each test category is shown in Figure 16. According to the SCORE system and the Framingham risk tool, 243/495 (49.1 %) and 169/495 (34.1 %) of the study subjects, respectively, were classified as having high cardiovascular risk.

The SCORE system estimated that 252/495 (50.9 %) patients have low cardiovascular disease risk, i.e. <5 % risk of dying from cardiovascular disease over ten years. In this group of hypertensive patients, 24.2 % (95% CI 19.1 to 30.0) (61/252) had ABI <1.00, 7.5 % (95% CI 4.6 to 11.5) (19/252) had eGFR <60 ml/min/1.73 m^2, and 13.9 % (95% CI 9.9 to 18.8) (35/252) had ECG-LVH.

According to the Framingham risk prediction model, 65.9 % (326/495) of the study subjects have a 10-year estimate of cardiovascular disease risk of <20 %. Among them, 25.8 % (95 % CI 21.1 to 30.9) had ABI <1.00, 8.0 % (95% CI 5.3 to 11.5) had eGFR <60 ml/min/1.73 m^2, and 15.3 % (95% CI 11.6 to 19.7) had ECG-LVH.

High-sensitive CRP <3 mg/l was measured in 69.7 % (345/495). Based on this criteria, 24.4 % (95 % CI 20.0 to 29.3) of the patients with low ABI, 7.8 % (95% CI 5.2 to 11.1) with low eGFR, and 16.0 % (95% CI 12.2 to 20.3) with ECG-LVH were classified as low risk subjects.

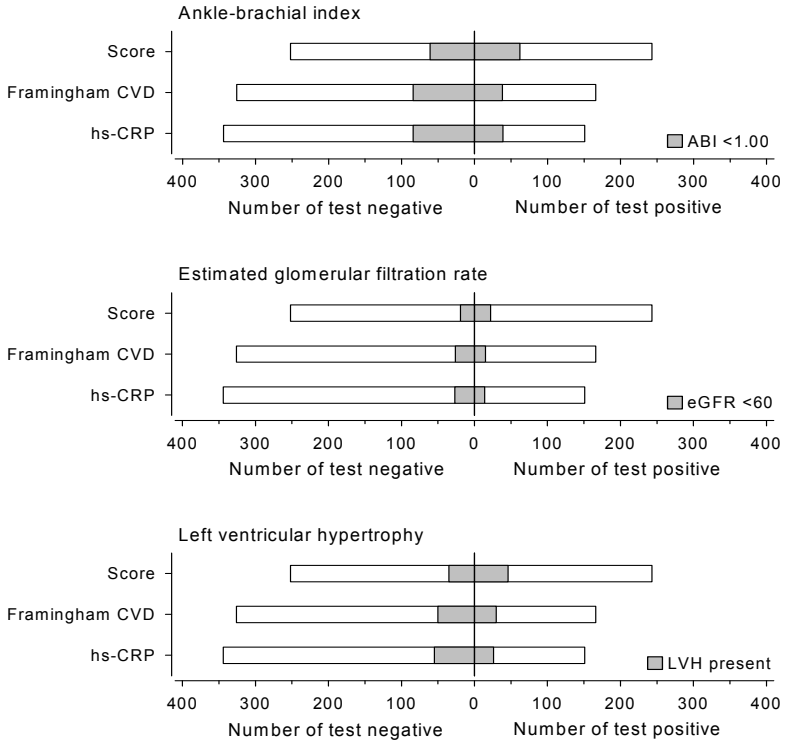


Figure 16. Number of the study subjects classified as high risk (test positive) or non-highrisk (test negative) subjects according to the risk estimation tests, and the number of patients with target organ damage within each test category. Cut-off points were 5 % in SCORE, 20 % in Framingham score and >3mg/l in hs-CRP. (Study V)

6 DISCUSSION

6.1 Study population

The study population of this thesis was drawn from a cross-sectional population-based survey, the Harmonica Project. A total of 6 013 subjects aged 45 to 70 years were invited to the project, and 4 421 men and women participated. The participation rate, 74 %, was quite high, indicating a need and interest in the general population to have information about aspects of health (Figure 17).

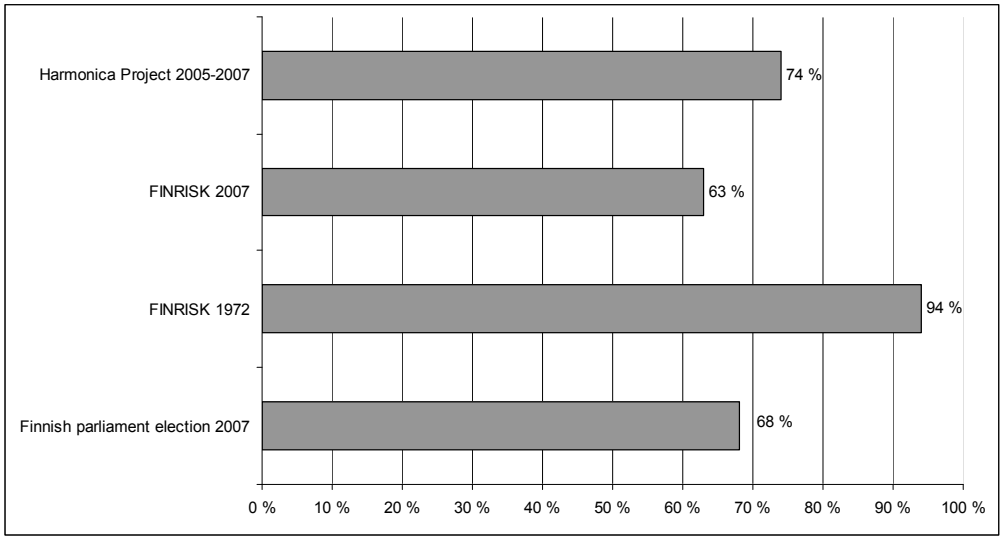


Figure 17. Participation rates in Finnish population health surveys and parliament election.

Out of the respondents, 69 % had at least one cardiovascular risk factor but no previously known diabetes or cardiovascular disease. These risk persons were further examined by the study nurses, and the test results form the database of the thesis. Thus, a representative cohort of persons at risk for cardiovascular diseases in the general population was formed.

By excluding the patients with known diabetes, cardiovascular or renal disease, a cohort of hypertensive subjects with no known major co-morbidities affecting arteries was identified, which sheds light on the impact of hypertension *per se* on glucose homeostasis, kidney function and peripheral arteries. However, due to the cross-sectional nature of the study, we cannot assess the causality of the associations between measured risk factors and organ damage.

6.2 Methods

With the invitation letter to the Harmonica Project, a tape for the measurement of waist circumference was posted to all invited persons. The purpose of this procedure was to awaken interest in matters of personal health.

The waist circumference home measurement was not as accurate as the measurement made by a nurse (Figure 18) and in the subsequent screening decisions only professionally measured waist circumferences were used.

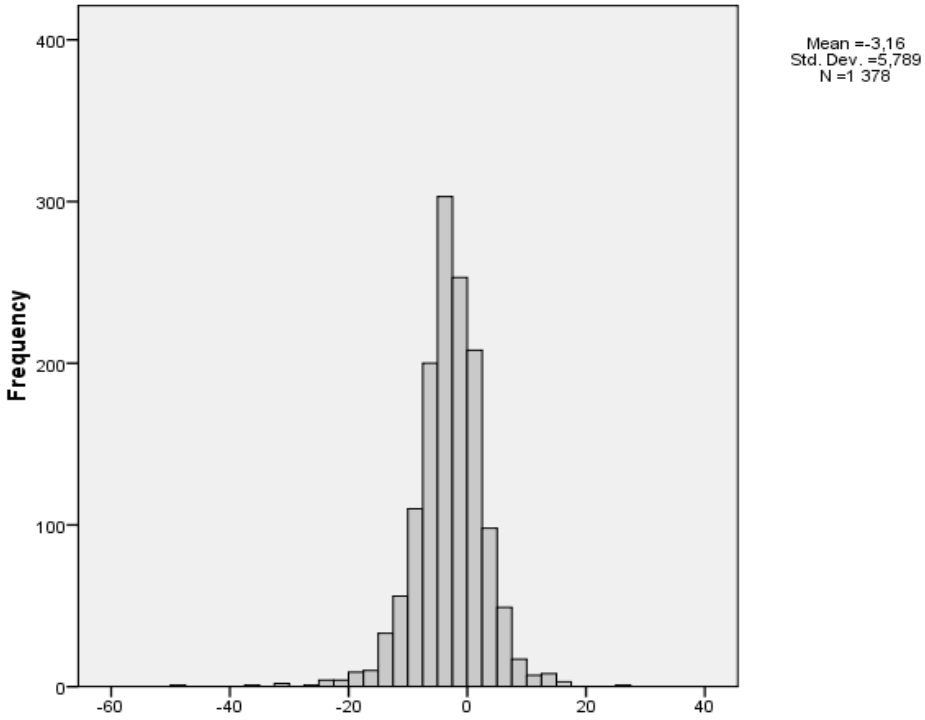


Figure 18. Difference between self-measured and nurse-measured waist circumference.

The anthropological measurements used in the Harmonica project were carried out following the standard WHO MONICA procedures [185].

For logistic reasons, glucose values were measured from capillary whole blood with an analyzer which converts the result to plasma glucose values. According to the Finnish Current Care Guidelines 2007 on Diabetes, the more preferable method to perform OGTT is to use venous plasma glucose values [186]. However, the current WHO criteria states reference values also for capillary glucose measurement, and in the Harmonica Project glucose disorders were classified according to these WHO criteria [182].

Because the results of OGTT and renal function in the Harmonica Project are derived from only one visit and single measurement, it is not possible to confirm the actual

duration of newly diagnosed glucose disorders or chronicity of renal insufficiency in the study patients. It has been estimated that 25 to 30 % of subjects initially categorized as stage 3 chronic kidney disease (eGFR 30 to 59 ml/min per 1.73 m^2) will subsequently no longer fall into this category when repeated measurements are obtained over 3 months after the "qualifying" test [187].

The strength of our study is that all plasma creatinine assays were made in one laboratory with one method which has been calibrated to be traceable to isotope dilution mass spectrometry (IDMS), the gold standard. Improved accuracy of eGFR is obtainable by using IDMS correction especially in the early stages of chronic kidney disease [188]. Unstandardized creatinine measurements from different laboratories may differ systematically by as much as 27 μmol/l [189]. A difference of this magnitude would have a large effect on the results of eGFR equations.

In the beginning of the Harmonica Project, the presence of urinary protein was searched in hypertensive subjects and in newly detected diabetics with overnight urine samples. However, because many study subjects found the urine test inconvenient, the decision about abandoning the test in the study protocol was made. Without evidence of urinary excretion of albumin, the diagnosis of hypertension or diabetes-induced renal damage is diminished. Therefore, only eGFR levels <60 ml/min/1.73m^2 are reported as kidney damage.

We used a simplified method to calculate ABI by measuring ankle systolic pressures from ADP only, and ATP was used if ADP pulsation was not reliably found. The lower ankle pressure was used for ABI calculation. The TASC II guidelines recommend measuring both ankle pressures and using the higher to calculate ABI, which may better address leg perfusion [83]. However, using the lower of the two ankle pressures has been shown to identify a higher number of patients with increased risk for future cardiovascular events [84]. The method used in the Harmonica Project somewhat overestimates the prevalence of PAD and borderline PAD compared to using higher of the ankle pressures as suggested by the TASC II guidelines, but on the other hand underestimates the prevalence if the lower of the two ankle pressures is used. However, the simplified method might be practical and less time-consuming in primary care practice to identify the persons at high cardiovascular risk.

6.3 A strategy to find out patients in cardiovascular risk in the general population (I)

With the two-stage screening method used in the Harmonica Project, middle-aged persons at risk for type 2 diabetes and cardiovascular disease were identified in the general population. Nurse-given lifestyle counselling was targeted to risk persons,

and the number of subjects needing a physician's appointment could be limited substantially for those who might benefit from preventive medication.

In 1993–1996, Vanhala used a two-stage screening strategy to identify middle-aged subjects with the metabolic syndrome in Pieksämäki municipality in eastern Finland. Non-invasive primary screening tools – family history of diabetes, body mass index ≥30 kg/m^2, elevated waist-to-hip-ratio and high blood pressure – were used as criteria for proceeding to confirmatory laboratory tests. [190]

In the Harmonica Project, an OGTT was performed to all women with waist circumference ≥80 cm and to all men with waist circumference ≥94 cm. This definition of central obesity by the IDF is a very sensitive (sensitivity 91 % in this study) screening method for glucose disorders, but it lacks specificity (specificity only 20 % in this study). Nevertheless, if only those with waist circumference >88 cm in women and >102 cm in men were screened, almost one fourth of the patients with type 2 diabetes and almost every other with prediabetes (IFG or IGT) had been missed. Such a high missing rate appears unacceptable because in the Whitehall Study, during 18–20 years of follow-up, cardiovascular mortality among people with IGT was about twice that among normal controls [191]. The problem is that central obesity defined by the IDF criteria is so common nowadays. Screening of all those subjects in the general population is an unreasonable demand for primary care.

The Nurses' Health Study showed that the smallest risk of developing type 2 diabetes is among women whose waist circumference is below 71 cm [192]. In the cohort of the Harmonica Project there were only 21 women out of 833 (2.5 %) whose waist circumference was below 71 cm. None of them had type 2 diabetes, one had IGT and two subjects had IFG. If the waist circumference was below 67 cm, there were no glucose disorders at all.

The Health Professionals Follow-Up Study of 27 270 men reported 83.6 % cumulative proportion of type 2 diabetes cases identified according to median of waist circumference ≥94 cm during 13 years of follow up [193]. The corresponding proportion was 50.5 % according to waist circumference ≥102 cm. In our cross-sectional study, the prevalence of diabetes and prediabetes was 36.6 % among men with waist circumference ≥94 cm, and 43.6 % among those with waist circumference ≥102 cm. Follow up will reveal how many of the subjects with prediabetes will turn out to be diabetics and how the lifestyle recommendations given in the Harmonica Project will manage to prevent this.

The diagnosis of the metabolic syndrome might hold promise for enhanced prevention of type 2 diabetes and cardiovascular diseases. According to our study, the IDF definition identified 75 % of the subjects with prediabetes and 92 % of the subjects

with type 2 diabetes while the definition of ATP III identified 53 % of the subjects with prediabetes and 82 % of the subjects with type 2 diabetes.

If OGTT was carried out for all people whose waist circumference was ≥80 cm in women and ≥94 cm in men, 87 % of the subjects with IGT and 95 % of the subjects with type 2 diabetes could have been identified. Using the IDF criteria of the metabolic syndrome as the criteria for carrying out OGTT, the number of investigations needed (n = 681 versus 1 168) could almost be halved without missing too many cases of prediabetes and type 2 diabetes. If we want to find all the cases of type 2 diabetes and IGT, we should carry out OGTT for all subjects whose waist circumference is ≥67 cm in women and ≥83cm in men. This would mean that we should examine 99.5 % of the middle-aged women and 97.2 % of the men in Harjavalta.

The Finnish Diabetes Risk Score (FINDRISC) was not as sensitive as the diagnosis of the metabolic syndrome to identify subjects with diabetes or prediabetes. But because risk assessment with the FINDRISC does not require any laboratory tests or other clinical measurements requiring professional skills, it is inexpensive and quite reliable primary screening tool to identify persons at risk for type 2 diabetes. If in the Harmonica Project we had used only the FINDRISC cut-off score 12 instead of the waist circumference as a primary screening tool for carrying out OGTT, we could have reduced the number of the subjects to be studied by 23 % (471/2085). FINDRISC is not as accurate as the metabolic syndrome to predict glucose disorders, but if the FINDRISC test is repeated in adults in every five years, as recommended in the Finnish Current Care Guidelines 2007 on Diabetes [186], it surely will find the cases of prediabetes and diabetes eventually.

Although the incidence of glucose disorders is growing, hypertension and dyslipidemia are by far the most common cardiovascular risk factors in the general population. Nurse-detected hypertension – whether true or isolated office hypertension – might be a useful screening test for cardiovascular diseases and glucose disorders in the general population.

Because cardiovascular diseases are the most common cause of mortality and long-term disability in Finland and other Western societies, even slight shifts in the prevalence of cardiovascular risk factors would have a large effect on public health. Primary care practitioners are in the front line of the battle against these preventable diseases, and early detection of high risk individuals is the corner stone of high quality of care. A good risk evaluation tool should be sensitive enough to detect risk persons for self-care and nurse led lifestyle interventions, and specific enough to assist doctors in the selection of the most effective treatment to high risk individuals [194].

As a conclusion, using FINDRISC form or hypertension as a primary screening tool, the people at risk for type 2 diabetes or cardiovascular diseases can be found non-invasively from the general population. The expertise of nurses could be utilized more in primary care to identify the high risk patients with OGTT or SCORE. Referral of these subjects to a doctors' appointment would be government of the best use of limited resources.

6.4 Glucose homeostasis in hypertensive subjects (II)

Impaired glucose homeostasis was found in 41 % of hypertensive subjects aged 45 to 70 years who had no previously diagnosed diabetes or cardiovascular disease. In a recent population survey among 4 500 randomly selected Finns aged 45 to 74 years, the prevalence of newly diagnosed impaired glucose homeostasis was 28 % in women and 32 % in men [143]. Thus, hypertensive subjects seem to have more glucose disorders than the general population. On the other hand, hypertension is common in subjects with impaired glucose homeostasis. In 1996, middle-aged inhabitants of Savitaipale in South Karelia were investigated with OGTT. Among the subjects with impaired glucose homeostasis, 53 % of men and 44 % of women were hypertensive [195].

IGT was found in every fifth hypertensive subject highlighting the importance of OGTT in the diagnosis of glucose disorders in hypertensive patients and in estimating the total cardiovascular risk of the patient. In the DECODE (Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe) study, people with IGT and a normal fasting glucose (≤6.0 mmol/l) formed the group with the largest number of excess deaths [196]. In our cohort, 67 % of the IGT patients had fasting glucose ≤6.0 mmol/l. Even among the 248 subjects who had fasting glucose ≤5.0 mmol/l, 37 (15 %) had IGT and 3 (1 %) had type 2 diabetes based on the 2-hour postload plasma glucose.

Because OGTT is a time- and effort-consuming test, it would be practical to select persons for proceeding to OGTT. If we would have carried out OGTT only for the hypertensive subjects with fasting glucose ≥5.6 mmol/l – the recommendation of the ESC/ESH 2007 guidelines – we would have missed approximately 40 % of the patients with IGT. But if OGTT is performed for the hypertensive subjects who meet the IDF criteria of the metabolic syndrome, approximately 90 % of IGT can be found. In this regard, the ATP III criteria were less sensitive. The IDF definition also better identified the patients with impaired fasting glucose compared with the ATP III definition (80 % versus 67 %).

The only difference between the IDF and the ATP III criteria of the metabolic syndrome is waist circumference (Table 5). In our cohort of 599 hypertensive women, 24 % had waist circumference 80–88 cm, and among them, the prevalence of type 2 diabetes was 5 % and the prevalence of IGT was 22 %. Of the 507 hypertensive men, 32 % had waist circumference 94–102 cm. Among them, 4 % had type 2 diabetes and 20 % had

IGT. Thus, using the ATP III criteria of the metabolic syndrome to select patients for proceeding to OGTT would reduce the number of investigations needed but would miss nearly 30 % of the patients with IGT compared with the 10 % who would be missed by using the IDF criteria. In the Hoorn Study, risk of conversion to type 2 diabetes during 6.5 years of follow-up was more than ten times higher in people with IGT than in people with normal glucose homeostasis [197].

OGTT has not been widely used in risk assessment among hypertensive patients. Salmasi et al. [198] studied 99 consecutive patients with unknown diabetes or cardiac history who were attending a hypertension clinic because of uncontrolled hypertension. OGTT was abnormal in 58 % of the patients, indicating IGT in 18 % and type 2 diabetes in 24 %. These figures are higher than in our cohort, possibly reflecting a more serious disturbance of metabolic homeostasis in uncontrolled hypertension. Lüders et al. performed an OGTT on 260 hypertensive patients in daily clinical practice in Germany [199]. Type 2 diabetes was diagnosed in 12 % and IGT in 39 % of the patients. In our cohort of 1 106 Finnish hypertensive subjects, type 2 diabetes was found in 6 % and IGT in 20 %, but we excluded the patients with known diabetes or cardiovascular disease.

The proportion of overweight and obese individuals among hypertensive subjects is alarming. In our cohort of 45 to 70 years old hypertensive subjects, the prevalence of central obesity according to the IDF criteria was 90 % in women and 82 % in men. In the Finnish general population aged 45 to 74 years, the corresponding figures were 76 % and 69 % [143]. In our study, glucose homeostasis and waist circumference had statistically significant correlation only in women and not in men, which is surprising and needs to be studied further. Nevertheless, it is well established that there is a linear relationship between reduction in weight and reduction in blood pressure [200]. Because in middle-aged individuals body weight frequently shows a progressive increase, weight stabilization should be considered an important goal to treat hypertension and to prevent diabetes. For a hypertensive individual, the motivation to lose weight might be higher when she or he has the knowledge of glucose homeostasis as well.

In conclusion, glucose disorders are more common in hypertensive subjects than in the general population. Using the criteria of the metabolic syndrome as the criteria for performing an OGTT, the number of tests can be reduced by one third and still find almost all the cases of type 2 diabetes and prediabetes.

6.5 Hypertensive subjects and the risk of renal insufficiency (III)

In the cohort of hypertensive subjects from general population, the prevalence of renal insufficiency defined as eGFR <60 ml/min per 1.73 m^2 was 6.7 % measured by the

MDRD formula and 3.0 % measured by the Cockroft-Gault formula, when known diabetics and people with cardiovascular or renal disease were excluded. Because the MDRD formula, unlike the Cockroft-Gault formula, is not biased by body weight, it is probably more accurate in this study cohort, in which most patients were overweight or obese. If renal function would be estimated on the basis of plasma creatinine alone, three fourth of the patients with renal insufficiency would have been missed. Thus, eGFR should be estimated in every hypertensive patient also in general practice.

The prevalence of renal insufficiency in hypertensive subjects in this study was much lower than in two Spanish studies in primary care setting [201, 202]. In these multicenter studies, the prevalence of eGFR <60 ml/min per 1.73 m^2 was over 20 % according to the MDRD study formula. In the study by Gomez et al. [201], the study population consisted of overweight or obese hypertensives of whom 32.9 % had previously diagnosed diabetes and 3.6 % had chronic kidney disease. In the study by Redon et al. [202], 41 % of the enrolled patients had type 2 diabetes, 49 % had impaired fasting glucose and only 18 % had normal fasting glucose. By excluding the patients with known diabetes, cardiovascular or renal disease we identified a cohort of hypertensives with no known co-morbidities affecting renal function, which probably explains the difference in the prevalence of renal insufficiency between these studies.

We used OGTT to detect previously undiagnosed glucose disorders in our study patients. Only 57 % of them had normal glucose homeostasis, but the fasting or 2-hour postload glucose values were not related to decreased eGFR. Although we cannot reliably assess the actual duration of newly diagnosed glucose disorders in this cross-sectional study, the result nevertheless suggest that new-onset diabetes or prediabetes do not independently affect renal function in hypertensive patients. This highlights the importance of early prevention, diagnosis and treatment of impaired glucose metabolism in hypertensive patients to prevent the deleterious effects of long-lasting diabetes on renal function.

The predominance of females in the renal insufficiency group of is noteworthy, but in concordance with other large-scale studies in hypertensive [199, 203] as well as in diabetic subjects [204, 205]. However, the risk of renal insufficiency in women in our cohort was also associated with the metabolic syndrome; the prevalence of renal insufficiency was 3.5 times higher in women with the metabolic syndrome than in women without the metabolic syndrome, and over four times higher than in men with the metabolic syndrome. Chen et al. were the first to demonstrate a strong relationship between the metabolic syndrome – defined by the ATP III criteria [150] – and the risk for chronic kidney disease in an analysis using the U.S. Third National Health and Nutrition Examination Survey dataset [206]. It has been demonstrated in autopsy studies that women have fewer glomeruli than men [120, 121], and that the number of nephrons is reduced in white patients with primary hypertension [122]. Susceptibility to renal failure

may be determined in large part by glomerular number [121]. Thus, in hypertensive women with reduced nephron numbers, the metabolic syndrome might be "the final straw to break the camel`s back".

In the large population-based cohort of the Atherosclerosis Risk in Communities study, the metabolic syndrome defined by the ATP III criteria, was independently associated with increased risk of incident chronic kidney disease in non-diabetic adults without cardiovascular disease at baseline [207]. The cohort was followed for nine years in which time 10 % of subjects with the metabolic syndrome developed chronic kidney disease (i.e. eGFR <60 ml/min per 1.73 m^2 calculated by the 4-variable MDRD formula) compared with 4 % of subjects without the metabolic syndrome. In our study, 600 out of 994 studied subjects met the metabolic syndrome criteria of the ATP III. If 10 % of them would develop chronic kidney disease in nine years, the amount of patients with renal insufficiency would double in the near future. Although controlling hypertension is the most important intervention to slow the progression of renal disease [208], the practitioners in primary care have to focus on all the components of the metabolic syndrome to prevent chronic kidney disease along with cardiovascular disease in their hypertensive patients.

In our study, reduced renal function was associated with the use of diuretics. Although we cannot assess the causality of this association solely from our cross-sectional study, our results are in concordance with prospective studies addressing the long term effects of diuretics on renal function in hypertensive patients. In the European Working Party on High Blood Pressure in the Elderly trial, serum creatinine increased more in patients with diuretics than in the placebo group [209]. In the Treatment of Mild Hypertension Study, serum creatinine increased with the use of thiazides, but was reduced by other types of treatment [210]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, estimated creatinine clearance was significantly better preserved with amlodipine than with thiazide or lisinopril [211]. Results from the Intervention as a Goal in Hypertensive Treatment Study show that renal function is better preserved with calcium channel blocker than with the diuretic combination hydrochlorothiazide-amiloride [212]. On the other hand, thiazide diuretics may also increase serum creatinine concentration by reducing tubular secretion of creatinine [213]. Therefore, it is currently unknown whether the use of diuretics is truly associated with an increased risk of subclinical organ damage in the kidney.

In conclusion, moderately decreased renal function is as common as newly detected diabetes in hypertensive subjects without co-morbidities affecting renal function. Especially hypertensive women with the metabolic syndrome are at risk of renal insufficiency. If renal function of the hypertensive subjects is estimated by plasma

creatinine alone, three-fourth of the patients with renal insufficiency would be overlooked compared to using estimated glomerular filtration rate as the screening method.

6.6 Ankle-brachial index in hypertensive subjects (IV)

The prevalence of asymptomatic PAD, defined as ABI ≤0.90, was 7.3 % (39/532) in hypertensive subjects aged 45 to 70 years without clinical cardiovascular or renal disease or known diabetes, and 2.3 % (10/440) in non-hypertensive subjects. This is, to our knowledge, the first study to report the prevalence of PAD in hypertensive population without previously diagnosed co-morbidities.

The MERITO study investigated Spanish patients aged 50 to 85 years (mean age 66 years) with hypertension and with no known vascular disease, but 62 % of the patients had diabetes [214]. This most likely explains the higher 27 % prevalence of PAD (defined as ABI <0.9) in the MERITO study compared to our study. Among an unselected cohort (history of cardiovascular disease in 20 %, diabetes in 8 %) of Chinese subjects, the age and gender matched prevalence of PAD (defined as ABI ≤0.9) was 8.7 % in hypertensive, and 5.0 % in normotensive subjects [215]. This quite low prevalence can be mainly explained by ethnicity. The Multi-Ethnic Study of Atherosclerosis showed that within the ethnic groups, the prevalence of PAD (defined as ABI <0.90) and borderline PAD (defined as ABI 0.90-0.99) was highest in African Americans, and lowest among Chinese in men and Hispanics in women [77].In our study all subjects were Caucasians.The Systolic Hypertension in the Elderly Program reported 27 % prevalence of PAD (defined as ABI ≤0.90) in subjects aged 60 years or older with isolated systolic hypertension, but this study also included patients with known diabetes and cardiovascular disease [216]. In our study, the prevalence of PAD was 8.5 % among the hypertensive subjects aged 60 years or older and without comorbidities (n = 279). Only 6 % (30/532) of the hypertensive subjects in our study population had isolated systolic hypertension defined as systolic blood pressure ≥160 mmHg and diastolic blood pressure <90 mmHg.

In our study population, the prevalence of borderline PAD (defined as ABI 0.91-1.00) was 24 % in the hypertensive subjects, and 15 % in the other high risk subjects. The significance of ABI values between 0.91 to 1.00, which are conventionally regarded as `no disease´, has recently been verified by a meta-analysis of 16 cohort studies, in which participants aged 47 to 78 years were derived from a general population [81]. In men with ABI 0.91–1.00, compared to reference ABI 1.11–1.20, the hazard ratios for total mortality, cardiovascular mortality and major coronary events were 1.61, 1.68 and 1.43, respectively. The corresponding figures in women were 1.52, 1.84 and 1.53. The magnitude of the increased risk in persons with borderline PAD was much lower than in those with ABI ≤0.90, but substantially higher than in

those with ABI >1.40. None of our study subjects had an ABI above 1.4, which is probably caused by media calcification frequently seen in patients with diabetes and kidney disease [217]. The inverse linear relationship between ABI and adverse cardiovascular outcomes across borderline ABI values 0.9 to 1.1 was also confirmed in two German follow-up studies [80, 218].

The TASC II guidelines recommend that ABI should be measured in all patients 70 years or older regardless of risk factor status, and in all patients between 50 and 69 years of age with at least one cardiovascular risk factor (particularly diabetes or smoking) [83]. In our study, hypertensive subjects aged 50 to 69 years consisted 95 % (506/532) of the hypertensive study population, and among them the prevalence of PAD and borderline PAD was 8 % and 24 %, respectively. It is noteworthy, that among the hypertensive subjects aged under 50 years of age (n = 45) none had PAD, but 22 % had borderline PAD. On the basis of the current evidence, there is no doubt that borderline PAD is a strong and independent predictor of cardiovascular events [80, 81, 218]. Thus, the decision of measuring ABI in hypertensive subjects may not be based on age or other cardiovascular risk factors.

The recent European guidelines for the management of hypertension and the United States guidelines for treating dyslipidemia use the cut-off point of ABI <0.9 to diagnose PAD and thus to initiate medical therapy for cardiovascular risk factors [8, 219]. It is interesting to compare this one-decimal cut-off point of ABI <0.9 with the two-decimal cut-off point ≤0.90 in the TASC II guidelines. Using the former would mean that 16 % (84/532) of the hypertensive subjects in our study have PAD, including a large number of patients with ABI 0.90–0.94. Using the latter threshold resulted in the prevalence of 7 % (39/532). This discrepancy stresses the importance of having uniform diagnostic criterions for PAD and borderline PAD not only for scientific purposes, but also to facilitate clinical decision making.

There was no association between either impaired glucose homeostasis or the metabolic syndrome and PAD in our study population without previously known diabetes or cardiovascular disease. Pande et al. have recently shown that insulin resistance, indicated by homeostasis model of insulin resistance, is associated with PAD [78]. However, when subjects with known diabetes were excluded from this unselected United States population sample, the associations between insulin resistance and PAD were no longer statistically significant. Taken together, these results suggest that newly diagnosed prediabetes or diabetes *per se* is not associated with the prevalence of PAD, whereas long-lasting diabetes remains a well established risk factor for PAD.

We found significant association between blood pressure levels and PAD (Table 12). When a linear model was used to determine the age and sex adjusted linearity across ABI levels >1.00, 0.91-1.00 and ≤0.90, the relationship between ABI and pulse pressure

or systolic blood pressure, but not diastolic blood pressure, was linear across ABI subgroups in hypertensive subjects. The majority (67 %) of the PAD cases was found among patients with widened pulse pressure; the prevalence of PAD was 12 % (26/216) among hypertensive patients with pulse pressure ≥65 mmHg.

In hypertensive patients, arterial compliance – estimated indirectly by increasing pulse pressure – was reduced already with borderline PAD. Instead, in non-hypertensive patients, increase in pulse pressure was seen only in patients with established PAD defined as ABI ≤0.90. While we cannot determine any causal relationships from our cross-sectional study, we find it possible that increasing arterial stiffness plays a major pathophysiological role in the development of both increased pulse pressure and atherosclerotic lesions in the peripheral arterial tree.

For logistic reasons, we used a simplified method to measure ankle systolic pressures from dorsalis pedis artery only, and posterior tibial artery was used if dorsalis pedis artery pulsation was not reliably found. The lower ankle pressure was used for ABI calculation. The TASC II guidelines recommend measuring both ankle pressures and using the higher to calculate ABI, which may better address leg perfusion [83]. However, Schröder et al. showed that using the lower of the two systolic blood pressures of a leg as the numerator in calculating ABI, had a sensitivity of 89 % and specificity of 93 % for PAD confirmed by arterial duplex ultrasonography. Using the higher of the systolic blood pressures of a leg as the numerator had a sensitivity of 68 % and a specificity of 99 % [220]. Using the lower of the two ankle pressures has also been shown to identify a higher number of patients with increased risk for future cardiovascular events [84]. The method used in our study somewhat overestimates the prevalence of PAD and borderline PAD compared to using higher of the ankle pressures as suggested by the TASC II guidelines, but on the other hand underestimates the prevalence if the lower of the two ankle pressures is used. However, the simplified method we used might be practical and less time-consuming in primary care practice to identify the persons at high cardiovascular risk.

In conclusion, peripheral arterial disease or borderline peripheral arterial disease was detected in every third of the hypertensive subjects, more often in those with widened pulse pressure over 65 mmHg. Hypertension is an independent factor associated with peripheral arterial disease (adjusted OR 3.20; 95% CI 1.56 - 6.58). Measuring ankle-brachial index using the lower of either one of the ankle pressures might be practical tool to detect subclinical atherosclerosis in the hectic office of a primary care physician.

6.7 The assessment of total cardiovascular risk in hypertensive subjects in primary care (V)

The prevalence of hypertension-related target organ damage among the 495 study subjects were 25 % for ABI <1.00, 16 % for ECG-LVH, and 8 % for eGFR <60 ml/min/1.73 m^2.

We chose ABI value <1.0 to indicate subclinical peripheral arterial disease. It has been shown that the relationship between ABI and cardiovascular disease in nonlinear and varies across the range of ABI [77, 81]. Individuals with ABI ≤0.90 are at the highest risk for cardiovascular events, but also ABI values from 0.91 to 1.10 and greater than 1.40 are associated with elevated total mortality and cardiovascular mortality rates [81]. We used the lower ankle pressure for ABI calculation, which has been shown to identify a higher number of patients with increased risk for future cardiovascular events [84].

GFR <60 ml/min/1.73 m^2 is selected as the cut-off value for definition of chronic kidney disease because it represents a reduction by more than half of the normal value of 125 ml/min/1.73 m^2 in young adults, and this level of GFR is associated with the onset of laboratory abnormalities characteristic of kidney failure, including increased prevalence of several cardiovascular risk factors [123]. We calculated eGFR using the MDRD formula [184] which is not biased by body weight, unlike the Cockroft-Gault formula [126]. Most of our study subjects were overweight or obese; 417/495 (84.2 %) had body mass index ≥25 kg/m^2 and 207/495 (41.8 %) had body mass index ≥30 kg/m^2.

The addition of the inflammatory biomarker hs-CRP to traditional risk factors has been shown to reclassify up to 30 % of women at intermediate risk according to Framingham risk score into clinically relevant high or low risk categories [221]. The SCORE system does not include the intermediate risk category and in this regard, hs-CRP has no established role in the European guidelines on cardiovascular disease prevention [10]. In our study, hs-CRP >3 mg/l predicted the presence of subclinical target organ damage with a sensitivity of only 30 % although the specificity of 70 % raised the accuracy of the high hs-CRP to approximately 60 %. Given the simplicity and suitability of ABI, ECG-LVH and eGFR measurements to daily clinical practise, and their potential ability to recognize high risk individuals who would be otherwise misclassified as having low cardiovascular risk based on conventional risk prediction tools alone, more systematic use of these measurements in the general hypertensive population seems justified.

In conclusion, SCORE and Framingham risk estimation tools or hs-CRP value >3 mg/l can not replace the measurements of ECG-LVH, ABI and eGFR in assessing the total cardiovascular risk of hypertensive subjects.

7 CONCLUSIONS

Cardiovascular disease is the major cause of premature death, an important cause of disability and contributes substantially to the costs of health care. Although these diseases and their risk factors are preventable, there is no evidence that mass screening is a cost-effective way to prevent cardiovascular disease. Key issues in the prevention of cardiovascular disease are to find the patients at risk and their willingness to maintain lifestyle changes in the long term. This is a huge task for primary care which has to face the growing tide of obesity and diabetes in the 21st century.

Clinical implications and recommendations from the Harmonica project

FINDRISC form or nurse-measured blood pressure are non-invasive, easy to perform and quite reliable primary screening tools suitable for identifying people at risk for type 2 diabetes or cardiovascular disease in the general population.

The expertise of nurses could be utilized more in primary care to identify the high risk persons with blood pressure measurement, OGTT and SCORE risk estimation. Referral of high risk subjects – who might benefit most from preventive medication – to a doctors' appointment, would be government of the best use of limited resources.

Glucose disorders are more common in hypertensive subjects than in the general population. However, PAD and moderately decreased GFR are as common as newly detected diabetes, and borderline PAD even more common than IGT in hypertensive subjects even without co-morbidities. Moreover, a substantial proportion of hypertensive subjects have ECG-LVH. These easily detectable target organ damage considerably increase the total cardiovascular risk of a hypertensive patient. However, neither SCORE nor Framingham risk prediction model has the potential to recognise these subclinical signs of atherosclerosis.

The results suggest that new-onset diabetes or prediabetes do not independently affect renal function or peripheral arterial disease in hypertensive patients. This highlights the importance of early prevention, diagnosis and treatment of impaired glucose metabolism in hypertensive patients to prevent the deleterious effects of long-lasting diabetes on renal function.

In attempting to prevent first time cardiovascular events among hypertensive subjects, it is important to search for target organ damage, impaired glucose homeostasis and other metabolic risk factors to thoroughly assess the total cardiovascular risk of a patient, and to adjust the intensity of the therapeutic approach accordingly. Oral glucose tolerance test is worth performing to subjects who meet the IDF criteria of the metabolic syndrome. Renal function should be estimated by calculating glomerular filtration rate with the MDRD formula. Measurement of ABI is indicated in those with widened pulse pressure.

8 ACKNOWLEDGEMENTS

When the deed is done and the work accomplished, it is the pleasure of the writer to look back and express gratitude to those who gratitude deserve.

I am grateful to each and every one of the staff and participants of the Harmonica Project, especially the nurses and the unprejudiced executives of the Central Satakunta Health Federation of Municipalities who helped to bring the project to fruition. All of their good work remains in this thesis.

I wish to express my deepest gratitude to my supervisors Docent Ilkka Kantola, Professor Pertti Aarnio and Docent Tarja Saaresranta.

Docent Ilkka Kantola knows everything there is worth knowing about hypertension. He has given many lectures that I have found fascinating, and they have been an inspiration for my own research. It is an honour for me to have him as my supervisor.

My gratitude goes to Professor of Surgery, Pertti Aarnio, who not only had an unwarranted faith in an internist like me to write this thesis, but also guided me academically in a remote place like Harjavalta far away from university. Professor Aarnio is brilliant in peripheral arterial disease, and he is also a rarity in being a true gentleman and scientist.

Docent Tarja Saaresranta is acknowledged for her continuous support to me in sometimes tricky academic world. She has always taken the time to help me during the Harmonica Project, from the beginning to the end.

I am very lucky to have had Doctor Risto Vesalainen as a co-author in studies III-V. His suggestions for many of the chapters were invaluable.

I warmly thank Docent Pekka Jaatinen for his kind and skilful help with statistical issues in studies I and II.

I extend my thanks to Hannu Kautiainen and Salme Järvenpää for their skilled statistical analyses of the studies III-V. I continue to be amazed at the world of numbers, and I am thankful for Katja Jäntti and Pia Jauhiainen who dragged me out for coffee from time to time during my instructive visits in Äänekoski.

I want to express my sincere gratitude to the reviewers of this dissertation, Professor Sirkka Keinänen-Kiukaanniemi and Docent Hannu Vanhanen. They have taken time out of their busy lives to advice me with valuable comments which greatly improved the quality of this thesis.

Early in my career as a clinician, Doctor Seppo Ojanen made me realize that research is an essential part of good medicine, and it also can be humane. I warmly thank Seppo for his friendship during all these years.

Financial support provided by Satakunta Hospital District, the Finnish Cultural Foundation, the Ida Montin Foundation, the Finnish Medical Foundation and the Finnish Foundation for Cardiovascular Research made writing of this thesis possible and was received with gratitude

I thank Jari Prehti, my beloved, for tolerating with such good grace the many evenings and weekends that I was mentally away preparing this thesis.

I am grateful to my parents Marja and Eero and to my brother Ari for all their support during my life. Those who are dearest to my heart, I too often take for granted.

Finally, I thank my nephews Markus and Lauri who have brought so much joy to my life, and to whom I dedicate this book.

Harjavalta, October 2009

Päivi Korhonen

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APPENDIX

KUTSU VALTIMOTAUTIEN EHKÄISYPROJEKTIIN

Suomessa sairastuu joka päivä 49 henkilöä sydäninfarktiin eli sepelvaltimon tukokseen ja 38 henkilöä aivoinfarktiin eli aivovaltimon tukokseen. Valtimotaudit ovat suomalaisten suurin terveysuhka, jolle altistavia tekijöitä ovat korkea verenpaine, korkea kolesteroliarvo, tupakointi ja sukurasite. Näiden lisäksi viime vuosina räjähdysmäisesti yleistyneet ylipaino, diabetes ja metabolinen oireyhtymä uhkaavat lisätä valtimotautien määrää niin, että vuonna 2020 oletetaan joka päivä 58 suomalaisen sairastuvan aivoinfarktiin. Valtimoprojektin tavoite on, että mahdollisimman monen harjavaltaisen valtimot ovat mahdollisimman hyvässä kunnossa eivätkä tukkeudu.

Tämän kutsun mukana saat mittanauhan, jolla voit mitata vyötärönympäryksesi navan kohdalta kevyen uloshengityksen aikana. Sinisen tyypin 2 diabeteksen sairastumis-riskin arviointilomakkeen täyttämällä voit arvioida riskisi sairastua aikuistyypin diabetekseen. Täytä myös oheinen vaaratekijäkysely. Mukana on kirjekuori, jolla toivomme Sinun palauttavan vaaratekijäkyselyn ja sinisen diabeteksen sairastumis-riskin arviointilomakkeen terveyskeskukseen. Postimaksu on maksettu puolestasi. Mittanauhan saat pitää.

Mikäli kyselykaavakkeiden perusteella arvioidaan valtimotautiin sairastumisriskisi olevan kohonnut, Sinut kutsutaan terveystutkimukseen Harjavallan terveyskeskukseen.

Terveystutkimuksessa terveydenhoitaja mittaa Sinulta verenpaineen, painoindeksin, vyötärönympäryksen ja keuhkojesi toimintakyvyn. Laboratoriossa otettavilla verinäytteillä määritetään mm. kolesteroliarvosi ja tehdään sokerirasituskoe, jossa verensokeriarvosi määritetään paastotilassa ja 2 tuntia sokeripitoisen nesteen nauttimisen jälkeen. Verinäytteet otetaan kyynärtaipeesta ja sormenpäästä, jolloin neulanpistot voivat aiheuttaa kipua. Sokerimittausten välisenä aikana kartoitetaan kyselykaavakkein vointiasi ja tottumuksiasi. Sinulta otetaan myös EKG eli ”sydänfilmi”.

Jos Sinulla todetaan verenpainetauti (yläpaine 140 tai yli tai alapaine 90 tai yli), metabolinen oireyhtymä, kolesteroliaineenvaihdunnan häiriö, terveyden kannalta merkittävä ylipaino, diabetes tai sen esiaste, saat terveydenhoitajalta kirjalliset ja suulliset lääkkeettömän hoidon ohjeet. Sinulle järjestetään myös 2-6 kuukauden kuluessa kontrollilaboratoriokokeet sekä sisätautien erikoislääkärin vastaanottoaika.

Valtimoprojektissa tehdyillä tutkimuksilla saadaan tärkeää tietoa valtimotautien ja niiden vaaratekijöiden esiintymisestä väestössä, ja siten toivotaan terveydenhuollon voimavaroja voitavan ohjata tulevaisuudessa aiempaa tehokkaammin. Jos haluat osallistua Valtimoprojektiin, pyydämme Sinulta terveystutkimukseen tullessasi kirjallisen luvan tutkimuksen yhteydessä tapahtuvaan tietojen keräämiseen ja niiden käsittelyyn niin, ettei henkilöllisyyttäsi voida niistä tunnistaa. Lisätietoja tutkimuksesta saat tarvittaessa terveydenhoitajalta puhelinnumerosta 02 - 533 6846. Tutkimuksen vastuuhenkilö on sisätautien erikoislääkäri Päivi Korhonen.

Terveystutkimukseen tullessasi Sinun tulee olla ravinnotta edeltävän 12 tunnin ajan, vettä saat juoda. Varaa tutkimukseen aikaa noin 2 ½ tuntia. Edeltävät 2 yötä Sinun tulisi olla nukkunut normaalisti, joten älä varaa tutkimusaikaa yövuoron jälkeen. Tutkimus on Sinulle maksuton, mutta koska kyseessä on terveystutkimus, matkakustannuksia ei voida korvata.

Ystävällisin terveisin Harjavallan terveyskeskus

VAARATEKIJÄKYSELY;
rastita oikea vaihtoehto tai kirjoita vastaus viivalle

Mikä on vyötärönympäryksesi? _____ cm

Mikä on tyypin 2 diabeteksen sairastumisriskin arviointilomakkeen pistemääräsi yhteensä? _____

Käytätkö verenpainelääkitystä? Kyllä □ En □

Mikä on Sinulta viimeksi mitattu verenpainearvo? _____

Koska tämä mittaus on tehty? _____

Onko vanhemmillasi tai sisaruksillasi todettu tyypin 2 diabetesta? (aikuistyypin diabetesta)? Kyllä □ Ei □

Onko vanhemmillasi tai sisaruksillasi todettu valtimotautia (sepelvaltimotauti, sydäninfarkti, aivohalvaus)? Kyllä □ Ei □

Jos vastasit kyllä, minkä ikäinen sukulaisesi oli, kun sairaus hänellä todettiin?
Äiti _____-vuotias Isä _____-vuotias
Sisar _____-vuotias Veli _____-vuotias

Onko Sinulla raskauden aikana todettu korkea verenpaine?
Kyllä □ Ei □

Onko Sinulla raskauden aikana todettu kohonnut verensokeriarvo?
Kyllä □ Ei □

VALTIMOPROJEKTI Terveydenhoitajakaavake **Pvm** _____

Nimi ja henkilötunnus:_____ **ID** _____

Ikä:_____v. **Tulosyy:**_____ **DM-riski** _____p

Paino _____kg (kevyet sisävaatteet ilman kenkiä – 1 kg; tarkkuus 0,1 kg)

Pituus _____cm
(ilman kenkiä: tarkkuus 0,5 cm)

BMI _____kg/m²

BMI	Painoluokka
18,5-25	Normaali paino
25,1-30	Lievä lihavuus
30,1-35	Merkittävä lihavuus
35,1-40	Vaikea lihavuus
> 40	Sairaalloinen lihavuus

Vyötärönympärys _____cm
Tutkittava:_____ cm
(suoliluun ja alimman kylkiluun puolivälistä kevyen uloshengityksen aikana;
tarkkuus 0,1cm)

VERENPAINE
Elohopeamittari ____/____ ja ____/____ Jos ≥ 140/90, lainaa kotimittari viikoksi
Kotimittari: 4 viimeisimmän II-mittauksen keskiarvo ____/___Jos ≥135/85, lääkäriin

	RRs	RRd	Toimenpide
Ihanteellinen	< 120	< 80	Kontrollimittaus 5 vuotta
Normaali	< 130	< 85	Kontrollimittaus 2 vuotta
Korkea normaali	130-139	85-89	Kontrollimittaus 1 vuosi
Lievä verenpainetauti	140-159	90-99	Jos kotimittarilla keskiarvo ≥155/95, lääkäri 1 kk ≥175/105, lääkäri 1-2 vko
Keskivaikea verenpainetauti	160-179	100-109	
Vaikea verenpainetauti	≥ 180	≥ 110	

SOKERIRASITUSKOE

Paastoarvo _____
klo _____
2 tunnin arvo _____

Jos todettiin diabetes,
GHbA1c_____%

	Heikentynyt paastosokeri	Heikentynyt glukoosinsieto	Diabetes
Paastoarvo	6,1-6,9	< 7,0	≥ 7,0
2 tunnin arvo	< 8,9	8,9-12,1	≥ 12,2

MBO

Merkitse X, jos tutkittavan arvo täyttää kriteerin.
IDF □ ATP □

IDF	**X**	**ATP vähintään 3 seuraavista:**	**X**
Vyötärönympärys ≥ 94 cm mies ≥ 80 cm nainen **ja vähintään 2 seuraavista:**		Vyötärönympärys > 102 cm mies > 88 cm nainen	
fP-Gluk ≥5,6 tai T2D		fP-Gluk ≥5,6 tai lääkitys	
RR ≥130/85 tai verenpainelääkitys		RR ≥130/85 tai verenpainelääkitys	
P-Trigly ≥1,7 tai lääkitys		P-Trigly ≥1,7 tai lääkitys	
P-HDL <1,03 mies <1,29 nainen tai lääkitys		P-HDL <1,03 mies <1,29 nainen tai lääkitys	

TUPAKOI □ **MINISPIROMETRIA: FEV1** _____ l, _____% viitearvosta

RASVANKÄYTTÖ _____ p.

ALKOHOLINKÄYTTÖ _____ p. Jos ≥15 p., puheeksiotto ja hoitoonohjaus.

DEPRESSIOKAAVAKE BDI _____ p. Jos ≥10 p., keskustelu.
Jos ≥19 p., vastaanotto.

LIPIDIT: Kol _____ **HDL** _____ **LDL** _____ **Trigly** _____

SCORE: _____% 60-vuotiaana _____%

LÄÄKÄRIN VASTAANOTOLLE □

VALTIMOPROJEKTI Lääkärikaavake Pvm _____

Nimi ja HeTu:_____ **Ikä** _____**v ID**_____

AIEMMAT SAIRAUDET_____
_____

PAINO _____kg (kevyet sisävaatteet ilman kenkiä – 1 kg; tarkkuus 0,1 kg)

BMI _____kg/m² **VYÖTÄRÖNYMPÄRYS** _____cm (tarkkuus 0,1 cm)

VERENPAINE _____/_____ **ja** _____/_____ **⇒ keskiarvo** _____/_____
Maaten_____/_____
4 viimeisimmän kotimittauksen keskiarvo _____/_____

ADP/ATP: oikea _____**mmHg vasen** _____**mmHg**

ABI: oikea _____ **vasen** _____

fP-Gluk _____ **GHbA1c** _____%
Kol _____ **HDL** _____ **LDL** _____ **Trigly** _____
ALAT _____ **TSH** _____ **Krea** _____ **K** _____ **Na** _____
Ca-Ion _____ **Hb** _____ **MCH**_____ **Leuk** _____ **Mo** _____**%**

MBO
IDF □
ATP □

MBO – IDF	**X**	**MBO - ATP; ≥ 3 seuraavista:**	**X**
Vyötärönympärys ≥ 94 cm mies ≥ 80 cm nainen **ja vähintään 2 seuraavista:**		Vyötärönympärys >102 cm mies > 88 cm nainen	
fP-Gluk ≥5,6 tai T2D		fP-Gluk ≥5,6 tai lääkitys	
RR ≥130/85 tai lääkitys		RR ≥130/85 tai lääkitys	
P-Trigly ≥1,7 tai lääkitys		P-Trigly ≥1,7 tai lääkitys	
P-HDL <1,03 mies <1,29 nainen tai lääkitys		P-HDL <1,03 mies <1,29 nainen tai lääkitys	

EKG

Sinusrytmi □ **Muu rytmi** □ _____
$SV_1 + RV_{5-6}$ _____mm
RaVL + SV_3 (+ 6 mm naisella) x QRS-kesto _____mm x ms

SCORE nyt _____% 60-vuotiaana _____%

Nykyinen säännöllinen lääkitys, myös estrogeeni- ja muut hormonivalmisteet

Lääkkeen nimi ja annostus, käyttötarkoitus ATC - koodi

1_____|__|__|__|__|__|__|

2_____|__|__|__|__|__|__|

3_____|__|__|__|__|__|__|

4_____|__|__|__|__|__|__|

5_____|__|__|__|__|__|__|

6_____|__|__|__|__|__|__|

7_____|__|__|__|__|__|__|

8_____|__|__|__|__|__|__|

Aloitettu säännöllinen lääkitys

Lääkkeen nimi ja annostus, aloituksen syy ATC - koodi

1_____|__|__|__|__|__|__|

2_____|__|__|__|__|__|__|

3_____|__|__|__|__|__|__|

4_____|__|__|__|__|__|__|

Lopetettu säännöllinen lääkitys

Lääkkeen nimi ja annostus, lopetuksen syy ATC - koodi

1_____|__|__|__|__|__|__|

2_____|__|__|__|__|__|__|

3_____|__|__|__|__|__|__|

4_____|__|__|__|__|__|__|