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Prevention of Cardiovascular Disease and Diabetes on a Population Level

by

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To my loved ones

"Energy cannot be created or destroyed,
it can only be changed from one form to another."
- Albert Einstein

Contents

Abstract

Background
Cardiovascular disease and diabetes are responsible for just over half of the global mortality, and these diseases are expected to increase. The upsurge is due to increased longevity and a westernisation of the global lifestyle. Preventive efforts have proven effective and are believed to be the only way to curb the rapid increase of these diseases. Still the implementations of preventive measures are reported as underused.

Aims
To study prevention by

1. Investigating the perception of key policymakers on cardiovascular disease
2. Examining if screening for diabetes online is feasible using FINDRISC
3. Assessing management of patients with coronary artery disease and diabetes
4. Determining the best screening test for dysglycaemia in patients with coronary artery disease

Policymakers' perception of cardiovascular disease
Policymakers in Europe agreed that national patterns of cardiovascular disease and its prevention are far from satisfactory. A similar rating of the perceived proximity to a specific target in two countries did not necessarily reflect a similar national situation when compared to available statistics on the actual situation. Policymakers had diverging opinions on what actions to take and what obstacles to overcome to improve population health.

Feasibility of using FINDRISC as an online questionnaire
It was feasible to incorporate a diabetes risk score such as FINDRISC in an online survey. A reasonable response rate was achieved and a group that could benefit from preventive intervention programs was identified.

Management of patients with coronary artery disease and diabetes
A large proportion of the patients are far from guideline recommended evidence based treatment targets for blood pressure, LDL-cholesterol and HbA1c. A potential reason is a consistent, relatively low combined use of four selected cardioprotective drug therapies and/or lack of dose titration. There was, however, some improvement over time.

Screening for dysglycaemia in patients with coronary artery disease
Screening by means of an oral glucose tolerance test (OGTT) identified the largest number of patients with undetected diabetes. The overlap in case-detection between fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG) and HbA1c was small. Screening with HbA1c alone would have left 83% of those with diabetes undetected. The total proportion of patients identified with diabetes and other forms of dysglycaemia varied from 90% using the American Diabetes Association's criteria for FPG + HbA1c, which may be an overestimate, to 73% using WHO criteria for OGTT = FPG + 2hPG, which may be more realistic.

Conclusion
Creating a coherent knowledge base and action agenda regarding prevention among key policymakers should be given high priority in future population based prevention programmes. The online questionnaire FINDRISC is a feasible way to identify high-risk individuals as well as risk typing populations. Despite some improvement, patients with coronary artery disease and diabetes are not managed according to best available knowledge. Efforts to improve this are needed to improve their still dismal prognosis. An oral glucose tolerance test has the best capacity to screen-detect dysglycaemia in patients with coronary artery disease.

SAMMANFATTNING

Bakgrund
Hjärt-kärlsjukdom och diabetes står för drygt hälften av alla dödsfall globalt och dessa sjukdomar väntas öka. Ökningen beror framför allt på en allt längre livslängd och vår moderna livsstil med brist på fysisk aktivitet och för högt kaloriintag. Det är välkänt att förebyggande åtgärder och behandling kan minska eller senarelägga insjuknandet i dessa sjukdomar. Trots denna kunskap rapporteras det ofta om ett bristfälligt genomförande av förebyggande insatser.

Mål
Att studera prevention genom att

1. Undersöka beslutsfattares uppfattning om kardiovaskulär sjukdom
2. Studera screening för diabetes på internet med hjälp av FINDRISC
3. Utvärdera vården av patienter med kranskärlssjukdom och diabetes
4. Identifiera det bästa testet för dysglykemi hos patienter med kranskärlssjukdom

Beslutsfattares uppfattning om kardiovaskulär sjukdom
Beslutsfattare i Europa är överens om att deras länder är långt ifrån att uppnå önskvärda hälsomål. Då två länders beslutsfattare uppfattade den nationella förekomsten av ohälsosamma faktorer eller vidtagna hälso-befrämjande åtgärder lika, överensstämde ofta inte deras respektive situationer baserat på tillgängliga data från epidemiologiska undersökningar. Beslutsfattarna hade olika uppfattningar om vilka initiativ som var viktigast för att förbättra befolkningens hälsa.

Screening för diabetes på internet med hjälp av FINDRISC
FINDRISC-frågorna kunde infogas i ett internetbaserat frågeformulär. Svarsfrekvensen var rimligt god och en grupp som kunde dra nytta av prevention identifierades.

Vård av patienter med kranskärlssjukdom och diabetes
En stor andel av patienter med kranskärlssjukdom och diabetes når inte de i riktlinjer angivna målen för blodtryck, LDL-kolesterol och HbA1c. En sannolik förklaring är att tillgängliga läkemedel inte kombineras eller doseras helt ändamålsenligt. Över tid har vården av dessa patienter förbättrats, trots bestående brister.

Dysglykemi-test hos patienter med kranskärlssjukdom
Ett oralt glukostoleranstest identifierar den största andelen av patienter med diabetes. Överenstämmelsen mellan plasmaglukos fastande (FPG) eller efter glukosbelastning (2hPG) och HbA1c för patienter som screenades med diabetes var liten. Screening med enbart HbA1c skulle lämnat 83% av patienterna med diabetes oupptäckta. Enligt kriterier angivna av American Diabetes Association för FPG + HbA1c hade 90% av patienterna dysglykemi jämfört med 73% med WHO:s kriterier för glukosbelastning. Den förra proportionen uppfattas som en överskattning och den senare som mer realistisk.

Slutsats
Att tydliggöra aktuella epidemiologiska data och information över vidtagna åtgärder måste ges högsta prioritet för att skapa samsyn mellan beslutsfattare och förbättra effekten av framtida preventiva initiativ. Genom att screena för diabetes på internet med hjälp av FINDRISC kunde såväl individer som en befolkningsgrupps risk kartläggas. Även om läget har förbättrats är patienter med kranskärlssjukdom och diabetes en grupp vars handläggning ännu inte uppnår uppsatta riktlinjebaserade behandlingsmål. Ur prognostisk synvinkel är en förbättring önskvärd med hänsyn till gruppens dåliga prognos. Ett oralt glukostoleranstest har den högsta tillförlitligheten vid screening för dysglykemi hos patienter med kranskärlssjukdom.

List of Original Papers

This thesis is based on the following studies, which will be referred to by their Roman numerals (I-V).

I

Viveca Gyberg, Lars Rydén
Policymakers' perceptions of cardiovascular health in Europe
European Journal of Cardiovascular Prevention Rehabilitation
2011;18:745-753

II

Viveca Gyberg, Dan Hasson, Jaakko Tuomilehto, Lars Rydén
Measuring risk online - Feasibility of using FINDRISC in an online workplace survey
Primary Care Diabetes
2012;6:103-107

III

Viveca Gyberg, Kornelia Kotseva, Jean Dallongeville, Guy De Backer, Linda Mellbin, Lars Rydén, David Wood, Dirk De Bacquer for the EUROASPIRE Study Group
Does pharmacologic treatment in patients with established coronary artery disease and diabetes fulfil guideline recommended targets? A report from the EUROASPIRE III cross-sectional study
European Journal of Preventive Cardiology
E-published ahead of print 2014 April 1

IV

Viveca Gyberg, Dirk De Bacquer, Guy De Backer, Catriona Jennings, Kornelia Kotseva, Linda Mellbin, Oliver Schnell, Jaakko Tuomilehto, David Wood, Lars Rydén
Improved but still not satisfactory management of patients with coronary artery disease and diabetes A report from EUROASPIRE IV
Manuscript

V

Viveca Gyberg, Dirk de Bacquer, Kornelia Kotseva, Guy de Backer, Oliver Schnell, Jouko Sundvall, Jaakko Tuomilehto, David Wood, Lars Rydén
Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test and HbA1c
Manuscript

Abbreviations

2hPG	Two hour post load plasma glucose
ADA	American Diabetes Association
AMI	Acute Myocardial Infarction
CABG	Coronary Artery By-pass Graft surgery
BMI	Body Mass Index
EHHC	European Heart Health Charter
ESC	European Society of Cardiology
EUROASPIRE	EUROpean Action on Secondary and Primary prevention of coronary heart disease In order to Reduce Events
FINDRISC	The Finnish Diabetes Risk Score
FPG	Fasting Plasma Glucose
HbA1c	Glycated Hemoglobin A1c
HDL-cholesterol	High Density Lipoprotein-cholesterol
IGT	Impaired Glucose Tolerance
IFG	Impaired fasting glucose
LDL-cholesterol	Low Density Lipoprotein
OGTT	Oral Glucose Tolerance Test
PCI	Percutaneous Coronary Intervention
RAAS-blocker	Renin-Angiotensin-Aldosterone-System blocker
RPG	Random plasma glucose
UN	United Nations
WHO	World Health Organisation

INTRODUCTION

Pathophysiology of Cardiovascular Disease & Diabetes

Cardiovascular disease

Cardiovascular disease is a chronic condition commonly defined as atherosclerosis in the arteries of the heart, brain and limbs.[1] Atherosclerosis is a chronic inflammatory disorder that develops in the arterial walls over many decades as illustrated in Figure 1.[2,3] This process can be triggered by a wide range of conditions such as hyperglycaemia, hyperlipidaemia and hypertension.[2] A thickening of the arterial wall occurs due to an accumulation of low density lipoprotein-cholesterol (LDL-cholesterol) in combination with a gradually increasing accumulation of inflammatory cells, smooth muscle cells and connective tissue. This process was originally believed to be localized but is now known to be generally spread throughout the arterial tree.[2] Atherosclerosis stiffens the vessel wall and can potentially cause plaque formation, which may limit blood flow due to luminal obstruction, possibly leading to ischemia in the supplied tissues. The atherosclerotic plaque may become unstable and rupture activating platelet accumulation, which triggers thrombus formation. This may lead to an acute blockage of the artery causing a myocardial infarction if in the coronary arteries, and ischemic stroke if in the cerebral arteries.[3,4]

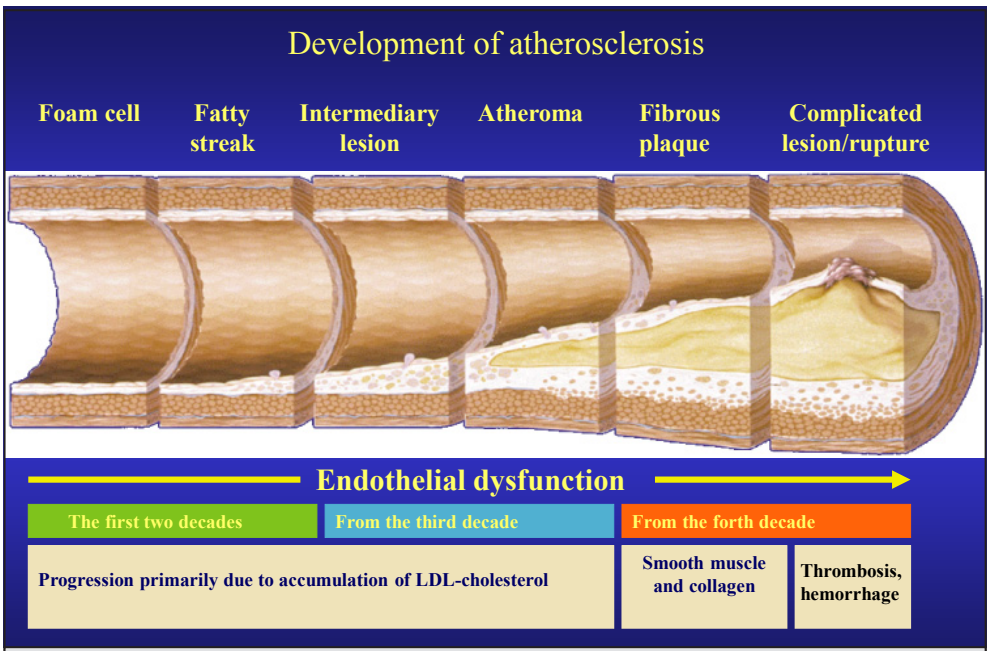


Figure 1. Development of atherosclerosis.
(By permission from Professor J Perk, who adopted it from Stary et al [3]).

Diabetes

Definition and classification

Diabetes, like cardiovascular disease is a chronic condition, and is defined by elevated blood glucose due to decreased sensitivity to and/or decreased production of insulin.[5, 6] The National Diabetes Data Group issued the first unified classification of diabetes in 1979[7] followed by the World Health Organization (WHO) in 1980[8]. The classification also includes early stages of hyperglycaemia: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), reflecting the natural history of relative or absolute insulin deficiency progressing from normoglycaemia to diabetes as presented in Figure 2.

Current diagnostic criteria (Table 1) have been issued by WHO[9, 10] and the American Diabetes Association (ADA)[11, 12]. The WHO recommendations are based on measuring both fasting plasma glucose (FPG) and two-hour post load plasma glucose (2hPG) concentrations and recommend that a standardized Oral Glucose Tolerance Test (OGTT) should be performed in the absence of overt hyperglycaemia.[13] Classification according to the ADA criteria encourages the use of glycated hemoglobin A1c (HbA1c), FPG and 2hPG in that order.[12] Both ADA and WHO approve a diabetes diagnosis based on symptoms such as polyuria together with an elevated random plasma glucose (RPG).[12, 14]

The thresholds for diabetes for all methods are primarily determined by the cut-off where the prevalence of diabetic retinopathy, a specific complication of hyperglycaemia, starts to increase.[6] Although macrovascular diseases such as coronary artery disease and stroke are major causes of death in patients with type 2 diabetes and individuals with IGT, the risk for future macrovascular disease is not considered in this diagnostic classification.

The diagnostic criteria adopted by WHO and ADA for prediabetes are similar for IGT but differ for IFG. Only ADA uses high risk HbA1c as seen in Table 1. The lower ADA threshold for IFG and the use of high risk HbA1c is not adopted by WHO. This is due to a belief in lack of evidence of benefits in terms of reducing progression to diabetes and cardiovascular events.[10, 13]

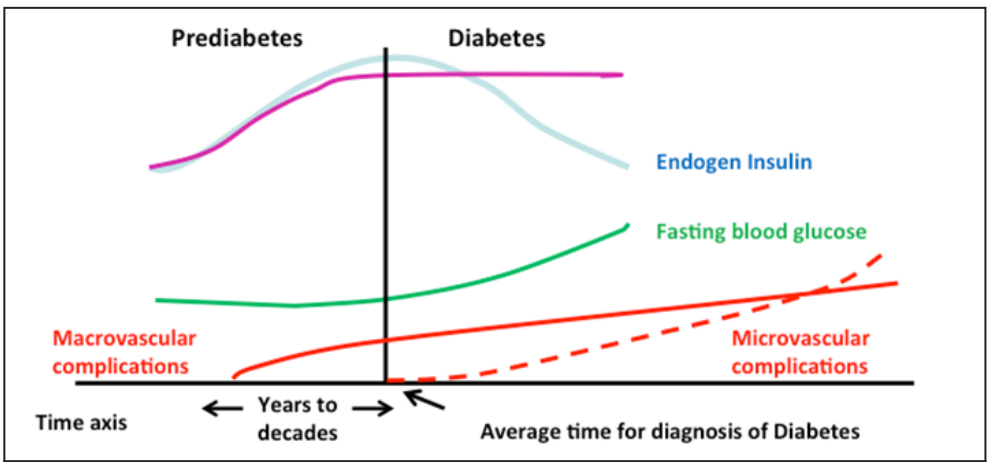


Figure 2. Development of diabetes mellitus type 2.
(By permission from Laakkso et al [15]).

Table 1. Comparison of the WHO[10, 14] and ADA[12] diagnostic criteria for dysglycaemia. All tests have to be repeated twice except RPG when symptoms are present. **Bold** indicates preferred tests.		
Diagnose/ measurement	**WHO[14, 10]**	**ADA[12]**
Diabetes		
HbA1c	≥6.5% (≥48 mmol/mol)	**≥6.5% (≥48 mmol/mol)**
FPG	**≥7.0 mmol/L (≥126 mg/dL)**	**≥7.0 mmol/L (≥126 mg/dL)**
2hPG	**≥11.1 mmol/L (≥200 mg/dL)**	≥11.1 mmol/L (≥200 mg/dL)
RPG	Symptoms + ≥11.1 mmol/L (≥200 mg/dL)	Symptoms + ≥11.1 mmol/L (≥200 mg/dL)
IGT		
FPG	<7.0 mmol/L (<126 mg/dL)	<7.0 mmol/L (<126 mg/dL)
2hPG	≥7.8 -11.0 mmol/L (≥140-199 mg/dL)	≥7.8 -11.0 mmol/L (≥140-199 mg/dL)
IFG		
FPG	6.1-6.9 mmol/L (110-125 mg/dL)	5.6-6.9 mmol/L (100-125 mg/dL)
2hPG	<7.8 mmol/L (<140 mg/dL)	<7.8 mmol/L (<140 mg/dL)
High Risk HbA1c	-	5.7-6.4% (39-47 mmol/mol)

Categories

Diabetes may be classified as belonging to one of four main etiological categories: type 1, type 2, gestational and other specific types [5, 7, 16]

Diabetes type 1 is an autoimmune disorder affecting the insulin producing β-cells of the pancreas. Usually it has an abrupt onset with thirst, polyuria and weight loss. The future survival depends on insulin treatment.[16, 17] Diabetes type 1 most frequently afflicts young individuals but may occur at all stages of life.[17] A subgroup of diabetes type 1 named latent autoimmune diabetes mellitus in adults (LADA) has a slow onset over a couple of years in adulthood.[17]

Diabetes type 2 is in its early stages characterized by an increased insulin resistance, but as the disease progresses insulin secretion becomes compromised as well.[16] The onset is often slow and the condition can remain undiagnosed for many years. This type of diabetes, which usually occurs in adulthood, is strongly associated with overweight and low physical activity.[16] It often coexists with other metabolic malfunctions such as high blood pressure and hyperlipidaemia.[18] This is the most common form of diabetes, comprising 85-95% of all diabetes in high-income countries and likely even more in the rest of the world.[16, 17] Diabetes type 2 is in focus of this thesis and will be referred to as diabetes.

Gestational diabetes is caused by a combination of increased resistance to- and demand for insulin that develops during pregnancy. Dysglycaemia is estimated to have been present in 17% of all live births globally during 2013.[16] It usually vanishes after delivery but about 20% of women with this form of diabetes progress to type 2 diabetes during the following decades.[16]

Other specific types of diabetes include genetic mutations leading to rare forms of diabetes such as maturity-onset diabetes in the young and secondary diabetes due to drugs or pancreatic disease.[17]

Prediabetes is a condition characterised by glucose values ranging between normal levels and what has been defined as the cut off for diabetes. People with prediabetes are at a

high risk for future type 2 diabetes and this condition is also linked to an enhanced risk for cardiovascular disease.[16] It is estimated that the annual proportion of people with IGT that progress to diabetes is 5-10% and that 90% have diabetes after 20 years without intervention.[19, 20]

Complications to diabetes

Diabetes can if uncontrolled lead to serious health problems due to microvascular complications such as retinopathy (causing blindness), nephropathy (causing renal failure) and neuropathy (causing autonomic dysfunction and paraesthesia). The most common cause of death in patients with diabetes is, however, cardiovascular disease.[16, 17] While manifest microvascular complications often develop during one or several decades with elevated blood glucose, the risk for cardiovascular disease is often present already before the diagnosis of diabetes is made as illustrated in Figure 2. Potential reasons are further elaborated on below.

The link between cardiovascular disease and diabetes

Taken together cardiovascular disease and diabetes account for more than half of the global mortality.[21] These two conditions are closely interlinked with at least half of all patients with diabetes dying, often prematurely, of cardiovascular disease.[22, 23] Furthermore, 30% of patients with coronary artery disease have diabetes and an additional 35-40% have prediabetes leaving only about one third with a normal glucose metabolism.[23-25] Moreover, patients with a combination of coronary artery disease and diabetes have a two times higher mortality than those without diabetes, making them a group at particularly high risk for a recurrent cardiovascular event or death.[26, 27]

The reason for the increased risk for cardiovascular disease in patients with diabetes is not fully understood, but diabetes has been proven to stimulate the development of multiple disadvantageous changes in the arterial wall.[15] It involves endothelial dysfunction, increased inflammatory activation, enhanced capability for thrombus development and decreased thrombolytic ability, all factors that lead to accelerated artheriosclerosis.[18] Insulin resistance is known to make the lipid distribution unfavourable, which increases lipid accumulation in the vessel walls. In addition LDL-cholesterol in patients with diabetes have an enhanced propensity to oxidize, leading to an inflammatory response and inhibition of production of vasodilatory nitric oxide.[15] Furthermore, vasodilatation is inhibited by increased presence of vasoconstriction due to a disproportionate dominance of the sympathetic nervous system. This relates to a hampered vagal nerve activity by autonomic dysfunction, which also contributes to a somewhat high heart rate and blunted diurnal variation of blood pressure and heart rate.[15] In addition, vasoconstrictors, such as endothelin-I and angiotensin II, increase.[15] High glucose concentration on its own is believed to damage the vascular wall perhaps by inducing an intensified oxidative stress that becomes a substrate for endothelial dysfunction.[18] Even though there is a continuous relationship between glucose levels and cardiovascular disease very few trials that attempted to decrease cardiovascular outcomes by means of strict glycaemic control have managed to do so.[28] Epigenetic changes are also believed to prompt processes causing the early rise in cardiovascular risk that also persist with adequate risk factor control, this is often referred to as glycaemic memory.[29] As of today, and beyond lifestyle adjustments, control of dyslipidaemia and blood pressure are the most effective treatments to prevent cardiovascular disease in individuals with diabetes.[30]

Epidemiology of Cardiovascular Disease and Diabetes

An epidemiological transition

During the last century there has been an epidemiological transition from morbidity and mortality dominated by infections and malnutritional conditions towards lifestyle oriented illness.[31] This first epidemiological transition, is often referred to as a shift from communicable to non-communicable diseases. The transition started in high- and middle-income countries and is now on going in low income parts of the world. Today non-communicable diseases are responsible for approximately 65% of global mortality.[21, 31] Out of these deaths cardiovascular disease account for 48% and diabetes specific causes 3,5%.[21] This transition has been made possible due to remarkable improvements in living conditions, initiatives to battle hunger, improved management of infections and better maternal care.[31] This change has led to a rise in global life expectancy from 48 years in 1950-1955 to 68 years in 2005-2010.[31] In areas with the longest life expectancy a current decline of premature deaths of non-communicable disease can be seen, which contributes to an even longer life expectancy. The prolongation of life is considered a second epidemiological transition.[31] This indicates what health care challenges lies ahead of us as more countries enter the second transition.

Changing risk factor patterns

An older global population is in itself an important risk factor for both cardiovascular disease and diabetes but cannot solely explain their increasing prevalence.[16, 31, 32] The proportions of causes of death divided by age groups are presented in Figure 3. Societal changes such as industrialisation, urbanization, the IT-revolution and the expanding use

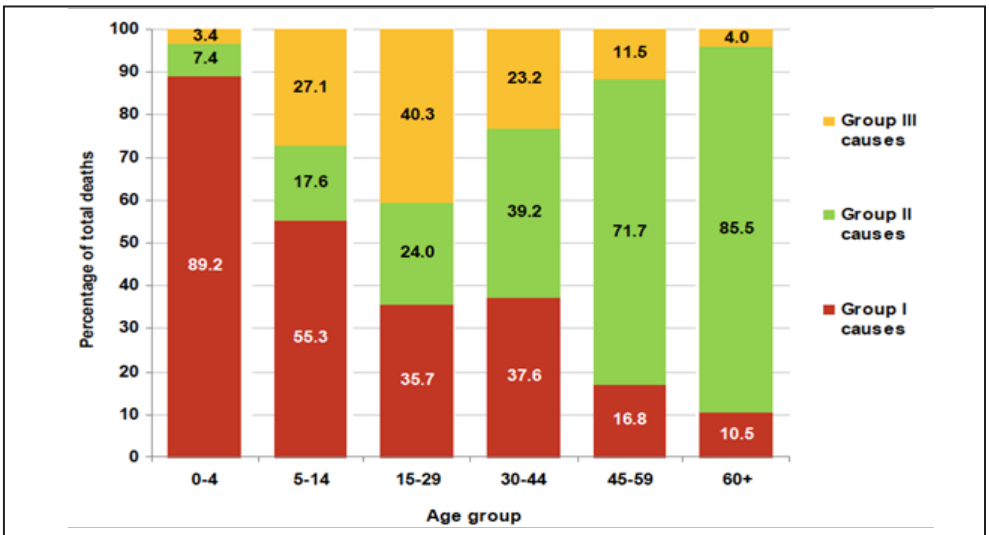


Figure 3. Distribution of causes of death by age groups. Group I includes: communicable diseases as well as maternal, perinatal and nutritional conditions, Group II: non-communicable diseases, Group III: death resulting from intentional and unintentional injuries.

(From: Changing Levels and Trends in Mortality: the role of patterns of death by cause (United Nations publication, ST/ESA/SER.A/318). United Nations, Department of Economic and Social Affairs, Population Division, © 2012 United Nations. Reprinted with the permission of the United Nations).

of processed (fast) food have increased exposure to unhealthy diet, physical inactivity and tobacco use.[21] This lifestyle has led to an increase of risk factors such as overweight and obesity, hypertension, hyperlipidaemia and abnormal glucose metabolism.[21] Risk factors are more likely to accumulate with age, and if several risk factors are present the risk for cardiovascular disease is multiplied.[31,32] Although cardiovascular disease and diabetes are often diseases of the elderly it should be underlined that cardiovascular illness causes 31% of deaths in men and 26% in women before the age of 65 in Europe.[33] Moreover about 50% of the people with diabetes are 40-59 years old[16] and half of the diabetes-related mortality occurs before the age of 60 years.[16]

Risk factors for cardiovascular disease

INTERHEART, a case-control study of about 14 000 people with acute myocardial infarction and a similar number of controls from all continents, showed that more than 90% of all events could be explained by nine factors, the same in men and women: abnormal blood lipids, smoking, hypertension, diabetes, abdominal obesity, poor psychosocial conditions and lack of regular physical activity. In contrast regular intake of fruit and vegetables and modest alcohol consumption decreased the risk.[32] Genetic susceptibilities to myocardial infarction was also analysed but could only explain one additional per cent of the population attributable risk when added to the nine risk factors.[32]

Analyses applying the by Capewell et al[34] introduced IMPACT model, combining data on time trends in risk factor patterns with the effect of medical and surgical treatment, in populations with increasing or decreasing cardiovascular mortality underline the importance of lifestyle changes.[35, 36] In the Chinese capital Beijing cardiovascular mortality increased from 1984 to 1999 by 50% in men and 27% in women primarily due to an increase in the prevalence of high cholesterol and diabetes in the population (Figure 4).[35] In USA a declining age-standardised cardiovascular mortality is attributed to a lowering of many risk factors in the population (Figure 5).[36] Similar results have been obtained in other countries (Figure 6).[36]

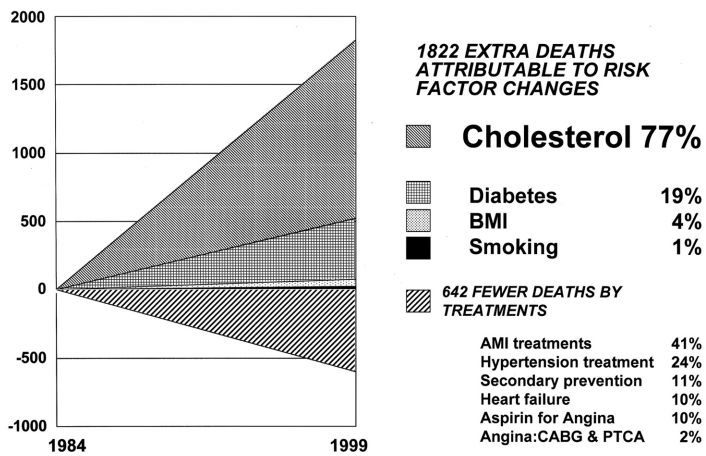


Figure 4. Coronary Heart Disease mortality trends in Beijing 1984 to 1999: additional deaths attributable to risk factor changes and deaths prevented or postponed by treatments.
(By permission from Critchley et al [35]).

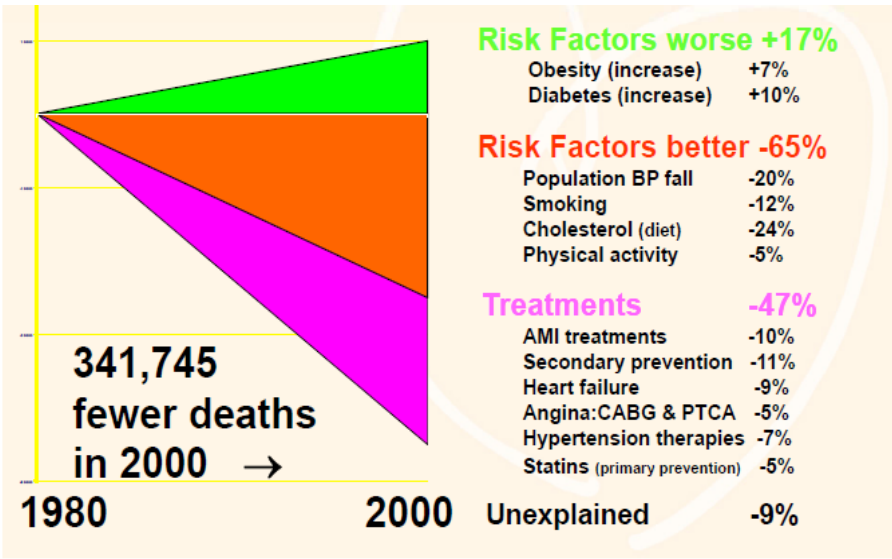


Figure 5. Coronary Heart Disease mortality trends in United States of America 1980-2000.
(By permission from Professor L Rydén, who adopted it from Ford et al [36]).

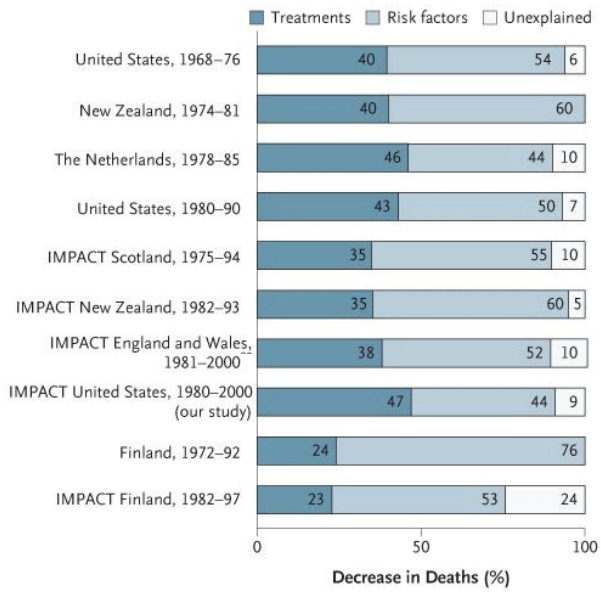


Figure 6. Percentage of the decrease in deaths from coronary heart disease attributed to treatments and risk-factor changes in some populations. In the New Zealand study, 1974 to 1981, the analysis focused on specific treatments and inferred contribution from risk factors. In the Finnish study, 1972 to 1992, the analysis focused on risk factors and inferred contribution from treatments.
(By permission from Ford et al[36]).

Risk factors for diabetes

The American Nurses' Health Study recruited almost 85 000 female nurses free from cardiovascular disease and diabetes and followed them for 16 years.[37] Individuals with the following five lifestyle traits - normal weight, a healthy diet rich in cereal fibre and polyunsaturated fat, regular physical activity, moderate alcohol consumption and no smoking - had a 90% lower incidence in diabetes than those without these traits.[37] Notably these factors were similar to those brought forward by the INTERHEART study for acute myocardial infarction.[32, 37] Even if several risk factors interact, obesity is considered the strongest for the development of diabetes and is believed to explain more than 80% of all cases.[19, 37] A similar risk pattern for diabetes has been observed in European and Asian populations.[19]

In USA overweight and obesity have increased rapidly the past three decades, presently affecting 70% of the adult population, thereby inducing a dramatic change of the risk factor pattern.[38] As can be expected, there has been an parallel increase in the prevalence of diabetes. Between the age of 20-79 there is currently 24 million people diagnosed with diabetes comprising around 9% of the adult American population.[16] Today the lifetime chance to develop diabetes in USA is 30-40% posing a great threat to public health.[38] Sadly the obesity epidemic has caused an increase of childhood diabetes leading to complications e.g. kidney failure in early ages.[39] All together obesity and its associated diseases, such as diabetes and cardiovascular disease, constitute such a big threat to public health that life expectancy is expected to decrease for the first time in centuries in USA if the epidemic is not stopped.[2, 40] In this respect recent reports that obesity has started to level out are encouraging for USA and Europe.[41] Unfortunately, reports indicate that there is a rapid increase of obesity in Asia and Africa bringing diabetes in its wake, calling for preventive initiatives.[35, 42, 43]

Changes in the risk profile of a population

As illustrated, the risk profile of a population can change rapidly over time when new trends in lifestyle become popular.[44] This is both encouraging and worrisome since it gives hope to preventive efforts, but should serve as an admonition for the changes caused by the increasingly common sedentary lifestyle. Given the slow adaptation of the human genome over thousands of years, genetic factors will have a miniscule impact on the prevalence of cardiovascular disease and diabetes compared to the fast changes in the lifestyle of a society.[45] This underlines the importance of keeping up to date with epidemiological changes and their reasons when working with prevention.[32 45, 46]

Regional differences

As has been empasised the risk factors for cardiovascular disease and diabetes are similar and seemingly universal[19, 32]. This does not contradict regional difference in disease burden.[21, 33] Although these conditions are more common in high income countries the age standardised mortality is higher in low and middle income countries.[21] The countries with the most pronounced burden are those experiencing a 'double burden' of disease, i.e. still not free from communicable diseases and malnutrition but at the same time suffering an increasing morbidity and mortality related to non-communicable diseases, due to the adoption of a western lifestyle.[31] It is unfortunate that the healthcare systems in these countries often are incapable of coping with the 'new' diseases.[21] Different

populations and regions of the world have to focus on their specific challenges. On a positive note countries starting their epidemiological transition towards predominance of non-communicable disease later than others often move faster than those originally challenged.[31] A summary of the disease burden and life expectancy of the world's regions is summarized in Figure 7.

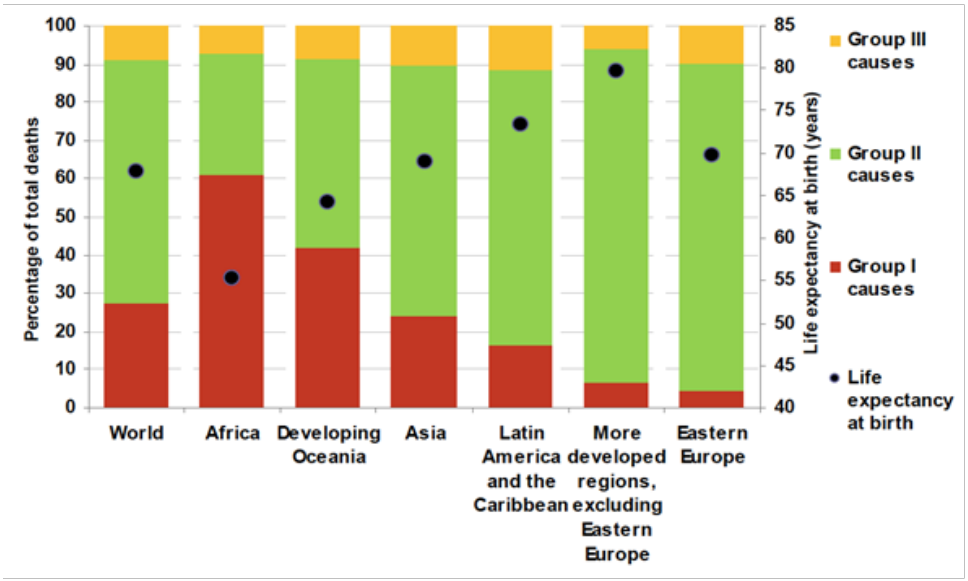


Figure 7. Percentage distribution of deaths by group of causes in 2008 and life expectancy at birth 2005-2010 for the world and in selected regions Group I includes: communicable diseases as well as maternal, perinatal and nutritional conditions, Group II: non-communicable diseases, Group III: death resulting from intentional and unintentional injuries.
(From: Changing Levels and Trends in Mortality: the role of patterns of death by cause (United Nations publication, ST/ESA/SER.A/318). United Nations, Department of Economic and Social Affairs, Population Division, © 2012 United Nations. Reprinted with the permission of the United Nations).

European health challenges

In Europe cardiovascular disease kills four million people each year which represents 50% of the regional mortality[33] putting it in focus for attempts to improve the health in this region.[31] The estimated prevalence of diabetes is 8.5%, affecting 56 million individuals across Europe, ranging from 15% in Turkey to 2% in Azerbaijan.[16] It is important to remember that even in Europe, a region which is well-off compared to others, there is a large variation between countries.[33] Despite a recent decline[33], populations from Eastern Europe have a higher mortality in cardiovascular disease than those living in the Northern and Western parts.[31, 33] This east-western gradient is explained by a multitude of factors including smoking habits, a diet high in saturated fat and low in fruit and vegetables and low physical activity, factors that at least partly relate to the socioeconomic climate.[47]

Prevention

Definitions

In medicine, prevention refers to all actions taken to prevent disease or disability at both the individual, group and societal levels.[48] The main objective of prevention is to reduce morbidity, improve quality of life and increase longevity.[18] The argument to encourage prevention is simply the assumption that '*it is better to be healthy than ill or dead*'.[46]

Preventive efforts can be instituted through all stages in life but is commonly divided into three levels more or less linked to each other:[48]

Primordial prevention is the prevention of the development of risk factors in healthy individuals and involves gaining healthy habits from birth throughout life.

Primary prevention comprises interventions designed to modify adverse levels of risk factors once present. Examples are smoking cessation, stimulating consumption of healthy food products and encouraging physical activity.

Secondary prevention comprises interventions designed to treat an already established disease to limit recurrent events and premature mortality. Examples are lipid lowering treatment and rehabilitation programs after a myocardial infarction.

Theoretical aspects

Prevention may be directed towards high-risk individuals or to entire populations, a distinction that is applied worldwide in preventive initiatives, guidelines and reports.[18, 21, 46, 49-51] High-risk and population approaches are illustrated in Figure 8. The high-risk prevention targets subgroups of people, who have a higher than average risk to develop a disease, such as smokers, the obese or post myocardial infarction patients.[46] It has been claimed that this is the most efficient form of prevention since it targets those who need help the most.[18] Furthermore the humanitarian aspect, that we have an

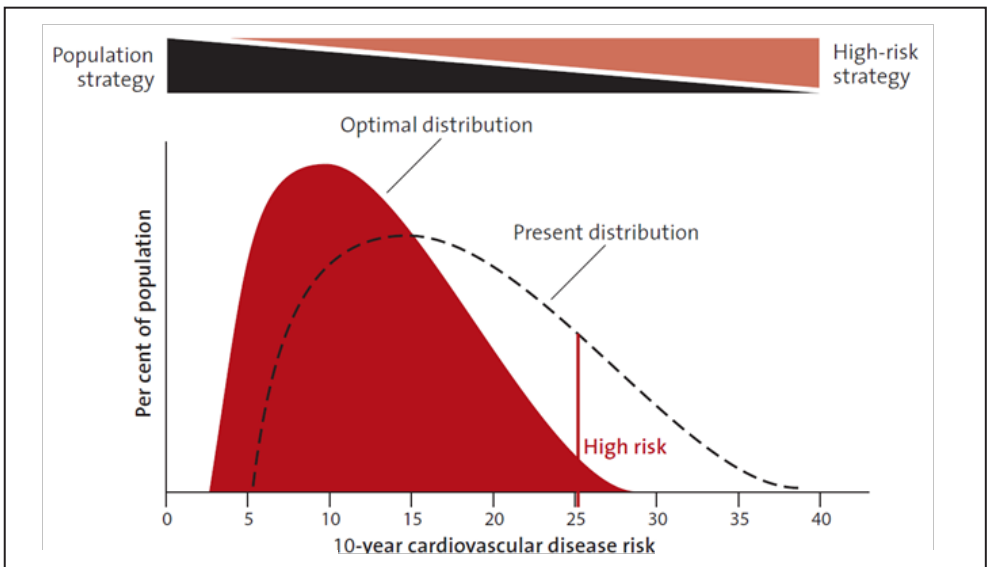


Figure 8. Population and high-risk strategy for prevention. (By permission from Professor L Rydén)

obligation to take care of individuals who are unhealthy since it could happen to anyone of us, has been brought forward.[46] A high-risk approach will improve morbidity and often mortality of these individuals but has a limited potential to change the population based morbidity and mortality pattern due to the relatively limited number of people addressed.

In contrast the population approach targets risk factors in an entire population regardless of individual risk profiles.[46] A pioneer in the field of prevention was Geoffrey Rose who emphasised that the high-risk individuals of a society are always dependent on the mean characteristics of a society in general.[46] This opinion is based on the assumption that an individual cannot be separated from the environment, social structures and culture in which they live.[45, 48, 52] Rose argues that even a modest lowering of a risk factor on the population level, e.g. a few mm Hg of blood pressure, will be followed by a substantial decrease in future illness due to the high number of people that will slightly decrease their risk factor level.[46] This theory gains further support by changes seen in the prevalence of cardiovascular disease and diabetes in USA[22,36,37] and China[35] as presented in Figure 4 and 5. Rose argued that preventive initiatives on a population level should always include both a population-wide approach, in order to target the environmental causes of illness, and a high-risk approach to help those in greatest need.[46]

Population-based prevention

As already emphasised, interventions aiming at the general population are considered to have the largest potential to make a major impact on the prevalence of non-communicable diseases.[21] Since atherosclerosis starts as early as during the teenage years primordial prevention should play an important role in preventing such disease.[48] Regarding cardiovascular disease and diabetes the evidence supporting primordial prevention is less conclusive than for primary- and secondary preventive initiatives.[48] The reason for this is that it is difficult from a methodological point of view to design trials in a large population. The selection of a control group is for example difficult considering the long follow-up period needed and the demands to completely avoid potential confounding factors. Interventions aiming at risk factor reduction such as lowering salt consumption and eliminating tobacco use as well as promoting a healthy diet and physical activity are, however, measures believed to prevent future disease in a population.[48] This kind of strategy often requires changing the cultural, social and physical environment to encourage healthy behaviour.[48] For a population approach to work, different stakeholders, among them politicians, corporations and non-governmental organisations, need to work together towards a common target.[48, 53]

A study investigating British middle-aged men estimated that mortality from cardiovascular disease may be reduced by 45% by reducing their average blood pressure and cholesterol levels by 10%.[51] As a comparison treating individuals at 30% risk of acquiring cardiovascular disease in the upcoming ten years (6% of the population) with a combination of statins, ß-blockers, ACE-inhibitors and aspirin would reduce mortality by 11% in the studied population.[51] It would have been possible to increase the mortality reduction to 34% if the 10-year risk threshold was set at 20% or to a 49% reduction if the threshold was reduced to 15%. At these latter risk levels, 25% and 50% respectively of the population without any symptoms of cardiovascular disease would be put on a range of cardioprotective drugs.[51]

A successful example of prevention by means of legislation at a population level are the presently widely spread smoking bans, limiting one of the strongest risk factors of cardiovascular disease. A systematic review and a meta-analysis showed that AMI declined about 17%, with the greatest effect in younger age groups and non smokers, adding further proof to the large impact of wide-spread health policies.[54]

The North Karelia Project

The Finnish North Karelia Project initiated in 1972 is the first example of the strength of a community-based prevention project.[53] It was launched in response to a local petition asking for urgent and effective help to reduce the world leading cardiovascular disease mortality in this area. The project was executed through cooperation by the health care services, schools, non-governmental organisations, media campaigns, supermarkets, food industry and politicians with the shared goal to reduce risk factors for cardiovascular disease by changing the lifestyle of the population. A comprehensive evaluation of the results was part of the initiative, which soon became an important model for national and international preventive programs. The North Karelia Project revealed that a major decline in cardiovascular disease mortality, indeed of an extent predicted before the project started, could be obtained by decreasing cardiovascular risk factors essentially by non-pharmacological tools as presented in Figure 9. During the project period age-adjusted mortality in coronary artery disease declined more in North Karelia than anywhere else in Finland amounting to a reduction in mortality from coronary heart disease by 80% in men and 83% in women until 2006.[53] Indeed life expectancy at the time of birth increased from 64 to 75 years in men and from 72 to 81 years in women thereby approaching the national average in Finland.[53, 55]

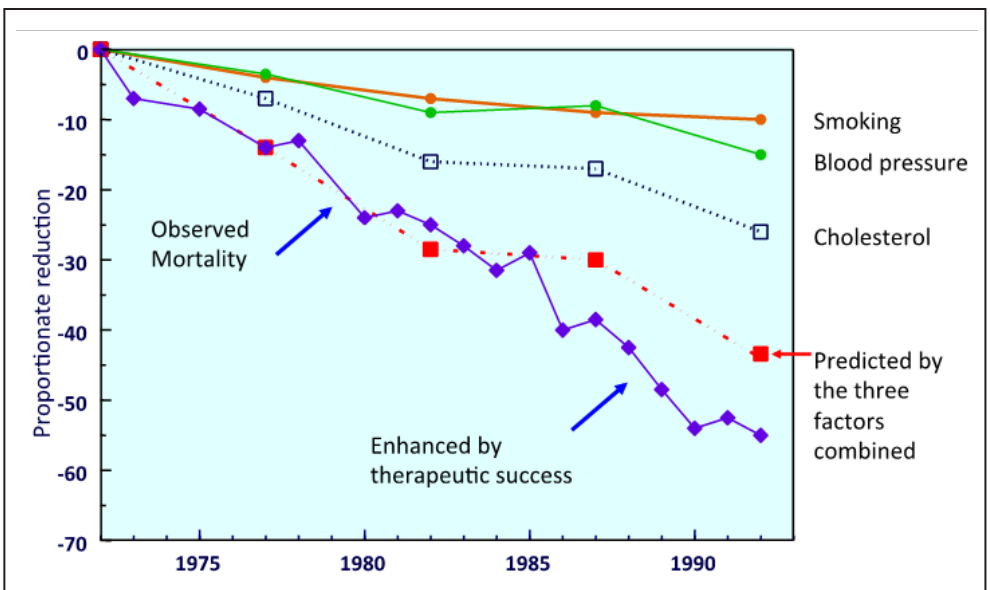


Figure 9. Decline in risk factors (smoking, blood pressure and cholesterol) and mortality in the North Karelia Project.
(By permission from Varitainen et al[55])

Prevention of high-risk individuals

Primary and secondary preventive programmes for patients with cardiovascular disease and diabetes usually includes smoking cessation, healthy food choices, regular physical activity and control of hypertension, hyperlipidaemia and dysglycaemia.[17, 49] A target-driven multifactorial treatment has the potential to improve the future prognosis in patients.[17, 30, 49] Interventions in individuals with risk factors present for diabetes have been shown to reduce the relative risk to develop diabetes between 28-67% and also to improve the cardiovascular risk profile.[17, 56-61] The Finnish Diabetes Prevention Program randomized middle-aged men and women with IGT to a four years long prevention program aiming at a modest weight reduction (5%), some dietary modifications and increased physical activity (4h per week or more) and were able to show a sustained diabetes risk reduction for thirteen years despite cessation of the program.[59]
In 1986 the prospective and randomised Da Qing Diabetes Prevention Study people with impaired glucose tolerance (n=439) were subjected to a six years long intervention program aiming at exercise and diet. When they were compared to persons serving as a control group (n=138) after 23 years of follow-up there was a reduction in the incidence of diabetes, (Hazard Ratio 0.45) and a lower cardiovascular (Hazard Ratio 0.71) and all-cause mortality (Hazard Ratio 0.59) in the intervention group.[20] The mechanism responsible for the decreased risk was believed to be the delayed onset of diabetes achieved by the program.[20] This highlights that the process leading to cardiovascular disease takes decades but that this process can be changed by a lifestyle intervention program.

While both primary and secondary prevention is based on non-pharmacological tools, secondary prevention always, and primary prevention sometimes, involves pharmacological treatment by drugs such as aspirin, β -blockers, Angiotensin-Converting Enzyme inhibitors/Angiotensin Receptor Blockers, statins and glucose-lowering drugs. A summary of the relative risk reduction achieved by different preventive interventions after myocardial infarction is presented in Table 2. In patients with the combination of diabetes and coronary artery disease the prognosis can be improved to a level almost equivalent to that in patients without diabetes by means of a comprehensive pharmacologic treatment.[62, 63] Given their higher absolute risk, the number needed to treat to avoid one cardiovascular event is substantially lower in patients with than in those without diabetes.[62]

Table 2. Relative lowering of mortality by institution of preventive interventions in patients with established coronary artery disease.

Intervention	Lowers mortality by (RR)	Reference
Smoking cessation + healthy diet + exercise*	54%	*Chow et al. Circulation 2010*[64]
Smoking cessation	36%	*Critchley et al. JAMA 2003*[65]
Statin	31%	*Wei et al. BMJ 2005*[66]
Stress management**	28%	*Gulliksen et al. Arch Intern Med. 2011*[67]
ACE/ARB	27%	*Hennekens et al NEJM 1996*[68]
Exercise	26%	*Taylor et al. Am J Med 2004*[69]
β-blockers	23%	*Freemantle et al. BMJ 1999*[70]
Aspirin	15%	*Collaborative meta-analysis. BMJ 2002*[71]

** Adherence to smoking abstinence, dietary advice and exercise advice.*
*** Non-significant lowering of mortality but a significant lowering of a recurrent myocardial infarction by 48%.*

Development and implementation of practice guidelines

Upon the initiative of the European Society of Cardiology (ESC) and in collaboration with other groups of European health care professionals, among them the European Atherosclerotic Society, the European Hypertension Society, The European Heart Net Work and the European Association for the Study of Diabetes, the first issue of evidence based guidelines for cardiovascular disease prevention in clinical practice was published in 1994. These guidelines have been updated regularly with the most recent version published in 2013.[17, 49] In parallel, and under the auspices of the European Society of Cardiology, the EUROASPIRE (EUROpean Action on Secondary and Primary prevention of coronary heart disease In order to Reduce Events) surveys were initiated to study the practice of prevention across Europe. Despite some improvement over time, EUROASPIRE I, II, III demonstrated a surprisingly high prevalence of unhealthy lifestyles, an inadequate use of drug therapies and an inability to achieve guideline recommended treatment targets for blood pressure and lipid control in patients with established cardiovascular disease and in people at high risk of such disease.[72] Moreover there was a wide practice variation between countries.[73] This ESC initiative has been supplemented by educational efforts and the release of supporting products e.g. pocket guidelines, educational kits, web-based questions with links to the guidelines and translations of the guidelines to most European languages. The intention is to work towards an improved patient management by bringing new knowledge and gain experience together and to evaluate the outcome as illustrated in Figure 10.

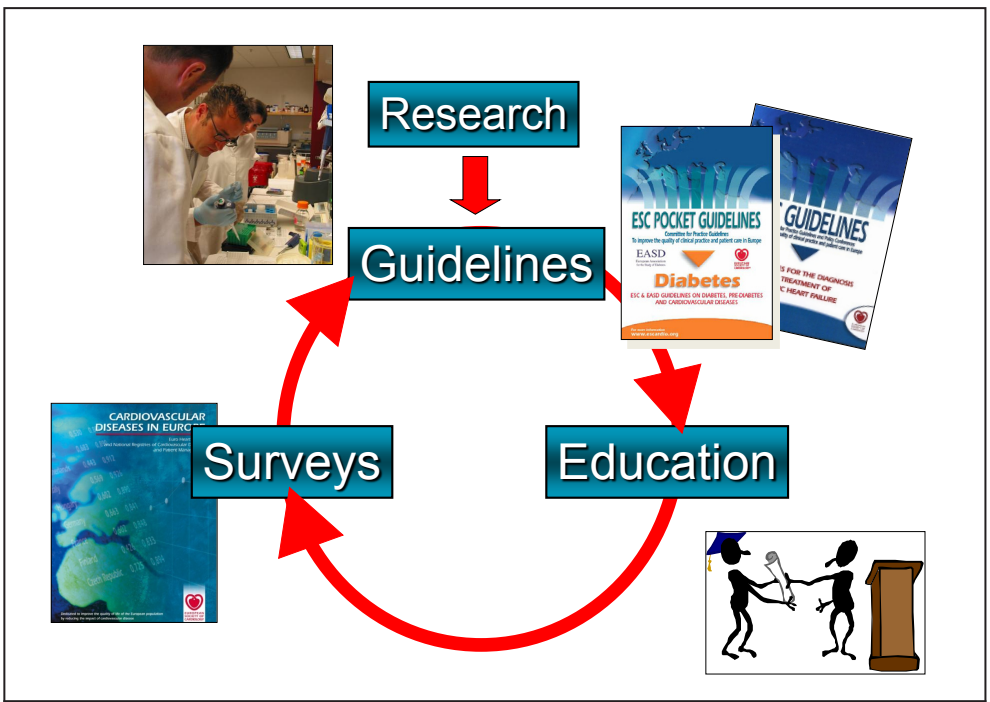


Figure 10. Research, implementation and surveys evaluating real world practice all contribute development of new guidelines. (By permission from Professor L Rydén)

Screening for people at risk

Screening for diabetes in a general population

A main concern is that many people with diabetes or its pre-states are unrecognized. The International Federation for Diabetes made a global estimate that as many as 175 million people with diabetes are unaware of their condition. In addition 316 million (6.9% of the adult population) are believed to have IGT.[16, 74] This means that there is an emerging need to identify these people, who may benefit from preventive initiatives if discovered, and several risk scores have been developed to help identify individuals with elevated risk for diabetes as well as coronary artery disease.[75-78]

The Finnish Diabetes Risk Score (FINDRISC) was created as a feasible way of identifying people at risk for diabetes the upcoming 10 years (Figure 11). According to a review of 145 risk scores, seven were brought forward as feasible in clinical or public health practice and FINDRISC was one of them.[78] A validation review from 2014 confirmed the discriminatory power of the FINDRISC-questionnaire in a European setting.[79] It is based on eight simple questions concerning age, BMI, waist circumference, intake of fruit and vegetables, physical activity, high blood pressure, history of high glucose value and family history of diabetes that in combination provides an accurate assessment of the risk of developing diabetes the upcoming ten years. FINDRISC also provides a good prediction of the risk to develop cardiovascular disease.[80] The risk score (points: 0-26) allocates the responding person to one of five risk groups with a sensitivity (that a person developing diabetes is identified as such) of 78%, a specificity (that a person not developing diabetes is identified as such) of 77% and a predictive value of a negative test of 99%.[77, 80] The FINDRISC, which was developed in a Finnish population, has been tested and found accurate in identifying individuals at risk for diabetes and/or cardiovascular disease not only in Finland but in several other countries e.g. Germany, Sweden, Spain, Greece, Iran, Turkey, the Philippines, Hungary, Mexico, Italy, Norway and the Netherlands.[77, 81-92] The simplicity of the questionnaire makes it possible to screen individuals and to initiate primary prevention in those presenting with high risk. The test in it self also provides information on important factors and thus serves as an intervention. It does also provide a potential of early diagnosis since those presenting with high risk are recommended a laboratory-based evaluation of their glycaemic state.

Screening for dysglycaemia in patients with coronary artery disease

Considering the serious prognostic implication of dysglycaemia in the presence of coronary artery disease it is of great importance to identify such patients. Still attempts to diagnose dysglycaemia are often neglected.[24] In asymptomatic patients three diagnostic tests are recommended, FPG, 2hPG and HbA1c, to identify dysglycaemia as presented in Table 1.[10, 17, 93] Current guidelines endorse the use of all three.[10, 14, 17, 93, 94] There is, however, an ongoing debate on which test is to be preferred. In brief, the objections to the OGTT are mainly focusing on the time (2 hours) needed to perform the test and its presumed lack of reproducibility. A low sensitivity to detect diabetes and a, compared to the 2hPG, limited ability to predict future cardiovascular events are objections to the use of FPG and HbA1c only.[95, 96] Lately the interest in replacing the OGTT, as recommended by European guidelines on the management of diabetes, prediabetes and cardiovascular disease[17], with HbA1c alone or in combination with FPG has increased.[97, 98]

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

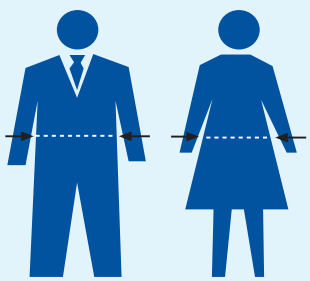
2. Body-mass index

(See reverse of form)

0 p. Lower than 25 kg/m^2
1 p. 25–30 kg/m^2
3 p. Higher than 30 kg/m^2

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 medication for high blood pressure on regular basis?

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

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki, and Jaana Lindström, MFS, National Public Health Institute.

Figure 11. The Finnish Diabetes Risk Score, continuing on next page.
(By permission from Professor J Tuomilehto).

Finnish Diabetes Association

WHAT CAN YOU DO TO LOWER YOUR RISK OF DEVELOPING TYPE 2 DIABETES?

You can't do anything about your age or your genetic predisposition. On the other hand, the rest of the factors predisposing to diabetes, such as overweightness, abdominal obesity, sedentary lifestyle, eating habits and smoking, are up to you. Your lifestyle choices can completely prevent type 2 diabetes or at least delay its onset until a much greater age.

If there is diabetes in your family, you should be careful not to put on weight over the years. Growth of the waistline, in particular, increases the risk of diabetes, whereas regular moderate physical activity will lower the risk. You should also pay attention to your diet: take care to eat plenty of fibre-rich cereal products and vegetables every day. Omit excess hard fats from your diet and favour soft vegetable fats.

Early stages of type 2 diabetes seldom cause any symptoms. If you scored 12–14 points in the Risk Test, you would be well advised to seriously consider your physical activity and eating habits and pay attention to your weight, to prevent yourself from developing diabetes. Please contact a public-health nurse or your own doctor for further guidance and tests.

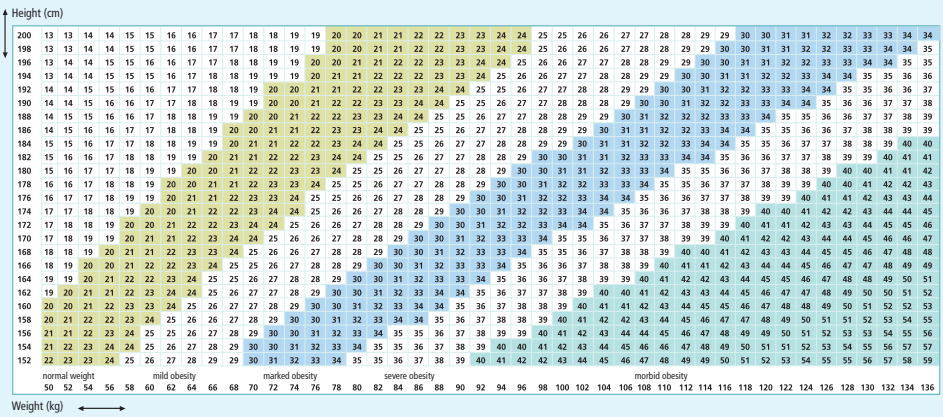
If you scored 15 points or more in the Risk Test, you should have your blood glucose measured (both fasting value and value after a dose of glucose or a meal) to determine if you have diabetes without symptoms.

BODY-MASS INDEX

The body-mass index is used to assess whether a person is normal weight or not. The index is calculated by dividing body weight (kg) by the square of body height (m). For example, if your height is 165 cm and your weight 70 kg, your body-mass index will be 70/(1.65 x 1.65), or 25.7.

If your body-mass index is 25–30, you will benefit from losing weight; at least you should take care that your weight doesn't increase beyond this. If your body-mass index is higher than 30, the adverse health effects of obesity will start to show, and it will be essential to lose weight.

BODY-MASS INDEX CHART



For instance the National Institute for Health and Care Excellence guideline from the United Kingdom discourages from the use of an OGTT in patients with acute coronary syndromes with normal FPG and HbA1c.[98] The ADA recently emphasised the lack of concordance between the different diagnostic methods and concluded that "Further research is needed to better characterise patients whose glycaemic status might be categorized differently by two different tests (e.g. FPG and HbA1c) obtained in close temporal approximation".[93]

Ethical considerations of estimating risk

The preventive paradox and the risk of risk awareness

Preventive measures applied on a population level may force people to change behaviour in order to decrease morbidity in a few.[46] This is what Geoffrey Rose calls the preventive paradox: *'a preventive measure that brings large benefits to the community offers little to each participating individual'*.[46] Furthermore, even if the estimation of risk is based on the best available data it is not the equivalent to the truth.[44, 99] This means that the risk may be both over- and underestimated. Obtained information on high risk may cause anxiety and stress in an individual - sometimes a disease in itself.[99] On the other hand, if the risk is erroneously estimated as low, an individual might take comfort in the already existing lifestyle not being able to prevent a potential deadly condition. The risk of a population might also be misclassified since the behaviour of a society changes over time making a once valid test inaccurate. This has been seen for SCORE, a risk score estimating cardiovascular risk, in Russia in the beginning of 2014 where the risk to develop cardiovascular disease was underestimated.[100] To translate epidemiological data derived from populations to individual risk is not uncomplicated and the estimation of risk always has to be cautiously interpreted in the light of societal trends and individual factors.[44, 99] In 1968 Wilson at the Ministry of Health in the United Kingdom and Jungner at the Sahlgrenska Hospital in Gothenburg, Sweden listed criteria that should be fulfilled before a screening program can be accepted as justified.[101] These criteria were revisited and further developed in 2008 by Andermann et al.[101] presented in Table 3. These criteria should always be considered before a screening program is initiated.

Policymakers' actions to battle cardiovascular disease and diabetes

The increase of cardiovascular disease, diabetes and other non-communicable diseases, in combination with available evidence that prevention is possible[54-71, 102] has caused the international community to act.[21, 31, 103-104] An important step was taken by the European Heart Network which together with the European Society of Cardiology on February 14, 2000 introduced the St Valentine's declaration that: *'Every child born in the new millennium has the right to live until the age of at least 65 without suffering from avoidable cardiovascular disease'*.[105] In 2002 the European Society of Cardiology launched *'a common strategy for member states to reduce cardiovascular deaths by 40%'*.[105] These initiatives led to an increased collaboration between health care professionals and politicians and the European Heart Health Charter (EHHC) was launched in June 2007 at the European Parliament in Brussels as a joint project by European Society of

Table 3. The Wilson and Jungner screening criteria developed by Andermann et al.[101]

1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognized disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognizable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case-finding should be a continuing process and not a "once and for all" project.

Synthesis of emerging screening criteria proposed over the past 40 years

- The screening programme should respond to a recognized need
- The objectives of screening should be defined at the outset
- There should be a defined target population
- There should be scientific evidence of screening programme effectiveness
- The programme should integrate education, testing, clinical services and programme management
- There should be quality assurance, with mechanisms to minimize potential risks of screening
- The programme should ensure informed choice, confidentiality and respect for autonomy
- The programme should promote equity and access to screening for the entire target population
- Programme evaluation should be planned from the outset
- The overall benefits of screening should outweigh the harm

Cardiology, European Heart Network with the support of the European Commission and the WHO region Europe.[105] The charter was summarised in a European phone number to health: 03514090530 as explained in Table 4.

In 2011 United Nations (UN) organised two high level meetings regarding health: the first concerned AIDS and the second non-communicable diseases, not the least cardiovascular disease and diabetes.[52] This meeting resulted in the Political Declaration on the Prevention and Control of Non-Communicable Diseases listing prevention as the most important action to control the threatening global flare of non-communicable diseases.[52] At the 65th World Health Assembly in May 2012 the 194 WHO member states adopted as a global target to reduce premature mortality from non-communicable diseases by 25% by 2025, also known as 25 by 25.[106] Important areas that needed to be addressed to achieve this goal were listed: improved lifestyle (decrease harmful alcohol use, decrease tobacco use, lower sodium intake, increased physical activity), control of risk factors (blood pressure,

Table 4. Healthy targets as set in the European Heart Health Charter.

0	No use of tobacco,
3	Three km of daily walking
5	Five daily servings of fruit and vegetables
≤140/90	In blood pressure
<5	mmol/l in total cholesterol
<3	mmol/l in LDL-cholesterol
0	No diabetes

obesity and diabetes) and better treatment (eligible individuals to be treated with adequate pharmacologic agents to prevent cardiovascular disease and drugs and new technologies to be made accessible to as many as possible).[106] Still many policymakers do not prioritise prevention of non-communicable disease.[21] The obstacles are complex, including difficulties in implementing research in clinical practice and a multitude of other factors involving social, economic, industrial and cultural forces. Relatively few studies have investigated the processes related to preventive interventions on a population level, processes that deserve to be further explored.[108-111]

One of the initiators of the North Karelia Project, the former director for the Department for non-communicable diseases at the WHO and Past President of the World Heart Federation Pekka Puska stated that:

'Although much will certainly still be learnt in the future, very much is thus known already to serve prevention. Actually so much is known that the main question for [non-communicable disease] prevention is not "what should be done", but "how it should be done". The key question is: how can existing knowledge best be applied for effective prevention in real life'.[112]

Aims

The overall aim of this thesis is to advance the understanding of different levels of prevention: primordial-, primary- and secondary prevention using both a population and a high-risk based approaches in patients with cardiovascular disease and/or diabetes.

Specific aims are

1. To investigate the perception of key policymakers on cardiovascular disease in Europe and what actions and obstacles they see to improve health on a population level. **(Study I)**

2. To investigate if FINDRISC as an online questionnaire, is a feasible way to identify high-risk individuals as well as risk typing the population of an organisation. **(Study II)**

3. To investigate if patients with coronary artery disease, with and without diabetes, are managed according to recommendations given in European Practice Guidelines. **(Study III and IV)**

4. To determine which screening test has the best capacity to detect dysglycaemia in patients with coronary artery disease. **(Study V)**

MATERIAL AND METHODS

Summary

This thesis used data from four different cohorts summarised in Table 5.

Table 5. An overview of the studies that comprises the fundament for the thesis.

Study	I	II	III	IV-V
Study/Data source	Gyberg-Rydén Policy-maker questionnaire	Webb-QPS	EUROASPIRE III	EUROASPIRE IV
Time of data collection	2008	2007	2006-2007	2012-2013
Source population	Policymakers in 32 European countries	Employees at the Karolinska University Hospital, Stockholm, Sweden	Patients with established coronary artery disease aged 18-80 in 22 European countries	Patients with established coronary artery disease aged 18-80 in Europe in 24 European countries
Design	Descriptive	Descriptive	Cross-sectional survey	Cross-sectional survey
Study population	Responders to the Gyberg-Rydén policy-maker questionnaire	Responders to the FINDRISC-questions in Webb-QPS	All patients with an established glucometabolic status	**IV**: All individuals with an established glucometabolic status **V:** All individuals without diabetes in whom FPG, 2hPG and HbA1c were available
Number in study population	116	3029	6588	**IV:** 6187 **V:** 4004
Outcomes	(1) Awareness and perceived proximity to the EHHC-targets (2) Perceived obstacles to cardiovascular health (3) Actions deemed important to improve cardiovascular health (4) What measures are used to promote cardiovascular health	(1) Response rate (2) Identification of a population that could benefit from preventive interventions	(1) Use of pharmacologic treatment. (2) Fulfilment of risk factor targets set in the European prevention guidelines	**IV:** (1) Use of pharmacologic treatment. (2) Fulfilment of risk factor targets in European prevention guidelines **V**: Number of individuals identified with dysglycaemia by FPG, 2hPG and HbA1c
Adjustments	None	None	Age, gender, clustering within centres	**IV**: Age, gender, BMI, waist circumference, clustering within centres **V**: Age and gender
Statistical analyses	Descriptive	Descriptive	Patient characteristics across groups: Chi-square. Analysis of risk factors: multilevel logistic modelling	**IV:** Patient characteristics across groups: Chi-square. Analysis of risk factors: multilevel logistic modelling **V:** Patient characteristics included/excluded: Fisher's exact test and the Mann-Whitney U test. Exclusive glycaemic groups: Logistic regression

Study I

Aim

To investigate the perception of key policymakers on cardiovascular disease in Europe and what actions and obstacles they see to improved health on a population level.

Design

A descriptive study among policymakers was performed using a by the authors created questionnaire

Study Population

A total of 116 leading representatives of four professional structures in 32 European countries were identified. Two of the professional structures were governmental: Ministries of Health (health politicians) and public health institutes (public health officials), and two were non-governmental: national cardiac societies (health professionals) and national heart foundations (public representatives). In each of these organisations the executive officer was addressed with the intention to assess the perception of individual, key policymakers. The responders were divided into the four defined professional categories and four European regions (north, south, east, west) as presented in Table 9 found in the results section.

The pilot investigation and development of the questionnaire

During the spring of 2007 a pilot questionnaire was distributed to representatives from the Ministries of Health, the Public Health Institutes and National Cardiac Societies in four countries: Sweden, Croatia, United Kingdom and Portugal. The pilot study tested a set of questions that had been produced with the aim to get an opinion on how different policymakers experienced the EHHC. The respondents were asked not only to reply to the questionnaire but also to express their opinion on individual questions in text. The conclusion was that, following modifications, the questionnaire had the prerequisite to provide the requested information. It was adapted into its final form and in 2008 e-mailed to all recipients together with a copy of the EHHC and an introductory letter.

The identified policymakers were asked to address four issues: (1) previous knowledge and perceived proximity to the EHHC-targets, (2) perceived obstacles to cardiovascular health, (3) actions deemed important to improve the cardiovascular situation, and (4) what measures are applied to promote cardiovascular health. Previous knowledge of the EHHC was responded to as either 'yes' or 'no'. Obstacles to and actions towards improving cardiovascular health were graded by identifying the, for the respondent, three most important factors out of eight listed possibilities (Table 6). National attainment of the targets set out in the EHHC (Table 4) was rated from 1 (far from goal) to 10 (on target). Two examples of the questions are presented below. These results were compared to European statistics on cardiovascular disease from the Euro Heart Survey.[113] The use of predefined measures to improve cardiovascular health, as presented in Table 7, were rated from 1 (not at all) to 10 (full extent).

Examples of two questions in the questionnaire:

In your experience/opinion, which are the three most important *actions or measures* to be taken at a national level in order to improve *cardiovascular health*? Number your answer 1 to 3 in order of importance.

	Political		*Economical*		*Organisational*		*Media related*
	Increase awareness		*Change attitudes*		*Lifestyle oriented*		*Other*

*Comments:*_____

The EHHC lists eight characteristics associated with cardiovascular health. If these characteristics were national goals, how far or how close to them is the population in your country at present?

No use of tobacco *(all targets in Table 4 were assessed similarly)*

	Far from goal						*Close to goal*		*On target*		
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*No opinion*
Male											
Female											
Children <18 years											

Table 6. Factors affecting obstacles to, and future actions needed to, improve cardiovascular health.
Political: Factors originating from individuals, groups or organisations connected to a government or multigovernmental organisation, such as your own government, the EU or the UN
Economical: Lack of adequate financial recourses to achieve wanted goals
Organisational: Lack of coordination of active organisations, lack of an organisation handling cardiovascular prevention, etc
Media/Media related: No consistent systematic promotion/debate/information on cardiovascular prevention in TV/Newspapers/Radio/etc
Awareness/Increase awareness: Lack of sufficient knowledge of why and how to prevent cardiovascular disease within the population
Attitudes/Change attitudes: Refers to that knowledge of why and how to prevent cardiovascular disease exists within the population but there is no will to do anything about it
Life style/Life style oriented: Refers to too expensive and/or low availability of healthy options such as cheap vegetables, sport facilities, sport classes in schools, tobacco control measures, etc
Other: None of the above

Table 7. Measures as part of public national attempts to improve cardiovascular health	
1	Tobacco tax
2	Legislation prohibiting smoking in public areas
3	Alcohol tax
4	Prevalence of national information campaigns promoting cardiovascular health initiated by governmental organisations
5	Prevalence of national information campaigns promoting cardiovascular health initiated by non-governmental organisations
6	Integration of relevant content into national school educational systems
7	Medical professionals identifying high-risk individuals in the healthcare system
8	Advocacy for healthy lifestyles by medical professionals
9	Subsidising physical activities through tax/other incentives at a corporate level

Statistical analysis

The information provided was analysed using Microsoft Excel. No statistical analysis was undertaken. Descriptive analysis was judged to be more suitable given the limited number of participants and the answers dependency on one individual key policymaker.

Ethical considerations

No specific ethical issues were identified and it was up to the discretion of the person asked to respond to the questionnaire. The results were grouped and presented anonymously whenever possible.

Study II

Aim

To investigate if FINDRISC as an online questionnaire is a feasible way to identify high-risk individuals as well as risk typing an organisation.

Design

A descriptive analysis was undertaken using answers obtained from a questionnaire.

Study population

The study population was 5166 employees in 2007 at the Karolinska University Hospital in Stockholm, Sweden. They all received a link to an online questionnaire, called the Webb-QPS, specifically sent out to explore leadership and health in an e-mail inviting them to respond. FINDRISC was incorporated in this questionnaire. In the present analysis study participants who answered the FINDRISC-questionnaire were included. All study participants with self-reported diabetes were excluded.

The questionnaire

The questionnaire assessed the psychosocial environment and major health issues as follows: 1. Back- and neck pain; 2. Mental disease; 3. Diabetes; 4. Chronic obstructive lung disease; 5. Cardiovascular disease.[114] It was adaptive, which means that the number of questions to be answered related to the response to the main question on a specific subject, i.e. a person with more problems received several questions. A slightly modified version of the eight FINDRISC-questions was incorporated into the questionnaire in order to adapt the questions to the technical structure of the Webb-QPS. Questions 1, 2, 3, 5, 7 and 8 were identical to the original FINDRISC (Figure 11). Question 4 had four options on physical activity instead of 2. Question 6 asked "if you currently are on any blood pressure lowering drugs" instead of "if you ever had taken such drugs". The amendments were approved by the creator of FINDRISC (J Tuomilehto: Personal communication). The FINDRISC-questions were scattered throughout the questionnaire. In order to measure waist circumference (Question 3), a tape measure was sent to all recipients of the questionnaire while it was assumed that tools to measure weight and height to calculate BMI (Question 2) would be easily available. Five reminders were sent out before study closure.

Statistical Analysis

The information provided was analysed using SPSS. No statistical analysis were undertaken since a descriptive analysis was judged to be sufficient. The study participants were divided into the FINDRISC-risk groups as presented in Figure 11.

Ethical consideration

The study was approved by the Regional Ethics Committee in Stockholm, Sweden DNR: 2006/844-31. Participation was voluntary and anonymous. All participants signed an informed consent. All were informed that the questionnaire would assess their work satisfaction and that feedback to managers was reported at a group level only if there was a minimum of 10 responders and 50% response rate in the group.

Study III

Aim

To investigate if patients with coronary artery disease with and without diabetes are managed according to recommendations given in European Practice Guidelines as presented in Table 8.

Design

Study III is based on data from the study EUROASPIRE IV, an observational, cross sectional survey conducted at 76 centres in 22 European countries between 2006-2007, interviewing and investigating patients with established coronary artery disease. A total of 13 935 medical records were scrutinised in the search for study participants and 8966 (64%) attended the interview. 6558 (73%) patients in whom the glycaemic state could be established as self-reported diabetes or incident- or no diabetes by means of FPG during the study visit were included in the analysis.

Table 8. Treatment targets according to the European Guidelines on Cardiovascular Disease Prevention in clinical practice issued 2003[115], and updated in 2012[49] and the European Guidelines for Diabetes, Pre-Diabetes and Cardiovascular Disease issued 2007[116], and updated in 2013[17]. The targets from 2003, 2007 and 2012 where used analysing the results in **Study III** and 2007, 2012 and 2013 in **IV.**

	Guideline			
Variable	**Prevention 2003**	**Diabetes 2007**	**Prevention 2012**	**Diabetes 2013**
Blood pressure (mm Hg) (no diabetes)	<140/90	<140/90	<140/90	<140/90
Blood pressure (mm Hg) (diabetes)	<130/80	<130/80	< 140/80	<140/85
LDL-cholesterol mmol/L (mg/dl) (no diabetes and diabetes)	≤2.5 (≤ 100)	≤1.8 (≤ 70)	≤1.8 (≤ 70)	≤1.8 (≤ 70)
HbA1c % (mmol/mol) (diabetes)	≤6.1% (≤ 48)	≤6.5% (≤ 48)	≤7.0% (≤ 53)	≤7.0% (≤ 53)

Population

The inclusion criteria were: age 18–80 years and established coronary artery disease defined as hospitalisation for (1) elective or emergency coronary artery by-pass graft surgery (CABG); (2) percutaneous coronary intervention (PCI); (3) acute myocardial infarction (AMI; with or without ST elevation) or (4) acute myocardial ischemia without evidence of infarction (troponin negative), ≥6 but <36 months before the interview. The median time between the index event and interview was 1.2 years (IQR 1.0–1.8). The patients were divided into three groups based on glycaemic state: prevalent-, incident- and no diabetes. Prevalent diabetes was defined as self reported diabetes diagnosed by a physician. The diagnosis of incident diabetes was based on a fasting glucose of >7 mmol/L (>126 mg/dl) at the time of the interview.

Identification & Study visit

Patients were identified from diagnostic registries, hospital discharge lists or other valid sources and contacted by phone or mail. Trained research staff reviewed the medical records, interviewed and examined the patients and entered the data into an electronic central database. Demographic details, anthropometrics, blood samples, self reported lifestyle and medication were obtained during an outpatient visit at the participating centres. Data collectors were trained to use standardised methodologies for physical measurements. All equipment was calibrated according to the manufacturer's recommendations.

Investigations

Blood lipids and plasma glucose were measured in the fasting state. Total- and HDL-cholesterol, triglycerides in serum were analysed while low LDL-cholesterol was calculated according the formula by Friedewald.[117] Plasma glucose was analysed in all patients and HbA1c in those with self reported diabetes. All laboratory investigations were performed at a central laboratory (Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland).

Height and weight were measured in light indoor clothes without shoes (scales 701 and measuring stick model 220; SECA Medical Measuring Systems and Scales, Birmingham, UK).

Blood pressure was measured twice on the right upper arm in the sitting position using automatic digital sphygmomanometers (Omron M5-I, Illinois, USA).

The use of four cardioprotective drug therapies (antiplatelet drugs, β-blockers, renin-angiotensin-aldosterone-system (RAAS) blockers and statins) was assessed at the time for the interview. The patient was asked to bring an updated list of medications or the medication itself.

Health Care-Providers seen were assessed by asking the patient.

Definitions

Treatment targets were those recommended in the Joint European Guidelines on Cardiovascular Disease Prevention from 2003[115.] Analysis was also perfromed for the 2007[116] and 2012[49] guidelines as presented in Table 8.

Data management

The database was kept at the ESC Euro Heart Survey Department at the European Heart House (Sophia Antipolis, France). Data were collected electronically using a unique identification number for country, centre and individual. All data were stored under the provisions of National Data Protection Regulations.

Statistical analysis

The statistical analyses were performed at the Department of Public Health, University of Ghent in Belgium by means of SAS statistical software release 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Descriptive statistics (means, standard deviation and proportions) were used to present information on patient characteristics. The distribution of patient characteristics across groups (Table 11) was compared according to the Chi-square test. Use of pharmacological treatments, proportions of patients reaching treatment targets for blood pressure, LDL-cholesterol and HbA1c and healthcare providers (Table 12-13, Figure 17-19) were compared between groups according to multilevel logistic modelling[118] accounting for clustering of patients within centres and in addition adjusting for potential confounding due to differences in distributions of age and sex. A p-level of <0.05 was a accepted as statistically significant.

Ethical considerations

National coordinators obtained approvals from Local Research Ethics Committees and all participants signed a consent form following oral and written information.

Studies IV and V

Aim

Study IV - To investigate if patients with coronary artery disease, with and without diabetes, are managed according to recommendations given in European Practice Guidelines from 2007[116], 2012[49] and 2013[17] as presented in Table 8.

Study V - To determine which screening test has the best capacity to detect dysglycaemia in patients with coronary artery disease.

Design

Studies IV and V are based on data from the study EUROASPIRE IV, an observational, cross sectional survey conducted at 79 centres in 24 European countries between 2012-2013, interviewing and investigating patients with established coronary artery disease. The study was a fusion of the protocols from **Study III** and the Euro Heart Survey of Diabetes and the Heart[62]. A total of 16 426 medical records were scrutinised in the search for study participants and 7998 (49%) attended the interview.

Study IV comprised all patients in whom the glycaemic state could be established as prevalent-, incident- or no diabetes by means of FPG, 2hPG or HbA1 during the study visit. Full information on the glycaemic state was available in 6187 (77%) of the participants of whom 2846 (46%) had no diabetes, 1158 (19%) incident diabetes and 2183 (35%) prevalent diabetes.

Study V included patients without prevalent diabetes in whom full information on FPG, OGTT and HbA1c was available (n=4004).

Population

The inclusion criteria were the same as for **Study III**. The median time between index event and interview was 1.35 years (interquartile range 0.95-1.93 years).

Identification & Study visit

Were the same as for **Study III.**

Investigations

HbA1c and *blood lipids* were measured similarily as in **Study III,** with the difference that HbA1c was collected in all patients.

An *OGTT* was performed using 75 grams of glucose in 200 ml of water in the morning after at least 10 hours of fasting. Plasma glucose was analysed locally with a photometric point-of-care technique (Glucose 201, HemoCue®, Ängelholm, Sweden). Regression analysis between the HemoCue® instrument and standard isotope dilution gas chromatography–mass spectrometry (IDGC-MS) showed a slope of 1.051 (95% confidence interval: 1.031–1.071) an intercept of -0.222 (95% CI -0.016 - -0.428; r = 0.994). The mean deviation was 0.24 mmol/L (2.0%). Values obtained with the HemoCue® instrument were in 69% within 5%, in 91% within 10%, and within 14,3% of the IDGC-MS method.[119] The HemoCue® method is cholesterol-sensitive due to the measurement in very small volumes resulting in higher levels of glycaemia with a lower cholesterol; therefore the glucose values were corrected for cholesterol according to the formula: HemoCue® glucose + 0.22 x (total cholesterol -5). Before final data analysis the values were converted from whole venous blood to plasma applying the formula established by Carstensen et al[120] : plasma glucose = 0.558 + 0.119 x whole blood glucose, as used by the DECODE study group[121] and in the Euro Heart Survey on Diabetes and the Heart[63]. Proper use of the equipment was assured through central training of the

data collectors, and retrieval of HemoCue®-cuvette storage information and validation sheets from a selection of the participating centres.

Height, weight and use of *cardioprotective drug therapies* were assessed in the same way as in **Study III** at study visit.

Blood pressure was measured in the same way as **Study III** but using the Omron M6; OMRON Corporation, Kyoto, Japan.

Waist circumference was measured using a metal tape applied horizontally at the point midway in the mid-axillary line between the lowest rim of the rib cage and the tip of the hip bone (superior iliac crest) with the patient standing.[122]

Definitions

Dysglycaemia was defined according to Table 1:

When the term 'high risk for diabetes' is used it includes IFG and IGT according to WHO's criteria or IFG and high risk HbA1c according to ADA's criteria.

Smoking at the time of interview was defined as self-reported smoking, and/or a breath carbon monoxide exceeding 10 ppm.[123]

Physical activity was assessed by international activity questionnaire (IPAQ). Low physical activity was defined as less than "moderate or vigorous physical activity for at least twenty minutes more than once/week".[124]

Low educational level was defined as primary school completed or less.

Data management

Was the same as for **Study III**.

Statistical analysis

Study IV

Was the same as for **Study III** but was, in addition to age and gender corrected for BMI and waits circumference.

Study V

Descriptive statistics (means, standard deviation and proportions) were used to present information on patient characteristics. Included and excluded patients were compared according to Fisher's exact test and the Mann-Whitney U test. P-values for the comparison between the three separate exclusive groups were obtained by means of logistic regression analysis adjusting for gender and age at interview. A double sided $p < 0.05$ was considered statistically significant. All statistical analyses were undertaken using SAS statistical software release 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Ethical considerations

Local ethics committees of all participating centres approved EUROASPIRE IV (In Sweden Dnr: 2011/1929-31/3). Written, informed consent was obtained from each participant. All data were introduced into the electronic database with the study number.

Results

Study I

The total response rate was 69% varying from 81% from the cardiologists to 57% from public health institutes. The northern parts of Europe responded more frequently (85 %) than the eastern part (57%) with the western and southern parts in between (Table 9).

Table 9. Response rate and regional division of countries. + = respons, - = no respons, o = no recipient identified.

	Ministry of health	Cardiologist	Public health institute	Patient representative	Total
North					**81%**
Denmark	+	+	+	+	
Finland	+	+	+	+	
Iceland	-	+	-	-	
Norway	+	+	+	+	
Sweden	+	+	+	+	
South					**68%**
Cyprus	+	+	o	-	
Greece	+	+	+	+	
Italy	+	+	-	+	
Malta	+	-	+	o	
Portugal	-	+	-	+	
Spain	-	+	-	+	
East					**57%**
Bulgaria	-	+	+	o	
Croatia	-	-	+	o	
Czech Republic	+	+	-	o	
Estonia	+	+	-	-	
Hungary	+	-	-	+	
Latvia	+	+	+	o	
Lithuania	-	+	+	+	
Macedonia	o	-	+	o	
Poland	-	+	+	o	
Romania	-	+	-	o	
Slovakia	-	+	-	-	
Slovenia	-	-	-	+	
Turkey	+	+	+	+	
West					**77%**
Austria	+	-	+	+	
Belgium	+	+	+	+	
France	-	+	-	-	
Germany	+	+	+	+	
Ireland	-	+	+	+	
Luxembourg	+	+	o	o	
Netherlands	+	+	-	+	
United Kingdom	+	+	-	+	
TOTAL	61%	81%	57%	78%	**69%**

Target fulfilment of the European Heart Health Charter

The perceived proximity to the EHHC targets was on average rated as five out of the maximum of ten by all professional groups and regions. There were only small differences between the four geographical regions with health policy leaders from Northern Europe rating their region somewhat closer to the targets and those from Western Europe somewhat further away. Health professionals and public representatives rated political initiatives as the type of action most needed to improve cardiovascular health while health politicians and public health officials rated improved organisation as most important (Figure 12). The northern region rated slightly higher on lifestyle and attitude and lower on economic factors compared to the other regions.

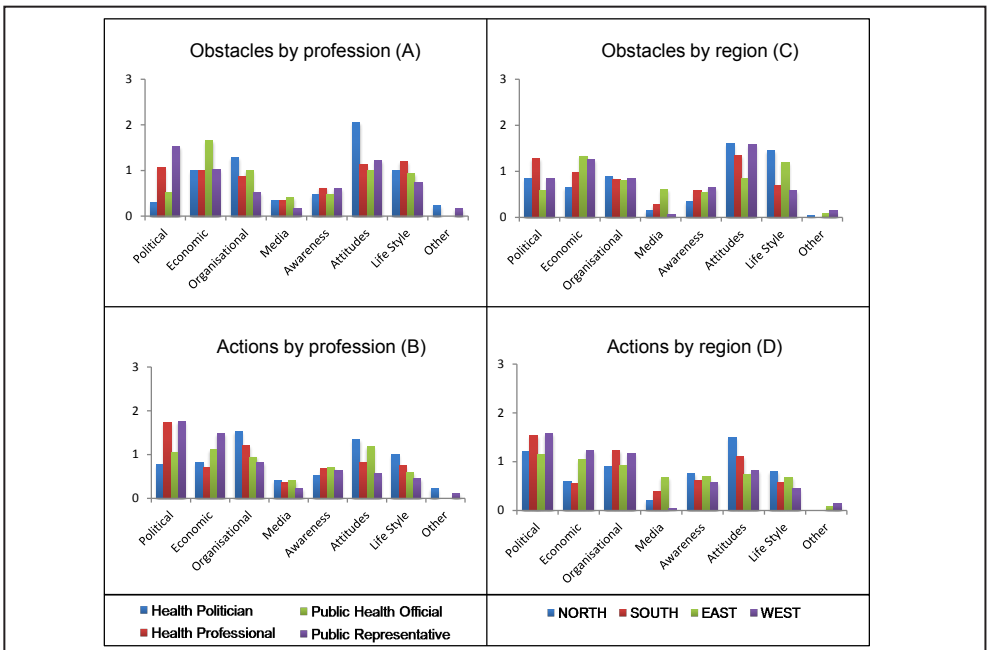


Figure 12. Predefined factors (as described in Table 5) rated as important obstacles (Panel A + C) or actions required (Panel B + D) to improve cardiovascular health by profession (A + B) and region (C + D). Y-axis 3 = most important; 2 = second most important; 1 = third most important; 0 = not among the three most important.

Figure 13 presents countrywide comparisons of the perceived proximity to the EHHC target of normoglycaemia, expressed as the average response from all leaders and the actual prevalence of diabetes obtained through the Euro Heart Survey cardiovascular statistics 2006[113]. A similar perception of the national situation in two countries did not mean that the actual situation observed was the same. There were small differences between the four professional groups on the perception of the extent to which the different types of measures were used. The measure believed to be used to the largest extent was prohibition of smoking in public areas, while the subsidisation of physical activities through tax or other incentives at a corporate level was believed to be used the least. One finding was a discrepancy between the perception of the use of a measure and its actual implementation. For instance a difference could be observed between the perceived use of public smoking bans and the actual existence of public smoking bans at a national level[125] as presented in Figure 14.

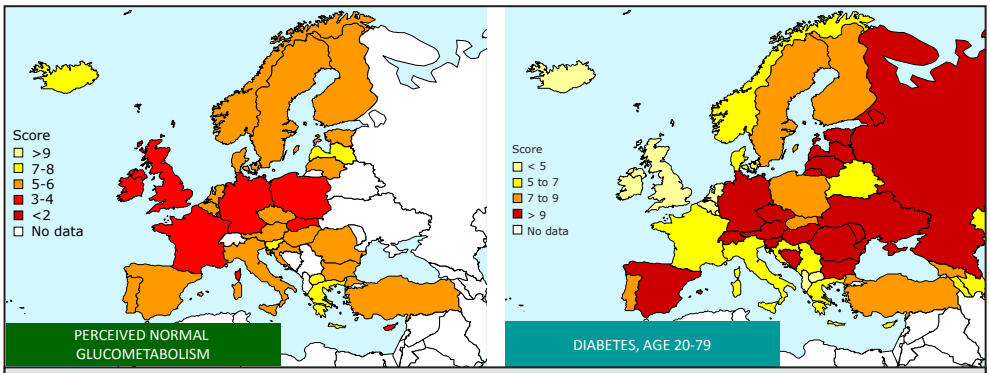


Figure 13. Perceived national proximity to the EHHC goal of normal glucometabolism (1= far away, 10 = on target) juxtaposed to the actual prevalence of diabetes in adults retrieved from the Euro Heart Survey Cardiovascular statistics 2006[113].

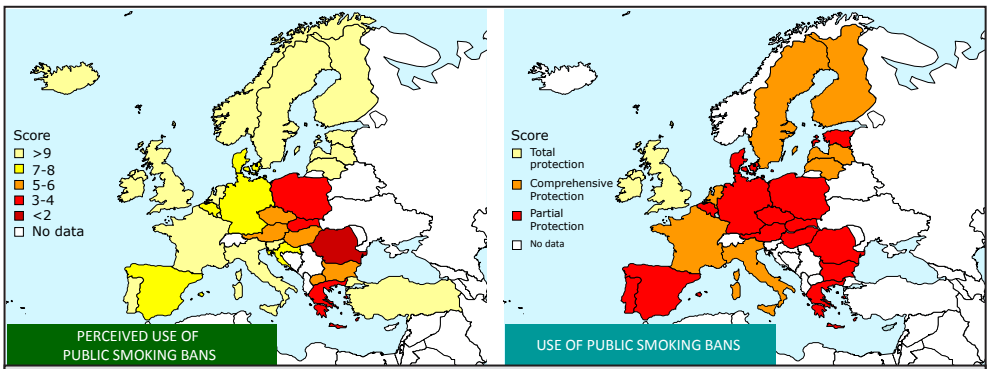


Figure 14. Perceived use of the prohibition of smoking in public areas (left panel) compared to the actual existence of smoking bans (right panel) retrieved from the European Commission[125]. In the right panel yellow indicates total protection in all enclosed workplaces and public places (smoking banned all together), orange indicates comprehensive protection (smoking allowed in separate smoking rooms), red indicates partial protection (smoking allowed in certain categories of venues, e.g. parts of the hospitality sector).

Study II

Response Rate

The response rate for the Webb-QPS-FINDRISC questionnaire is summarised in Figure 15. The group was composed of 10% doctors, 67% nurses, 7% medical secretaries and 16% other hospital staff, it was a similar distribution in non-responders to FINDRISC. Of those responding 3029 (84%) replied to one or more questions in the FINDRISC section, which is 59% of the original population. A total of 1948 (54%) completed the entire FINDRISC. Apart from age (100%) the response rate was similar for all the questions (82-93%) (Figure 15). If a study participant had an incomplete answer to FINDRISC, usually only one question was omitted. Individuals with self-reported diabetes, 1.6% of the population answering to Webb-QPS, were excluded from the analysis.

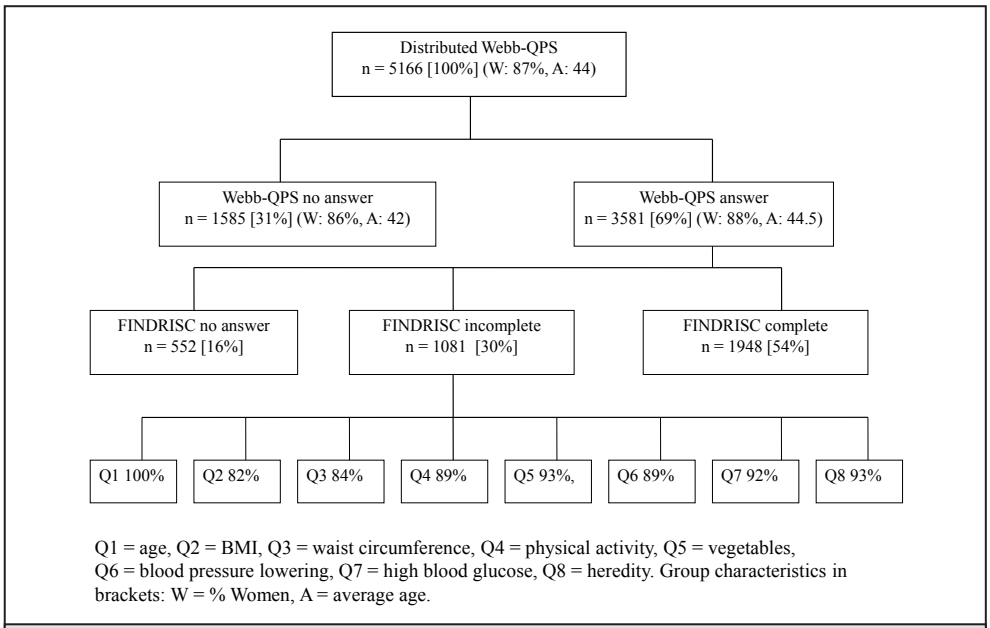


Figure 15. Response rate to Webb-QPS and FINDRISC.

Risk groups identified

Study participants belonging to different risk groups were distributed as outlined in Table 10 and Figure 16 regarding numbers and gender. The risk score predicts that 298 (9.8%, 8.6% women, 10.0% men) of the participants in Webb-QPS are likely to have diabetes if tested with an OGTT or will develop diabetes over the coming decade if no intervention is initiated. Individuals who are considered to benefit from preventive interventions are those at moderate (*n* = 828), high (*n* = 196) and very high (*n* = 58) risk (total group *n* = 1028; 19.8%). When the average answer from individuals with complete and incomplete FINDRISC are compared, those with complete answers seem to present a slightly higher risk profile. There was no data avaliable on non-responders to Webb-QPS.

Table 10. Identified risk groups.

Risk group	Low	Slightly elevated	Moderate	High	Very high
Total % (n)	16 (481)	48 (1466)	27 (828)	7 (196)	2 (58)
Women % (n)	16 (421)	48 (1271)	28 (732)	7 (180)	2 (54)
Men % (n)	16 (60)	53 (195)	26 (96)	4 (16)	1 (4)

Study III

A total of 13 935 medical records were reviewed and 8966 (64%) patients interviewed. The present study population comprises 6588, 74% of those interviewed, with available information on their glycaemic state. In the study population 65% had no diabetes, 11% incident diabetes and 23% prevalent diabetes. Patient characteristics are presented in Table 11.

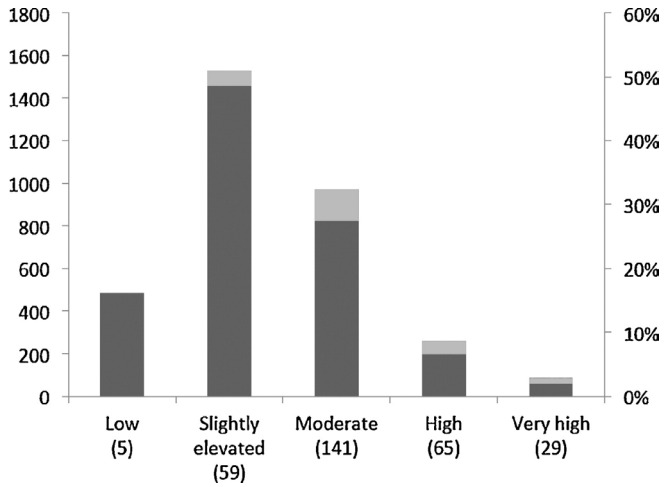


Figure 16. Number (left y-axis) and percentage (right y-axis) of individuals at the Karolinska University Hospital divided into risk groups for diabetes. The number predicted to develop diabetes the upcoming ten years are indicated by the light gray part of the bar and by the numbers in brackets below each risk group. The risk groups are defined as follows: low = estimated 1 in 100 will develop diabetes, slightly elevated = estimated 1 in 25 will develop diabetes, moderate = estimated 1 in 6 will develop diabetes, high = estimated 1 in 3 will develop diabetes, very high = estimated 1 in 2 will develop diabetes.

Table 11. Patient characteristics. Data presented are % with number of patients in brackets if not stated otherwise.

Variable	Diabetes			P-value[1]
	No	Incident	Prevalent	
	n= 4295	n= 752	n= 1541	
Age				P<0.0001
< 50 years	12 (510/4295)	7 (52/752)	6 (86/1541)	
50–59 years	28 (1198/4295)	29 (218/752)	26 (406/1541)	
60–69 years	36 (1550/4295)	39 (292/752)	41 (625/1541)	
>70 years	24 (1037/4295)	25 (190/752)	28 (424/1541)	
Sex				P<0.0001
Women	24 (1008/4295)	21 (159/752)	30 (469/1541)	
Men	77 (3287/4295)	79 (593/752)	70 (1072/1541)	
Inclusion event				P=0.0002
CABG[2]	18 (789/4295)	17 (128/752)	23 (360/1541)	
PCI[3]	45 (1926/4295)	42 (319/752)	42 (639/1541)	
AMI[4]	20 (874/4295)	21 (158/752)	19 (290/1541)	
Ischemia	16 (706/4295)	20 (147/752)	16 (252/1541)	
AMI ever[5]	65 (2788/4293)	65 (488/752)	64 (988/1541)	P=0.84
Non smoker	82 (3525/4289)	83 (619/750)	87 (1330/1538)	P=0.0005
BMI[6]*, kg/m*^{2}				P<0.0001
<25	22 (934/4278)	14 (101/750)	12 (176/1528)	
25 - 29.9	50 (2119/4278)	44 (329/750)	41 (633/1528)	
≥30	29 (1225/4278)	43 (320/750)	47 (719/1528)	

[1] Significance of differences between the groups, [2] CABG = Coronary Artery By-pass Graft, [3] PCI = Percutaneous Coronary Intervention,[4]AMI = Acute Myocardial Infarction, [5] Composite of AMI as an index event, CABG or PCI as an index event because of AMI (information from medical records) and self reported AMI (information at interview)., [6] BMI = Body Mass Index

Table 12. Use of pharmacological therapy in % (n/total n).

Ongoing therapy	Diabetes			
	No	Incident	Prevalent	P-value[1]
Aspirin or other antiplatelet agents	91 (3902/4284)	93 (693/749)	91 (1400/1533)	P=0.34
β-blockers	79 (3391/4279)	84 (631/750)	81 (1243/1533)	P=0.01
Whereof β-blockers in patients with AMI[2] ever	81 (2263/2788)	86 (420/488)	84 (826/988)	P=0.02
RAAS-blockers[3]	68 (2919/4277)	76 (567/749)	77 (1180/1532)	P<0.0001
Whereof ACEi[4]	59 (2525/4277)	67 (500/749)	62 (951/1532)	P<0.0001
Statins	79 (3385/4275)	80 (597/750)	80 (1230/1533)	P=0.72
All of the above[5]	44 (1865/4271)	51 (384/749)	50 (766/1530)	P<0.0001
Glucose lowering				
Oral	-	-	60 (916/1534)	
Insulin	-	-	24 (369/1520)	

[1]Taking into account clustering of patients within centres and adjusted for age and sex [2] Acute Myocardial Infarction [3]Renin-Angiotensin-Aldosterone-blockers including Angiotensin Converting Enzyme inhibitors and Angiotensin Receptor Blockers [4]Angiotensin Converting Enzyme inhibitors [5] The combination of aspirin or other antiplatelet, β-blocker, RAAS-blocker and statins.

The use of the four cardioprotective drug therapies is described in Table 12. In all three groups >97% of the patients reported that they never or seldom missed or altered their medication.

Figure 17 shows the proportion of patients reaching three selected blood pressure target levels. Half of the patients with no diabetes and one fifth of those with prevalent diabetes reached the recommended blood pressure target of <140/90 mmHg and <130/80 mmHg respectively as recommended in the 2007 Prevention Guidelines. When applying a blood pressure target of <140/80 mmHg as recommended in the 2012 prevention guidelines[49] 28% of the patients with prevalent diabetes reached the target.

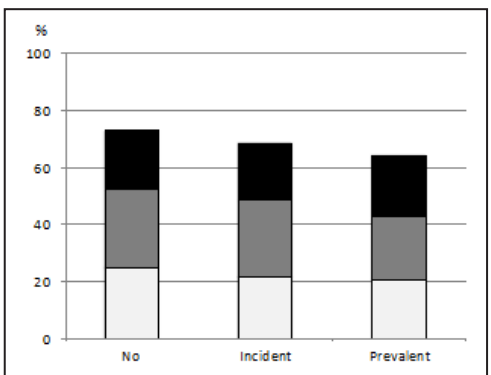


Figure 17. Percentage of patients reaching blood pressure treatment target by diabetes state (no, incident, prevalent) accounting for clustering of patients within centres and adjusted for age and sex. White: <130/80 mmHg (differences between groups p<0.005). Grey: <140/90 mmHg (differences between groups p<0.0001). Black: <150/100 mmHg (differences between groups p<0.0001).

Figure 18 shows the proportion of patients reaching three different LDL-cholesterol levels. Forty-four per cent of the patients with no diabetes, 40% of those with incident diabetes and 53% with prevalent diabetes reached the treatment target for LDL-cholesterol of <2.5 mmol/l (<97 mg/dL).

Out of the patients with prevalent diabetes 22% reached the guideline treatment target of HbA1c <6.1% (<43 mmol/mol) as shown in Figure 19. When

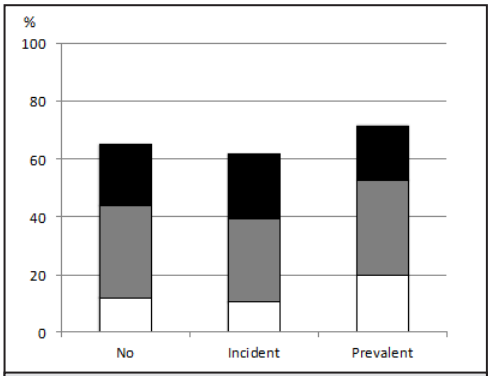


Figure 18. Percentage of patients reaching LDL-cholesterol treatment target by diabetes state (no, incident and prevalent) accounting for clustering of patients within centres and adjusted for age and sex. White: LDL-cholesterol <1.8 mmol/L (<70 mg/dL) (differences between groups p<0.0001). Grey: LDL-cholesterol <2.5 mmol/L (<97 mg/dL) (differences between groups p<0.0001). Black: LDL-cholesterol <3.0 mmol/L (<116 mg/dL) (differences between groups p=0.0002).

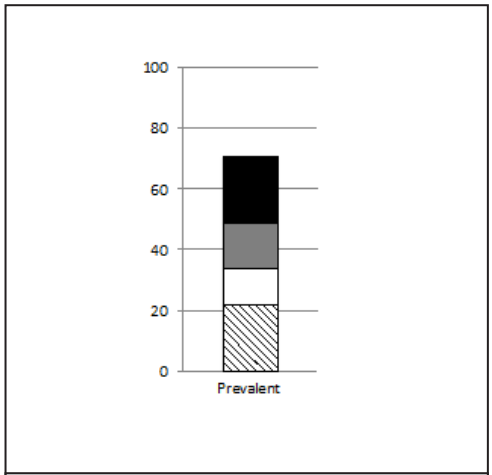


Figure 19. Percentage of diabetes patients reaching HbA1c (DCCT) treatment targets accounting for clustering of patients within centres and adjusted for age and sex. Striped: HbA1c <6.1% mmol/L (<43 mmol/mol). White: HbA1c <6.5% mmol/L (<48 mmol/mol). Grey: HbA1c <7.0 mmol/L (<53 mmol/mol). Black <8.0 mmol/L (<64 mmol/mol).

asked about access to healthcare providers 17% of the patients with prevalent diabetes reported being seen by an endocrinologist/diabetologist. A majority of the patients went to multiple healthcare providers as presented in Table 13.

Table 13. Health-care provider providing the care presented as % (n/total n).

Health-care provider	Diabetes			
	No	Incident	Prevalent	P-value[1]
General practitioner	53 (2285/4290)	51 (383/752)	51 (775/1536)	P=0.66
Cardiologist	70 (3016/4290)	75 (561/752)	73 (1121/1536)	P=0.68
Endocrinologist/Diabetologist	1 (47/4290)	1 (8/752)	17 (267/1536)	P<0.0001
Cardiac specialist nurse	2 (80/4290)	1 (9/752)	2 (23/1536)	P=0.86
Cardiac rehabilitation program	35 (1504/4247)	33 (248/748)	32 (486/1522)	P=0.48

[1]Taking into account clustering of patients within centres and adjusted for age and sex.

Study IV

Clinical characteristics are presented in Table 14. Those with incident and prevalent diabetes were older and more obese. Patients with prevalent diabetes were least physically active.

The use of antiplatelet agents (primarily aspirin), β-blockers, RAAS-blockers and statins are presented in Table 15. The highest proportion of patients prescribed a combination of the four drugs was in those with prevalent diabetes.

Table 14. Patient characteristics of the 6187 included and 1811 excluded patients. Data presented are % (n/total n) if not stated otherwise.

Variable	Diabetes			P-value[1]	Missing info
	No	Incident	Prevalent		
Participants	46 (2846/6187)	19 (1158/6187)	35 (2183/6187)		1811
Age (years)					
Mean (±SD)	63 (10.0)	65 (9.2)	65 (8.6)	<0.0001	64 (9.6)
< 50	11 (320/2846)	6 (68/1158)	5 (102/2183)		11 (191/1811)
50–59	25 (714/2846)	23 (263/1158)	21 (451/2183)		27 (492/1811)
60–69	36 (1026/2846)	38 (437/1158)	41 (900/2183)		34 (622/1811)
>70	28 (786/2846)	34 (390/1158)	33 (730/2183)		28 (506/1811)
Sex				0.006	
Women	24 (674/2846)	23 (268/1158)	27 (594/2183)		23 (412/1811)
Men	76 (2172/2846)	77 (890/1158)	73 (1589/2183)		77 (1399/1811)
Inclusion event				0.002	
CABG[2]	11 (304/2846)	12 (143/1158)	14 (315/2183)		15 (262/1811)
PCI[3]	55 (1576/2846)	53 (619/1158)	52 (1143/2183)		54 (983/1811)
AMI[4]	24 (671/2846)	24 (273/1158)	21 (468/2183)		23 (414/1811)
Ischemia	10 (295/2846)	11 (123/1158)	12 (257/2183)		8 (152/1811)
AMI ever[5]	66 (1888/2842)	65 (753/1158)	65 (1407/2178)	0.37	67(1214/1809)
Smoker	16 (464/2846)	14 (165/1158)	14 (304/2183)	0.04	19 (346/1811)
BMI[6]*, kg/m*^{2}	28 (4.2)	29 (4.5)	31 (5.0)	<0.0001	29 (4.7)
<25	23 (638/2841)	14 (164/1158)	11 (239/2171)		21 (384/1792)
>25 – 29.9	48 (1349/2841)	46 (533/1158)	39 (846/2171)		46(818/1792)
≥30	30 (854/2841)	40 (461/1158)	50 (1086/2171)		33 (590/1792)
Central Obesity	51 (1439/2806)	63 (724/1146)	71 (1510/2135)	<0.0001	51 (895/1768)
Low physical activity	60 (1591/2647)	60 (643/1069)	69 (1318/1904)	<0.0001	58 (914/1581)
FPG (mean + SD)	6.0 (0.6)	7.3 (0.9)	8.6 (2.9)	<0.0001	6.1 (1.7)
2hPG (mean + SD)	7.1 (1.7)	10.1 (3.4)	--	<0.0001	--
HbA1c (mean + SD)	5.6 (0.3)	6.0 (0.6)	7.2 (1.4)	<0.0001	5.8 (0.7)

[1] Significance of differences between the groups, [2] CABG = Coronary Artery By-pass Graft, [3] PCI = Percutaneous Coronary Intervention,[4]AMI = Acute Myocardial Infarction, [5] Composite of AMI as an index event, CABG or PCI as an index event because of AMI (information from medical records) and self reported AMI (information at interview)., [6] BMI = Body Mass Index

Table 15. Use of cardioprotective pharmacological therapy in % (n/total n).

Ongoing therapy	Diabetes			
	No	Incident	Prevalent	P-value[1]
ASA or other anticoagulants	94 (2655/2834)	92 (1064/1154)	94 (2046/2172)	0.23
β-blockers	81 (2301/2834)	83 (961/1154)	86 (1873/2172)	<0.0001
Whereof in patients with AMI[2] ever	83 (1571/1879)	85 (639/750)	88(1223/1398)	0.004
RAAS-blockers[3]	73 (2064/2834)	77 (883/1154)	80 (1727/2172)	<0.0001
ACEi[4]	58 (1637/2834)	61 (698/1154)	59 (1280/2172)	0.89
Statins	85 (2409/2894)	85 (982/1154)	87 (1880/2172)	0.61
All of the above[5]	53 (1501/2894)	55 (634/1154)	60 (1295/2172)	<0.0001

[1]Taking into account clustering of patients within centres and adjusted for age and sex [2]Acute Myocardial Infarction
[3]Renin-Angiotensin-Aldosterone-blockers including Angiotensin Converting Enzyme inhibitors and Angiotensin Receptor Blockers
[4]Angiotensin Converting Enzyme inhibitors [5]The combination of aspirin or other antiplatelet, β-blocker, RAAS-blocker and statins.

Dietary treatment was used in 65% of the patients with prevalent diabetes. The most commonly used glucose lowering drugs in patients with prevalent diabetes were metformin (57%), insulin (27%), sulfonylurea (25%) and sitagliptin (6%). The most common combinations of glucose lowering drugs were metformin + sulfonylurea (15%) and metformin + insulin (11%).

In all three groups >97% of the patients reported that they never or seldom missed or altered their medication, the same result obtained in **Study III**.

Patients with no-, incident- and prevalent diabetes reached a blood pressure target of 140/90mmHg in 68, 61 and 54%, a target of 140/85 mmHg in 63, 56, 49% and a target of 130/80 mmHg in 40%, 32% and 26%. The distribution of systolic blood pressure levels in the three patient groups are presented in Figure 20 panel A. Patients with no diabetes had the lowest systolic blood pressure levels and those with prevalent diabetes the highest. Differences in diastolic pressure was less apparent (Figure 20 panel B). Moreover 15% of patients with no diabetes had a systolic blood pressure >150 mm Hg. The corresponding proportions for patients with incident and prevalent diabetes were 21 and 24 % respectively.

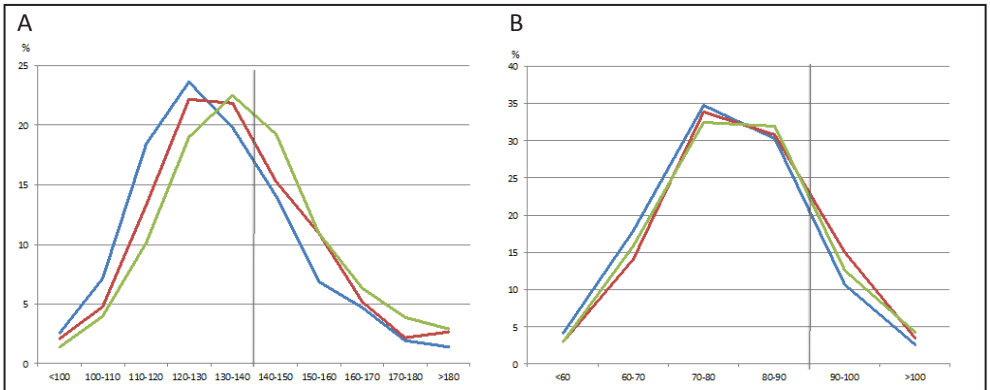


Figure 20. Distribution of systolic (panel A) and diastolic (panel B) blood pressure in patients with no diabetes (blue), incident diabetes (red) and prevalent diabetes (green). The difference between groups is statistically significant (systolic blood pressure: p<0.0001, diastolic blood pressure: p=0.003) adjusted for BMI, waits circumference, age and sex. The vertical lines represent the targets of 140 mmHg and 90 mm Hg respectively.

Patients with no-, incident- and prevalent diabetes reached a LDL-cholesterol target of 1.8 mmol/L (70 mg/dL) in 16, 18 and 28% respectively. Patients with prevalent diabetes had a better control of LDL-cholesterol than the two other groups (Figure 21). Twenty six per cent of the patients with no- and incident diabetes and 17% of those with prevalent diabetes had a LDL-cholesterol >3.0 mmol/l (>116 mg/dL). The total cholesterol <4.5 mmol/L (<174 mg/dL) was reached in 59, 59, 68% respectively.

Glycaemic control expressed as the level of HbA1c is depicted in Figure 22. Patients with incident- and prevalent diabetes reached an HbA1c <7.0% (53 mmol/L) in 95% and 53% respectively. The proportion of patients with prevalent diabetes that had an HbA1c >9.0% (>75 mmol/mol) was 11% compared to 0.2% in those with incident diabetes.

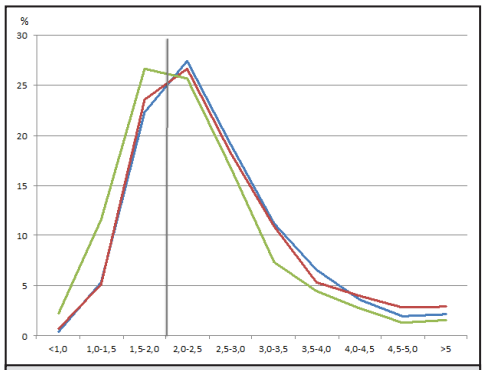


Figure 21. Distribution of LDL-cholesterol in patients with no diabetes (blue), incident diabetes (red) and prevalent diabetes (green). The difference between groups is statistically significant (p<0.0001) adjusted for BMI, waits circumference, age and sex. The vertical line represent a target of 2.0 mmol/L.

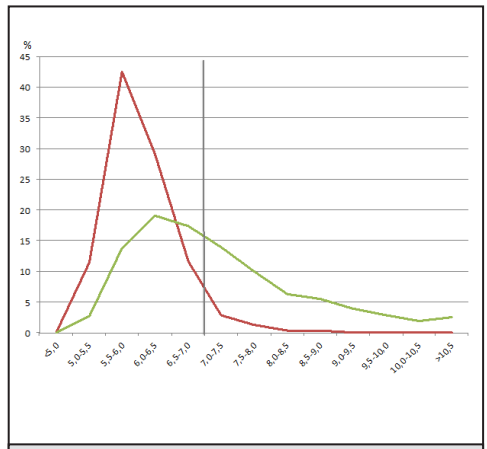


Figure 22. Distribution of HbA1c in patients with incident diabetes (red) and prevalent diabetes (green). The difference between groups is statistically significant (p<0.0001) adjusted for BMI, waits circumference, age and sex. The vertical line represents a target of 7.0% (53 mmol/mol).

An overview of healthcare providers is presented in Table 16. Patients with prevalent diabetes were more frequently seen by an endocrinologist (34%) while patients without diabetes more often attended a cardiac rehabilitation program (43%). Twenty seven per cent of the patients with prevalent diabetes attended a diabetes school.

Table 16. Health-care provider delivering the care presented as % (n/total n).

Health-care provider	Diabetes			
	No	Incident	Prevalent	P-value[1]
General practitioner	58 (1662/2845)	62 (717/1158)	65 (1408/2183)	0.07
Cardiologist	67 (1916/2846)	73 (848/1158)	74 (1618/2183)	0.69
Endocrinologist/Diabetologist	1 (40/2846)	2 (18/1158)	34 (731/2183)	<0.0001
Cardiac specialist nurse	5 (134/2846)	3 (30/1158)	5 (114/2183)	0.001
Cardiac Rehabilitation Program	43 (1201/2824)	39 (451/1145)	36 (777/2154)	<0.0001

[1]Taking into account clustering of patients within centres and adjusted for age and sex.

Study V

Clinical characteristics at interview of those who were included and excluded in the present analyses are shown in Table 17.

There were no major differences in the characteristics of patients with diabetes identified by only one of the three tests (Table 18), although those detected by HbA1c alone had a lower education level, a higher prevalence of obesity and were less physically active.

Table 17. Pertinent characteristics at the time of interview of the patients included in the analysis (i.e. with Fasting Plasma Glucose (FPG), Oral Glucose Tolerance Test (OGTT) and HbA1c available) and those excluded (i.e. with missing FPG (n=71) and/or OGTT (1,195) and/or HbA1c (n=220). Values presented are % (numbers) if not stated otherwise.

Variable	Patients included in the analysis n = 4004	Patients excluded from the analysis* n =1391	P-value
Age (years; mean ± SD)	63.6 (9.8)	62.9 (10.0)	0.065
< 50 years	10 (388/4004)	10 (142/1391)	
50–59 years	24 (977/4004)	28 (386/1391)	
60–69 years	37 (1463/4004)	34 (478/1391)	
>70 years	29 (1176/4004)	28 (385/1391)	
Sex			0.86
Men	76 (3062/4004)	77 (1067/1391)	
Women	24 (942/4004)	23 (324/1391)	
Current smokers	16 (629/4004)	19 (266/1391)	0.0032
BMI	28.6 (4.3)	28.5 (4.6)	0.59
<25 kg/m^2	20 (802/3999)	21 (295/1383)	
25.0-29.9 kg/m^2	47 (1882/3999)	46 (638/1383)	
≥30 kg/m^2	33 (1315/3999)	33 (450/1383)	
Central Obesity**	55 (2163/3952)	51 (693/1361)	0.015
Blood pressure ≥140/90 mmHg	34 (1349/3994)	40 (552/1388)	<0.0001
Laboratory values			
Fasting plasma glucose ≥7 mmol/l	22 (867/4004)	25 (331/1320)	0.01
HbA1c ≥6.5%	5 (193/4004)	7 (81/1100)	0.0009
Total cholesterol ≥ 4.5 mmol/L	41 (1642/3999)	42 (473/1117)	0.45
Triglycerides ≥ 1.7 mmol/L	30 (1199/3966)	31 (336/1090)	0.71
Pharmacological treatment			
Aspirin/antiplatelets	93 (3719/3988)	94 (1305/1385)	0.21
Beta-blockers	82 (3262/3988)	81 (1125/1385)	0.64
ACE-inhibitors	59 (2335/3988)	60 (832/1385)	0.32
AT-II receptor antagonists	16 (636/3988)	13 (178/1385)	0.0056
Diuretics	25 (980/3988)	28 (385/1385)	0.018
Statins	85 (3391/3988)	87 (1199/1385)	0.16
Low physical activity	60 (2234/3716)	59 (723/1223)	0.54

[1]Denotes patients with known diabetes and incomplete information on FPG, OGTT and HbA1c as presented in Figure 1. [2]Denotes waist circumference of ≥ 88 cm for women and ≥ 102 cm for men.

Table 18. Pertinent characteristics in patients with screen-detected diabetes by means of Fasting Plasma Glucose alone (FPG), 2 hour Postload Glucose alone (2hPG) and HbA1c alone.
Data presented are % (n) if not stated otherwise.

	FPG ≥7 mmol/L (n=606)	HbA1c ≥6.5% (n=49)	2hPG ≥11.1 mmol/L (n=218)	P = [1]
Age (years; mean±SD)	65 (9.4)	61 (11.2)	67 (8.8)	0.03
Female gender	22 (135/606)	12 (6/49)	28 (60/218)	0.18
Low educational level	18 (107/603)	29 (14/49)	16 (35/216)	0.06
Current smoking	15 (91/606)	20 (10/49)	11 (23/218)	0.35
BMI (kg/m^2; mean±SD)	29 (4.1)	30 (4.4)	30 (4.8)	0.006
BMI ≥ 25	84 (507/606)	86 (42/49)	85 (186/218)	0.78
BMI ≥ 30 kg/m^2	35 (209/606)	53 (26/49)	42 (91/218)	0.01
Central obesity	58 (349/601)	66 (31/47)	62 (133/213)	0.31
Blood pressure ≥140/90 mmHg	39 (237/606)	31 (15/49)	41 (89/216)	0.52
Total cholesterol ≥ 4.5 mmol/L	43 (262/605)	37 (18/49)	37 (81/218)	0.24
Triglycerides ≥ 1.7 mmol/L	27 (163/603)	41 (20/49)	31 (66/216)	0.12
ASA/antiplatelets	91 (551/603)	98 (48/49)	96 (209/218)	0.03
Beta-blockers	82 (497/603)	92 (45/49)	83 (180/218)	0.26
ACE-inhibitors	59 (357/603)	63 (31/49)	67 (146/218)	0.07
AT-II Receptor antagonists	16 (96/603)	10 (5/49)	16 (34/218)	0.67
Diuretics	31 (185/603)	25 (12/49)	31 (68/218)	0.83
Statins	84 (506/603)	90 (44/49)	89 (193/218)	0.16
Low physical activity	54 (307/569)	71 (30/42)	63 (125/199)	0.01

[1]Significance of the difference between groups, adjusted for age and gender

The proportions screened as having diabetes using different tests and the overlaps between them are presented in Figure 23. Of the 1158 screened with diabetes the proportions identified were by FPG: 75%, 2hPG: 40%, %, HbA1c 17%, OGTT = FPG + 2hPG: 96% and by HbA1c + FPG: 81%. There was little overlap in individuals detected by different methods and the proportion that had diabetes according to all three methods simultaneously was 7%, similar in men and women. Of the 466 patients with diabetes based on an elevated 2hPG a total of 218 (47%) would not have been detected with diabetes without the glucose load.

Applying the WHO criteria, based on the OGTT (= FPG+2h-PG), a total of 1065 (27%) had normal glucose metabolism while the corresponding proportion was 420 (11%) according to the ADA criteria, based on FPG+HbA1c (Figure 24). Screening according to the ADA criteria for FPG + HbA1c identified 2643 (66%) of patients as having a 'high risk for diabetes' where IFG contributed 91% and High risk HbA1c 53%. The overlap, i.e. patients identified as having high risk by both tests, was 44%. The WHO criteria identified 1829 patients (46%) as having a 'high risk for diabetes' where 76% was identified by IFG and 53% by IGT with an overlap of 29%.

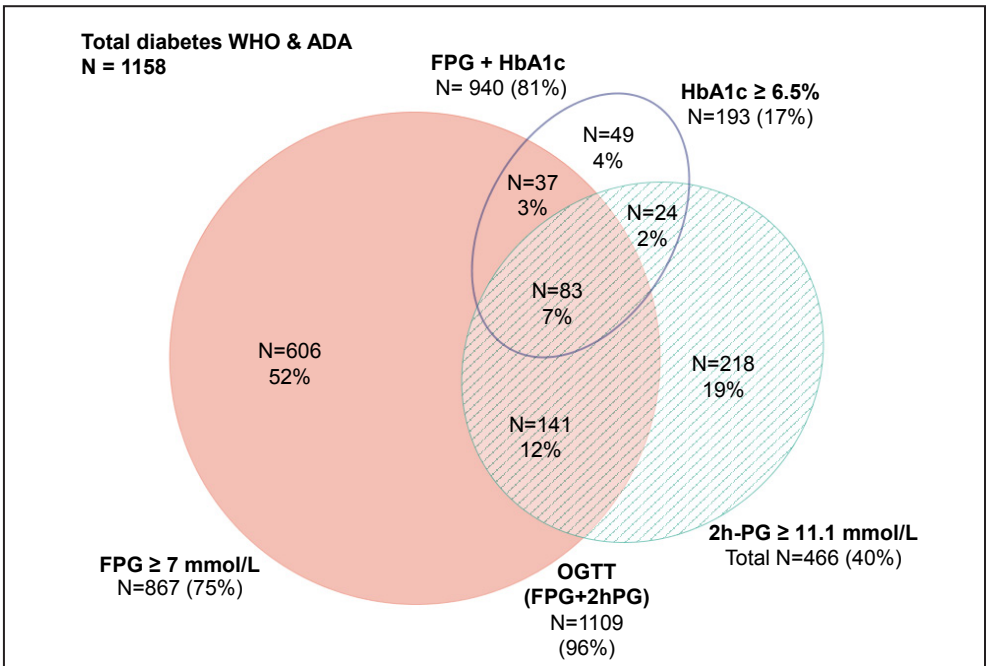


Figure 23. Proportions and their overlap between screening with fasting plasma glucose (FPG=pink), plasma glucose 2 hours after a glucose load (2hPG=green stripes), glycated hemoglobin A1c (HbA1c=clear with blue line) and their combinations in patients with coronary artery disease.

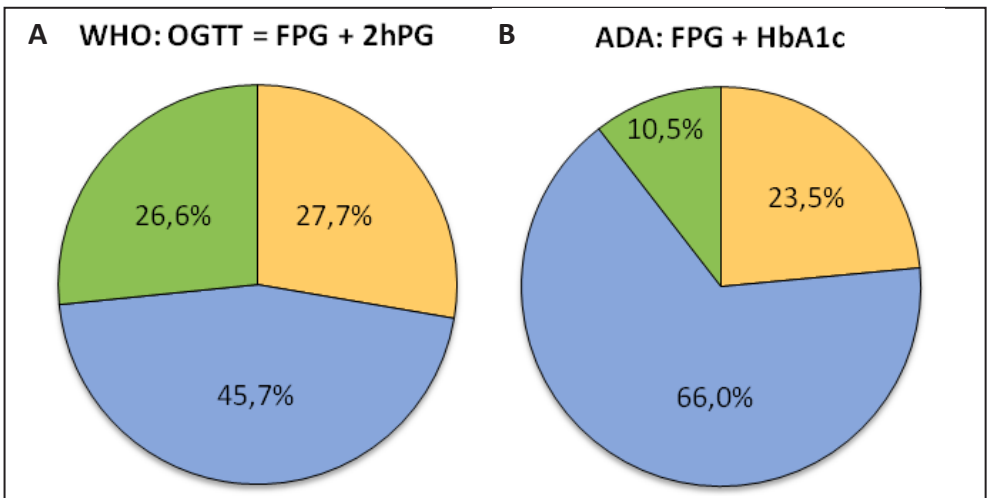


Figure 24. Patients with newly detected diabetes (yellow), high risk to develop diabetes (blue) and normoglycaemia (green) using different tests and criteria to define dysglycaemia. These are according to WHO (panel A): diabetes: FPG ≥7.0 mmol/l (126 mg/dl) and/or 2hPG value ≥11.1 mmol/l (200 mg/dl), IFG: FPG 6.1- 6.9 mmol/l (110 - 125 mg/dl) and IGT: 2hPG 7.8-11.0 mmol/mol (140-198 mg/dl; and according ADA (panel B): diabetes: FPG ≥7.0 mmol/l (126 mg/dl) and/or HbA1c ≥48mmol/mol (DCCT ≥6.5%). IFG: FPG 5.6- 6-9 mmol/l (101 – 125 mg/dl) and high risk HbA1c: HbA1c 39-47 mmol/mol (DCCT = 5.7 – 6.4%).

General Discussion

Cardiovascular disease and diabetes are major causes of morbidity and mortality worldwide but a premature impact of these diseases is possible to postpone by prevention. The present thesis focuses on different levels of prevention: primordial, primary and secondary, using both population and high-risk based approaches in patients with cardiovascular disease and/or diabetes.

Policymakers' perception of cardiovascular health

The main finding in **Study I** was that policymakers in Europe agreed that national patterns of cardiovascular disease and its prevention are far from the targets set in the EHHC. A similar rating of the perceived proximity to a specific target in two countries did not necessarily reflect a similar national situation when compared to available statistics on the actual situation. The perception of the use of various measures as part of national attempts to improve cardiovascular health differed little between the four professional groups. However, when perceptions of the implementation of smoking bans were analysed more in detail it showed that a similarly perceived use did not necessarily relate to a similar utilisation, just as for the targets.

Interestingly policymakers expressed diverging opinions on the most important measures to achieve an improved cardiovascular health. Health politicians rated political initiatives lower than the other groups, who in contrast believed that political actions are key for success. The implication is that some groups regretfully make cardiovascular health into a problem of 'somebody else'. This kind of projection will certainly limit cooperation between different stakeholders, and a prerequisite for a successful investment in health must commence with mutual agreements on what is needed and how responsibility should best be shared.[126, 127]

All professional groups rated the attitude within the population as an important obstacle to overcome while media was the factor rated lowest. Considering their likely important role of public information this may seem surprising. An explanation can perhaps be that all groups were of the opinion that media already worked well with regards to health promotion and information. Another possibility is that the interviewed groups underestimate the importance of a systematic collaboration with media i.e. it is a underused tool by policymakers when it comes to changing attitudes, awareness and lifestyle in a population regarding their health.

The reasons for the discrepant views between different countries and policymakers from the four organisations are probably multifactorial covering a wide range of areas, such as culture, history and politics, as well as the individual's own interests, opinions and knowledge. The discrepancy between perception and statistics in **Study I** will likely affect the possibility of achieving a wider penetration of the preventive targets listed in the EHHC. If the policymakers perceived risk factors as relatively unimportant or already appropriately dealt with, they are likely less interested in adopting the charter

recommendations in their country. Existing variations in cardiovascular health across Europe[33], with higher mortality and morbidity in eastern countries, will likely affect the priority of cardiovascular prevention. The findings in **Study I** underscore the importance of accurate epidemiological information, such as provided in **Study III and IV**, as well as knowledge of suited targets and available measures when building national plans to improve prevention.

Research investigating political factors shaping public health is limited, and mainly focused on the transfer of scientific evidence into public health policy, making it hard to compare the present findings to other studies.[108-111, 128] An on-going study, Kidney Health for Life, has been initiated using **Study I** as a template to organize their work (personal communication: A Levin, MD Chair, International Steering Group Kidney Health for Life). It is encouraging that health policy is getting more attention. Hopefully these two investigations will encourage further research in this important area. Increased insights in how different stakeholders experience actions and obstacles to improved health as well as knowledge on potential discrepancies in their opinion are fundamental in order to create consolidated health oriented programmes. Efforts from the medical profession to better understand the political process are required, as well as efforts by policymakers to be up to date with medical research, when launching societal endeavours aiming at shifting the risk pattern in a population.

Strengths and limitations of Study I

The small sample size of the present study makes it hard to draw definitive conclusions. Nevertheless the aim of the study was to investigate the perception of key health policymakers, which is likely to influence health policy. As such, the findings in **Study I** invite reflections of the importance for future population wide preventive initiatives.

Feasibility of using FINDRISC in an online questionnaire

FINDRISC incorporated in a workplace survey yielded a reasonably good response rate in **Study II**. This holds true not the least considering that many individuals, who would normally not participate in any risk assessments, were included. Studies following white-collar workers longitudinally were able to reach response rates around 85% to Webb-QPS (D Hassan: personal communication). The main predictors of such a high response rate include a well-orchestrated implementation procedure and a high involvement from the workplace managers.

The estimated prevalence of diabetes in the Stockholm area is 5% for men and 3% for women,[129] and about 30% of all Swedes with diabetes are considered to be undiscovered.[129, 130] The annual incidence of diabetes in Sweden is 0.2% i.e. 2% per decade.[131] Only a low proportion of the screened population in **Study II** had diabetes (1.6%) while the 10-year risk to develop diabetes was higher than expected (men 8.6%; women 10%). A partial explanation may be that the targeted population in **Study II** belonged to an age-group in which diabetes starts to increase and another reason may be that more people aware of their potential risk choose to answer the FINDRISC questions than those who considered themselves at a low risk. Contradicting this is that the responders and non-responders to the FINDRISC part of the questionnaire had

similar characteristics as regards to gender, age and profession. Unfortunately there was no information available on those who did not answer the Webb-QPS at all.

The investigated population in **Study II,** educated and working in the health-care sector should reasonably have a well-developed health awareness, which may have contributed to both positive and negative selection biases. E.g. by increasing the willingness to answer health related questions or decreasing the interest in responding due to an already established awareness of their own risk pattern. Hospital staff may also have easier access to health-care than the general population and thereby choose a traditional medical consultation rather than a questionnaire as a way to get health related information. The fact that the questionnaire was distributed at the workplace could have provided a barrier. Potentially some responders did not want to share this type of private information with their employer and colleagues. Another potential problem with web-based data collection is availability and experience in the use of computers. This was not a likely concern in the present group where computers are used on a daily basis as a part of work, but must be taken into account in other less computer friendly populations.

A web-based questionnaire makes it possible to calculate and communicate the individual risk for diabetes immediately. This is reassuring for people at low risk while actions may be instituted without delay in those at a high risk as e.g. in the Finnish Type 2 Diabetes Prevention Programme.[132] Another possibility of risk characterisation of an entire organisation is that the employer becomes aware of a high-risk profile among the employees, which may stimulate specifically tailored preventive initiatives for the workplace. An advantage with a web-based questionnaire is that it is easy to repeat providing a follow up both for the individual and for the workplace. Thus the on-line use of FINDRISC may serve as a tool to address prevention on the individual as well as the population level.

Despite the availability of a large number of screening tools for the detection of the risk for diabetes research on their implementation and use in all day practice is limited.[133] The present study provides support for future attempts to implement FINDRISC to a wider audience. A recent review of implementation of diabetes risk assessment tools, including **Study II,** concluded that although risk scores are cheap and effective, physicians often neglect to take advantage of them and little is studied about their implementation.[133] Perhaps a way forward would be to create technical solutions, similar to **Study II**, to identify individuals and even populations at risk outside the traditional health care system.[134] This could relieve the traditional care from working with screening and only direct individuals with increased risk to see a physician.

Strengths and limitations of Study II

To our knowledge this the first time FINDRISC has been used as a web-based screening tool.[133] The large number of individuals participating in the present survey shows that FINDRISC is possible to implement on a larger scale. To further consolidate this finding it would be of interest to make similar web-based screenings in populations outside the health care sector. A weakness is the lack of information on the non-responders to the Webb-QPS.

Management of patients with coronary artery disease and diabetes

A large proportion of the patients in **Studies III and IV** are far from the guideline treatment targets for blood pressure, LDL-cholesterol and HbA1c. There was some improvement comparing the outcome of **Study III** with that of **Study IV.** It was, however, less than aspired considering the European guidelines for the management of patients with diabetes, prediabetes and coronary artery disease 2007, release in between the two studies. A potential reason is a consistent, relatively low combined use of four selected cardioprotective drug therapies. Alternate explanations to the poor target achievement may relate to an incomplete dose titration of individual drugs and lack of patient compliance even though the patients did not report such behaviour.

In **Study III,** conducted 2006-2007, and in **Study IV**, conducted 2012-2013, the combined use of antiplatelet agents (primarily aspirin), β-blockers, RAAS-blockers and statins was 50 and 60% respectively. This shows a positive trend in patients with prevalent diabetes when comparing with EUROASPIRE II[135], conducted 1999-2000, where 23% used four or more out of eight specified drugs and the Euro Heart Survey on Diabetes and the Heart[63] in 2003, where 43% used the four selected drug therapies. It is noteworthy that in **Study IV** patients with prevalent diabetes had the highest use of individual drugs, as well as their combination.

Blood pressure control improved in all groups between **Study III and IV** and was the best in patients with no diabetes. Comparing proportions of patients with no-, incident- and prevalent diabetes reaching a target of 140/90 mmHg, it was 52, 49 and 43% in **Study III** increasing to 68, 61 and 54% in **Study IV**. Both surveys reflect that it is more often difficult to reach an adequate blood pressure control in patients with diabetes in whom a satisfactory control often depends on the combination of three or even four different classes of blood pressure lowering drugs. Even though patients with diabetes had the highest use of RAAS-blockers and β-blockers it seems that further drug classes need to be added or that dosages should be further titrated to reach at least a similar proportion at target as in the group with no diabetes.[136] An important observation in **Study IV** is that there is a group of patients with blood pressure levels well below the recommended targets. Considering the J-shaped curve of blood pressure control with increasing events among coronary patients with pressures considerably and consistently below the recommended level this observation should induce caution.[137]

In **Study III** 12, 11 and 20% of the patients with no-, incident- and prevalent diabetes reached the recommended LDL-cholesterol target of <1.8 mmol/L (<70mg/dL) compared to 16, 18 and 28% in **Study IV** which is an improvement.[138] The target fulfilment may possibly be better since present guidelines state that lowering of the LDL-cholesterol level by 50% is an alternative to a fixed target.[49] The fulfilment of this particular option was unfortunately not possible to explore within the framework of the surveys. Even taking the slight improvement between **Studies III and IV** into account the present findings must be considered as disappointing especially for patients with diabetes, in whom an adequate blood pressure- and LDL-cholesterol control is of crucial importance as demonstrated by the STENO 2 study.[30] When the investigators behind the latter study used the UKPDS risk engine based analysis of the most important contributors to the decreased morbidity and mortality in the intensively managed arm of the trial, lipid control was estimated to be behind 73% of the effect. The corresponding

proportions for blood pressure and glucose control were 11 and 13% respectively.[139] Furthermore a fully developed pharmacological treatment improved one-year survival in patients with diabetes and coronary artery disease to approach the one in those free from diabetes in the Euro Heart Survey on Diabetes and the Heart.[62]

Almost all patients with incident diabetes in **Study IV** were within the HbA1c goal of <7.0% (<53 mmol/mol), indicating that patients with a truly poor glycaemic control had been identified before or in proximity to their index event. Such comparison was not possible in **Study III** since HbA1c was only collected in patients with prevalent diabetes. That patients with newly diagnosed diabetes had a relatively low HbA1c is probably explained by the results in **Study V** in which HbA1c used alone turned out to be very blunt as a diagnostic test. Never the less the number of patients in **Study III, IV and V** with newly detected diabetes indicates that a sizeable proportion of such patients remained undiagnosed during the 6–36 months after their index coronary event.

Glycaemic control in patients with prevalent diabetes had not changed much since **Study III** in which 49% had an HbA1c <7.0% (53 mmol/L) compared to 53% in **Study IV**. More alarming is that one out of ten patients with prevalent diabetes in **Study IV** had an HbA1c >9.0% (>75 mmol/mol). This must be considered unacceptable not the least considering the risk of microvascular complications.[28,140] An explanation to a therapeutic inertia may be recent discussions on the failure of large clinical trials attempting to impact macrovascular events by means of tight glycaemic control.[28,141] It must, however, be underlined that this does not mean that glucose control at a level given by present guidelines has become obsolete. Patients with a relatively short diabetes duration and without a history of cardiovascular complications are still believed to benefit from a more strict glycaemic control.[141] Thus it is still important to care for an individually adapted, reasonable glycaemic control in people with diabetes.[17]

There was no difference between **Study III and IV** in the proportion of patients with a cardiologist as their health-care provider. General practitioners cared for more patients and patients partaking in cardiovascular rehabilitation programmes had increased between the two surveys. Notably, there was a two-fold increase in patients with prevalent diabetes taht saw an endocrinologist. It may be assumed that the higher use of pharmacologic treatment and improved target fulfilment seen in **Study IV** partly relates to the changing pattern of caregivers. Considering the complex nature of the combination of diabetes and coronary artery disease it is reasonable that patients with less well controlled risk factors should be referred to a specialist team with representation of all involved specialties. Furthermore, participation in cardiac rehabilitation and 'diabetes schools' have the potential to improve the personal engagement of the patients assuring better compliance to not the least lifestyle changes.[142] Given the evidence that nurse led programs are achievable and efficient it is hard to understand the low proportion in **Study III** (1-2%) and in **Study IV** (3-5%) that were offered such care.[142] Many patients were seen by multiple healthcare providers, opening for the possibility that none of them took full responsibility for a truly comprehensive management including the use of efficient drug combinations and a proper dose titration.

Following the partially disappointing outcome of the Euro Heart Survey on Diabetes and the Heart[63], the European Society of Cardiology and European Association for the Study of Diabetes joined efforts in 2007 issuing practice guidelines for patients with

Diabetes, Prediabetes and Cardiovascular disease.[116] The comparison between **Study III**, reflecting all day practice before 2007, and **Study IV**, conducted five to six years after the release of the guidelines, can therefore be seen as a measure of the impact of such guidelines. It is reasonable to say that the improvement seen between the surveys relates to the educational efforts made in association of the distribution of the European preventive and diabetes guidelines. This assumption gains support by an evaluation of the distribution and use of the guidelines conducted as part of the EuroHeart II project supported by the European Commission. It revealed that 21 National Cardiac Societies across Europe had endorsed the guidelines. The guidelines has of today been downloaded 34 787 times from the ESC web portal, in addition 5000 paper copies and 7500 pocket guidelines were distributed by the ESC.[143] Based on e-surveys among different networks of European physicians with an interest in prevention and diabetes (cardiologists, primary care and family physicians) it was concluded that almost nine out of ten of those asked had the guidelines at their workplace and that eight out of 10 used them.[143] These improvements show that a change is possible to achieve although it takes time. Still, and considering the disappointingly small improvements, it is evident that there is a great need of further efforts and new ways to distribute knowledge and to get it implemented. Many patients face an unnecessarily poor prognosis due to a less than optimal use of evidence based management. Perhaps the information gained from **Study I** could help to involve other policymakers to further encourage the implementation of the guidelines.

Strengths and limitations of study III and IV

Studies III and IV are large cross-sectional European studies, which enabled the investigation of a large group of well-characterized individuals with coronary artery disease. The methods were standardised and information was collected at a study visit ensuring high quality data. Methods used were at large uniform between the surveys. In **Study IV** a fusion of the Euro Heart Survey on Diabetes[63] and the Heart and **Study III**[138] enabled a comparison over a time period just before and five years after the release of European Guidelines on the management of patients with diabetes and pre-diabetes[17]. The size of the two studies allowed statistically robust comparisons between different glycaemic groups. A drawback is that a large proportion of the (via hospital records) identified patients never attended the interview. One reason is believed to be that contemporary rules on how patients can be contacted in many countries only allow contact via mailed material prohibiting personal contact. Furthermore, **Studies III and IV** likely have a positive selection bias. Participating centres included university hospitals and specialist cardiac centres. Such centres may have a particular interest in cardiovascular prevention. This would, however, if anything underestimate the true problem. In **Study III** the classification of a patient as having incident diabetes was based on only fasting glucose. As made clear by **Study V,** this likely means that 27% of the patients with incident diabetes remained undetected and were included in the group with no diabetes in **Study III**. In **Study IV,** misclassification was limited by the use of a combination of FPG, 2hPG and HbA1c to allocate patients into their respective glycaemic category. According to present recommendations one sample of FPH, 2hPG or HbA1c is not sufficient for a final diagnosis of diabetes, which should be based on at least two measurements. This was, however, not possible due to study logistics but should not be of major importance for the interpretation of the results.

Screening for dysglycaemia in patients with coronary artery disease

The most important finding in **Study V** was that screening by means of an OGTT identified the largest number of patients with undetected diabetes. The overlap in case-detection between FPG, 2hPG and HbA1c was very small. Moreover, screening with HbA1c alone would have left 83% of those with diabetes based on glucose criteria undetected. In addition, the total proportion of patients identified with diabetes and other forms of dysglycaemia varied from 90% using the ADA criteria for FPG + HbA1c, which may be an overestimation, to 73% using the WHO criteria for OGTT = FPG + 2hPG, which may be a more realistic estimate.

Screening with FPG alone is known to leave many patients with diabetes undetected.[24, 144] Recent reports in smaller patient populations with acute coronary syndromes[145], stable coronary artery disease[146] or referral for coronary angiography[147] reveal that a HbA1c ≥6.5% only detects a small proportion of patients with unknown diabetes compared with screening based on OGTT.[148-150] The present study confirms and extends these findings to a broader and larger population of coronary patients. In the Euro Heart Survey of Diabetes and the Heart the proportion of newly detected diabetes and IFG + IGT was 14% and 37% according to the WHO criteria[144] in patients with stable coronary artery disease screened with OGTT. This is lower than the present 28% and 46% in **Study V**. Thus, the proportion of patients with undetected diabetes and IGT appears to have increased since 2003-2004. This highlights the great importance of investigating the glycaemic state of people with coronary artery disease as emphasised in the Joint European Guidelines for Diabetes, Prediabetes and Cardiovascular Disease.[17] The findings in **Study III, IV and V** indicate that such screening is poorly practiced. One reason may be that an OGTT is considered a time-consuming test, and that it is easier to use HbA1c alone or in combination with FPG. Another possible interpretation is that diabetes and other forms of dysglycaemia are becoming more common over time as seen in the general populations.[16]

There was a limited overlap in the detection of dysglycaemia between the three screening methods. When HbA1c was combined with FPG the yield of patients with diabetes increased, approaching but not reaching the proportion identified by an OGTT. Moreover these two methods did not identify the same patient population. An important problem with the combination of HbA1c and FPG, as proposed by the ADA, is that it labeled nine out of ten patients as dysglycemic. The corresponding proportion was 73% applying the OGTT based WHO criteria. In addition an HbA1c between 5.7-6.4% (39-47 mmol/mol) is less predictive than FPG and 2hPG for the risk of developing diabetes.[10, 151] Thus the proportions identified by the WHO criteria based on an OGTT compared with the ADA criteria based on HbA1c + FPG, indicate that the latter overestimates the prevalence of people at high risk for diabetes but underestimates the prevalence of previously undiagnosed diabetes in patients with coronary artery disease. The present results support that the WHO recommendation[14] should be kept due to the significant increase in the prevalence of IFG with a lower cut-point. This impacts not only individuals but health-care providers as well. There is solid evidence for people with IGT, as detected by an OGTT, that lifestyle and pharmacologic interventions can reduce progression to diabetes by about 50%.[17] Such evidence is not yet available for people with IFG and high risk HbA1c.

Under-diagnosing dysglycaemia would be less important if this state had little or no impact on the future prognosis of patients with coronary artery disease.[26, 27, 63, 152-156] In addition the 2hPG from an OGTT provides additive prognostic information. There is a stronger association between the 2hPG and the level of carotid intima media thickness, extent of coronary artery disease as well as cardiovascular risk according to the Framingham score than for FPG and HbA1c.[157, 158] In fact the relationship between FPG or HbA1c and the future risk for cardiovascular mortality is completely blunted following correction for post load glycaemia and other cardiovascular risk factors.[95] Additionally, people with IGT (i.e. diagnosed by a high 2hPG) are more prone to cardiovascular disease progression than those with IFG, while such information is limited regarding HbA1c.[154, 159] Moreover, HbA1c between 5.7-6.4% (39-47 mmol/mol) is less sensitive than IFG and IGT to detect individuals with β–cell dysfunction and insulin resistance.[151]

Over-diagnosing dysglycaemia due to low thresholds of FPG and HbA1c may have negative implications causing patient anxiety and unnecessary use of health care resources. Future clinical practice should evaluate potential differences in prognostic implication by the three tests used to detect previously unknown dysglycaemia in patients with coronary artery disease. When dysglycaemia is discovered in a patient with coronary artery disease, a clinician should be alerted to the high risk for recurrent coronary events and mortality. This risk can, however, be lowered, approaching that of normoglycemic patients, through multifactorial management, including lifestyle, pharmacotherapy and revascularization, as recommended by the current guidelines.[17, 30, 49, 62, 63] Given the low yield of an isolated HbA1c it is perhaps better to abstain from this test in patients with coronary artery disease if resources are scarce, until more data supporting its value is available or algorithms intended to limit the use of OGTT are properly validated.[149, 160]

The OGTT has been criticized for high variability. This may relate to a dichotomization of the continuous variable plasma glucose. Wallander et al[161] performed an OGTT at five days, three months and 12 months after an acute myocardial infarction in 122 patients. Of those who were diagnosed with diabetes at discharge from hospital, 93% were still classified as dysglycemic (diabetes 64%; IGT 29%) after 12 months indicating that an OGTT is a reliable test of dysglycaemia over time. These results were recently verified by a Spanish study that performed OGTT in patients at the occasion of PCI and repeated three years later.[149] A way to further simplify the procedure of the OGTT might be to use point-of-care technology as used in **Study V,** providing immediate test results.[119]

Finally, there are discrepancies in the views expressed in different guidelines and by expert groups on what levels should define a patient as being at high risk of developing diabetes based on FPG and HbA1c.[10, 17, 98, 162] The OGTT is the only method on which there is an agreement on the definition of "high risk" i.e. IGT.[10] There is a need for further research on the clinical value of the high-risk classification by FPG and HbA1c, before it is integrated into clinical practice as an evidence-based recommendation for patients with coronary artery disease.

Strengths and limitations of Study V

Study V is the largest study that, to the best of our knowledge, compares the three currently recommended screening tests for dysglycaemia in patients with coronary

artery disease. In addition the same strengths and limitation as already discussed for **Study IV** can be applied.

Ethical considerations of screening

In **Study II** a large population was subjected to a screening procedure. It is important to consider if opening a possibility for preventative initiatives in high risk people outweighs the worries raised by informing them on their situation and asking them to change their lifestyle. Another question to address is whether the recourses used are spent in the best health promoting way. Looking at the Wilson-Jungner criteria, screening for diabetes covers an important health problem and has been brought forward as a prioritised area by several organisations.[52, 106] The pathophysiology of diabetes is well known and an early detection and early institution of treatment decreases or postpones the onset of diabetes. There are available programs within the already existing health care system to take care of people identified with a high risk for diabetes. An outstanding question has been whether future micro- and macrovascular disease can be prevented by a programme based on lifestyle interventions. Observations in this direction have been identified as reviewed by Paulweber et al[19]. These observations have recently gained strong support by long term follow up data from the randomised, prospective Chinese Da Qing study showing a reduction of serious retinopathy[163] and even cardiovascular- as well as all-cause mortality[20] in people with IGT subjected to a programme incorporating weight reduction and promotion of physical activity. These new data strongly supports that screening for IGT should be encouraged. The cost for the screening program, especially if performed online, is judged reasonably small in comparison with the potential savings by preventing disease. Participation should, however, as always in such circumstances be voluntary. Furthermore, and seen from a population perspective, repeated screening on a larger scale provides important epidemiological information on the direction of changes in important factors for public health. Potential population wide interventions could be commenced if the risk seems to rise in the population. Thus FINDRISC enables something as unusual as combining a high-risk approach together with a population wide approach if done on a larger scale.

Study V differs from an ethical point of view than **Study II**. This study involved screening in patients with a very high likelihood for diabetes and in whom the derived information has important prognostic information and implications for future management. Accordingly such screening should have high priority as indeed underlined by available guidelines.[17] In this context an important ethical question is what test and what criteria to be preferred and what potential consequences it will have. The ADA criteria based on FPG and HbA1c classifies 90% of a coronary population as dysglycaemic without any available evidence that this is advantageous in terms of treatment or prognosis. Thus the label of dysglycaemia will be put on patients where the health-care system will have no evidence based treatment to offer, likely with both economic and personal consequences. In contrast there is evidence based information on both the prognostic value and benefits of prevention of patients screen detected with IGT or diabetes according to the WHO OGTT based criteria. Thus, based on the Wilson-Jungner criteria the OGTT should be the first hand choice at least until there is an agreement and evidence available for another test.

Future perspectives

Cardiovascular disease and diabetes are responsible for just over half of the global mortality, and these diseases are expected to increase. The upsugre is due to increased logevity and a westernisation of the global lifestyle. Preventive efforts have proven effective and are believed to be the only way to curb the rapid increase of these diseases. Thus the question on how to implement what we know into clinical practice and population wide interventions are more important than ever.

On a population level more knowledge on how health is formed through e.g. societal planning, culture and history is needed rather than further investments in the search for, nowadays, often minor improvements in cardiovascular disease management. So far only small fractions of health-care budgets have been dedicated to prevention, while a larg amount is allocated to the diagnosis and treatment of non-communicable disease that can be postponed but often not cured.[164, 165] Importantly researchers and health care personnel should study the political arena and take action at that stage expanding their influence on how health care is planned and budgeted. As already underlined in this thesis it is only through population initiatives that large changes in the prevalence of cardiovascular disease and diabetes can be made. Accordingly such measures deserve much more attention than they have gotten so far.

The use of web-based screening and health tools have great potential and will likely be more common in the near future. The concept of using screening online offers an opportunity to identify high-risk individuals as well as organisations and potentially also entire communities. Risk typing different parts of a region would provide a basis to further study how societal planning, culture and the workplaces affect our health. Furthermore, online tools provide the opportunity to give instant feedback and an interesting scenario would be to develop an online prevention program, perhaps supplemented by advice via a web-based platform for personal questions answered by trained personnel.

To further improve and simplify guideline compliance checklists and order sets incorporated in electronic medical records would be interesting to study. In these systems the doctor and the patient could become automatically alerted if a target is not reached. Such an alerting system may activate improved management or a note in the patient record on why, in a specific situation, treatment can or should not be driven further.[166] This strategy might help to decrease the impact of both doctor and patient inertia that is often seen in the management of cardiovascular risk factors.[167]

Furthermore, the forms for an efficient and feasible transfer of patients from hospital to the outpatient care should be further studied in an attempt to improve their management.[168] An observation from the recruitment of patients in **Study IV and V** was that the information provided in the final medical note was often incomplete and lacked a plan for the future care. In this perspective education, not only of the healthcare providers, but also the patients and their relatives, may serve as a tool to accomplish better transfer and treatment between health-care providers. Patients would be more involved in their care, taking joint responsibility and working towards the same targets as their health-care provider.[169] Such a position is strongly supported in the most recent issue of the European Guidelines for Diabetes, Prediabetes and Cardiovascular Disease in which a chapter has been added on Patient Centred Care.[17]

Regarding diagnosis of diabetes there is a need from a clinical point of view to create a helpful algorithm on what glucose measures should be used when, where and in what order of priority. It would be helpful if cut-off levels could be identified for each measure where no other glucose tests are positive for diabetes. Another intriguing scenario would be to identify a level for FPG, 2hPG or HbA1c where patients with and without diabetes have an increased cardiovascular risk, in analogy with the current diagnostic thresholds for diabetes, which are related to retinopathy.

Conclusions

1. Policymakers in Europe perceive that we are far from the targets outlined in the European Heart Health Charter but differ on what they see as important obstacles and actions needed to improve cardiovascular health in their country. Their perception of national obstacles to improved cardiovascular health did not necessarily correspond with the actual situation.

2. Creating a coherent knowledge base and action agenda regarding prevention among policymakers seem to be a key element in future programmes aiming at prevention.

3. The online questionnaire FINDRISC is a feasible way to identify high-risk individuals and risk-type a workplace population.

4. Patients with coronary artery disease, with and without diabetes, are to a relatively low extent managed according to the European Practice Guidelines, although adherence seems to improve over time.

5. Improved efforts must be made to increase guideline adherence, not the least in patients with a combination of cardiovascular disease and diabetes who have a poor prognosis.

6. An oral glucose tolerance test has the best capacity to screen-detect dysglycaemia in patients with coronary artery disease.

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