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SCREENING STRATEGIES FOR DYSGLYCAEMIA IN RELATION TO CARDIOVASCULAR RISK

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Screening strategies for dysglycaemia in relation to cardiovascular risk

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“There is nothing so stable as change”
-Bob Dylan

ABSTRACT

Background: Dysglycaemia, defined as type 2 diabetes (T2DM) or impaired glucose tolerance (IGT), is a major risk factor for cardiovascular disease (CVD). Dysglycaemia and CVD together account for more than half of worldwide mortality. Despite abundant evidence stressing the need for early detection and improved cardiovascular prevention in patients with dysglycaemia, approximately 50% of people with T2DM are undiagnosed. The early identification of dysglycaemia is key to initiating lifestyle changes and pharmacological interventions successfully to prevent cardiovascular complications.

Aims: The general aim of this thesis was to evaluate different screening strategies for dysglycaemia with respect to CVD. There were four specific goals:

1) Compare the prognostic value of fasting plasma glucose (FPG), 2h postload glucose (2hPG) and HbA1c in patients with coronary artery disease (CAD) (**Study I**)
2) Study the prevalence of dysglycaemia in people treated for hypertension and/or dyslipidaemia but without CVD and examine whether using the Finnish Diabetes Risk Score (FINDRISC) decreases the need for blood tests in this patient population (**Study II**)
3) Examine the effectiveness of different outreach strategies to detect people at high risk of T2DM and/or CVD using FINDRISC (**Study III**)
4) Study the accuracy of a point-of-care technique used for glucose measurement compared with laboratory-based methods (**Study IV**).

Methods: Studies I and **II** were based on data from the EUROASPIRE IV survey, a multicentre study of two large cohorts of patients, providing both questionnaire data and blood samples: one patient cohort with established CVD and one with hypertension and/or dyslipidaemia but without established CVD. In **Study III**, FINDRISC questionnaire data were collected through several outreach channels in the municipality of Södertälje. Response rate, risk level and cost effectiveness were compared across channels. In **Study IV**, glucose measurement data from the same patients using different laboratory methods were obtained from the EUROASPIRE V survey.

Results: In **Study I**, 4,004 patients with CAD but no history of dysglycaemia at baseline were followed for a median of 2.03 years. The 2hPG was a significant predictor of future cardiovascular events ($p=0.01$) in contrast to FPG ($p=0.45$) or HbA1c ($p=0.36$).

In **Study II**, of 2,395 patients with hypertension and/or dyslipidaemia but no history of dysglycaemia, 19% had undetected T2DM and 20% IGT. Contrary to the hypothesis, a relatively large proportion of patients with low FINDRISC scores had dysglycaemia.

In **Study III**, the highest response rate to the FINDRISC was obtained through workplaces. The largest proportion of individuals at high risk (≥15/26 points) were outreached through the Syrian Orthodox church. The cost of identifying a person at high risk varied greatly depending on the choice of outreach strategy.

Finally, in **Study IV**, glucose values obtained from the HemoCue® point-of-care system correlated well with gold standard hospital laboratory measurements (FPG $r=0.94$ and 2hPG $r=0.96$; $p<0.05$) in CAD patients in the EUROASPIRE V survey.

Conclusions: Future cardiovascular events were only predicted by 2hPG in the present cohort of CAD patients. A large proportion of patients with CVD risk factors but without established CVD had undetected dysglycaemia. The use of the FINDRISC did not reduce the need for blood testing in patients with hypertension and/or dyslipidaemia. The outreach strategy affected participation rate, risk level and cost in a large-scale dysglycaemia screening. The HemoCue® point-of-care system is accurate for dysglycaemia screening, which should save time and costs when performing OGTT.

SAMMANFATTNING

Bakgrund: Dysglykemi, definierad som typ 2 diabetes (T2DM) eller nedsatt glukostolerans (IGT), är en allvarlig riskfaktor för kardiovaskulär sjukdom (CVD). Tillsammans står dessa två tillstånd för drygt hälften av alla dödsfall globalt. Screening för dysglykemi är viktigt för att tidigt upptäcka och initiera behandling och därmed förbättra prognosen för denna patientgrupp. Trots detta beräknar man att ungefär 50% av alla individer med T2DM är oupptäckta.

Mål: Huvudsyftet med denna avhandling var att undersöka olika screeningstrategier för dysglykemi i relation till kardiovaskulär sjukdom via fyra specifika delmål:

1) Jämföra det prognostiska värdet av fasteblodsocker (FPG), två timmars glukosbelastning (2hPG) från ett oralt glukostoleranstest (OGTT) och HbA1c avseende framtida kardiovaskulära händelser hos individer med kranskärlssjukdom **(studie I)**.
2) Undersöka prevalensen av dysglykemi med FPG, 2hPG och HbA1c hos patienter utan kranskärlssjukdom under behandling för de kardiovaskulära riskfaktorerna hypertoni och/eller dyslipidemi samt undersöka om användning av riskskattningsformuläret FINDRISC i ett första screeningsteg skulle kunna minska behovet av blodprover **(studie II).**
3) Undersöka effektiviteten beroende på val av kommunikationskanal vid storskalig screening för dysglykemi (**studie III**).
4) Undersöka hur tillförlitlig patientnära teknik är för mätning av blodglukos jämfört med ackrediterade metoder vid sjukhuslaboratorier (**studie IV**).

Metoder: Studie I och **Studie II** baserades på den europeiska multicenterstudien EUROASPIRE IV, som inkluderar en kohort av patienter med och en utan kranskärlssjukdom men den senare med kardiovaskulära riskfaktorer. Dessa patienter screenades med blodprover och riskskattningsformulär. I **Studie III** användes flera kommunikationskanaler för att screena för dysglykemi med hjälp av FINDRISC bland Södertäljes invånare. Deltagandegraden, risknivån samt kostnadseffektiviteten för de olika kanalerna jämfördes. I **Studie IV** analyserades blodglukos från patienter inkluderade i EUROASPIRE V med både HemoCue®, patientnära teknik och standard-metoder på ackrediterade laboratorier.

Resultat: I **Studie I** gav 2hPG prognostisk information (p=0.01) avseende framtida kardiovaskulära händelser hos 3775 patienter med kranskärlssjukdom. FPG (p=0.45) och HbA1c (p=0.36) var ej prognostiska indikatorer. I **Studie II** var prevalensen av okänd T2DM 19% och IGT 20% hos 2395 patienter med hypertoni och/eller dyslipidemi. Prevalensen av tidigare oupptäckt dysglykemi var relativt hög även i de lägre riskkategorierna enligt FINDRISC. I **Studie III** var arbetsplatser den kanal som hade högst deltagandegrad vid screening med FINDRISC. Däremot var den syrisk ortodoxa kyrkan den kommunikationskanal som hade störst andel högriskindivider (≥15/26 poäng enligt FINDRISC). Kostnaden för att identifiera en högriskindivid varierade stort beroende på val av kommunikationskanal. I **Studie IV** hade HemoCue® patientnära teknik god överensstämmelse med standardmetoderna på sjukhuslaboratorierna (FPG r=0.94 and 2hPG r=0.96; p<0.05).

Slutsatser: Bland de tre rekommenderade testerna för screening av dysglykemi var 2hPG den enda som kunde predikterade risken att insjukna i en ny kardiovaskulär händelse under en tvåårsperiod hos patienter med CAD. En hög andel av primärvårdspatienter behandlade för hypertoni och/eller dyslipidemi hade tidigare oupptäckt dysglykemi. FINDRISC var inte ett tillförlitligt första screeningsteg. Val av kommunikationskanal för storskalig screening verkar spela stor roll, både för att få hög deltagandegrad, risknivå och öka kostnadseffektiviteten. Den patientnära glukosmätningstekniken, HemoCue®, var tillförlitlig för screening av dysglykemi.

LIST OF SCIENTIFIC PAPERS

I

Shahim B, De Bacquer D, De Backer G, Gyberg V, Kotseva K, Mellbin L Schnell O, Tuomilehto J, Wood D, Rydén L

The prognostic value of Fasting Plasma Glucose, Two-hour Postload Glucose and HbA1c in patients with coronary artery disease.

A report from EUROASPIRE IV, a survey from the European Society of Cardiology

Diabetes Care 2017 Sep;40(9):1233-1240

II

Shahim B, Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Tuomilehto J, Wood D, Rydén L

Undetected dysglycaemia common in primary care patients treated for hypertension and/or dyslipidaemia: On the need for a screening strategy in clinical practice.

A report from EUROASPIRE IV, a registry from the EuroObservational Research Programme of the European Society of Cardiology

Cardiovascular Diabetology 2018 Jan 24;17(1):21

III

Shahim B, Bolt Christmas O, Gyberg V, Hasselberg S, Mellbin L, Rydén L

Effectiveness of different outreach strategies to identify individuals at high risk for diabetes in a heterogeneous population

A study of the Södertälje municipality in Sweden

European Journal of Preventive Cardiology 2018 Dec;25(18):1990-1999

IV

Shahim B, Kjellström B, Gyberg V, Jennings C, Smetana S, Rydén L

The Accuracy of Point-of-care Equipment for Glucose Measurement in Screening for Dysglycaemia in patients with Coronary Artery Disease

A report from EUROASPIRE V, a registry from the EuroObservational Research Programme of the European Society of Cardiology

Diabetes Technology & Therapeutics 2018 Sep;20(9):596-602

CONTENTS

LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
ADDITION	Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CABG	Coronary Artery By-pass Graft surgery
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
DECODE	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe
ESC	European Society of Cardiology
EUROASPIRE	EUROpean Action on Secondary and Primary prevention In order to Reduce Events
FINDRISC	Finnish Diabetes Risk Score
FPG	Fasting Plasma Glucose
HADS	Hospital Anxiety and Depression Score
HbA1c	Haemoglobin A1c
HDL	High Density Lipoprotein
HR	Hazard Ratio
IDF	Internationl Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
LADA	Latent Autoimmune Diabetes in Adults
LDL	Low Density Lipoprotein
OGTT	Oral Glucose Tolerance Test
PCI	Percutaneous Coronary Intervention
TIA	Transient Ischaemic Attack
2hPG	2 hour Postload Glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

1 INTRODUCTION

1.1 DYSGLYCAEMIA

1.1.1 History

Reference to polyuria, one of the main symptoms of diabetes, is made as early as 1500 BC in the Papyrus of Ebers written by Hesy-Ra (Figure 1).[1,2] The Indian physicians, Charaka and Sushruta (400-500 AD), recognised diabetes as a syndrome with the hallmark of honey-like urine. They also identified "krisha" (asthenic) individuals who developed diabetes earlier in life compared with "sthula" (obese) individuals who had a later and slower disease onset.[3] The Greek physician, Aretaeus of Cappadocia, who lived in the first century AD, is credited with the first accurate description of the disease likening it to *"a remarkable affliction... being melting down of the flesh and limbs into urine.....The flow is incessant, as if from the opening of aqueducts.....; It takes a long period to form.....; But the patient is short-lived.....; For, the melting is rapid, the death speedy.....; one cannot stop them either from drinking or making water.....they are affected by nausea, restlessness and a burning thirst, and at not distant term they expire"*.[4] The term "diabetes"**,** meaning *'to go through'* or '*siphon' (dia=through, bêtes=to go),* is believed to have been coined by Apollonius of Memphis in 250 BC. The term 'mellitus' (*=from honey*) was added by Thomas Willis at Oxford in 1674.[2]

Figure 1. Ebers Papyrus (left) and Hesy-Ra (right)[7]

In the past two centuries, research has improved our understanding of the pathogenesis and treatment of diabetes. In 1869, Paul Langerhans reported on two cellular systems in the pancreas and several years later one of them was named the "islets of Langerhans".[5] In 1889, Joseph von Mering and Oskar Minkowski demonstrated that dogs in which the pancreas had been removed developed diabetes.[6] This discovery was important for the future experiments by a quartet of researchers at the University of Toronto, Frederick Banting, Charles Best, JJR Macleod and James Collip, who, in 1921, extracted pancreatic gland serum from dogs that could reverse hyperglycaemia.[2] Their discovery of insulin dramatically changed the lives of patients with diabetes. Frederick Banting and JJR Macleod were awarded the Nobel Prize in Medicine in 1923. However, Frederick Banting shared his prize money with Charles Best, while JJR Macleod shared his with James Collip.

In 1939, a study of autopsies of patients with diabetes reported an association between diabetes and cardiovascular disease (CVD).[8] In the 1940s, CVD was the main cause of death in the USA.[9] To clarify the cause of CVD, the US Public Health Service embarked upon the first large-scale cardiovascular epidemiology study in 1948, the Framingham Heart Study, which identified several cardiovascular risk factors, including hyperlipidaemia, hypertension and, not least, T2DM.[9] The latter condition increases the risk of CVD two to four times and together T2DM and CVD account for more than half of the global mortality.[10] The cardiovascular complications of glucose perturbations already begin to develop in prediabetic states such as impaired glucose tolerance (IGT).[11,12] This is the reason why IGT and T2DM are clustered as dysglycaemia in the present PhD project.

One problem with dysglycaemia is that it remains undiagnosed for many years. As many as 50% of people with T2DM were undiagnosed in 2017, according to the International Diabetes Federation (IDF).[13] The identification and multifactorial management of individuals with dysglycaemia is crucial for the prevention of CVD. The overarching aim of this thesis was to bridge gaps in knowledge regarding dysglycaemia screening with respect to CVD.

1.1.2 Definition and classification

The WHO and the American Diabetes Association (ADA) have defined diabetes as a group of metabolic disorder characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.[14,15] The development of diabetes involves several pathogenic processes, from the autoimmune destruction of the pancreatic beta cells, with insulin deficiency as a consequence, to different types of abnormality that result in resistance to insulin action. The first unified classification of diabetes, based on insulin dependence, were developed by the National Diabetes Data Group in 1979[16], followed by the WHO in 1980.[17] Diabetes is currently classified as belonging to one of the four main aetiological categories described below, as proposed by the ADA in 1997[15] and the WHO in 1999.[14]

Type 1 diabetes mellitus (T1DM) accounts for 5-10% of all diabetes and is characterised by autoimmune or idiopathic beta cell destruction of the pancreas, leading to absolute insulin deficiency. The onset usually occurs early in life, but it can occur at any age; for example, latent autoimmune diabetes in adults (LADA) where, despite the presence of islet antibodies, the progression of autoimmune beta cell failure is slow.

Type 2 diabetes mellitus (T2DM) accounts for 90-95% of all diabetes. The specific aetiologies are not known, but the autoimmune destruction of beta cells does not occur. However, deficient insulin secretion, frequently in the setting of insulin resistance in the liver and muscle, appears to be the common denominator. To compensate for the insulin resistance, the pancreatic beta cells initially increase their insulin production.[18] With time, the beta cells fail to compensate for the insulin resistance and, as a consequence, the postprandial glucose levels and subsequently also the fasting glucose levels become elevated. At the time of diagnosis, up to 80% of beta cell function is considered lost.[19] The onset of T2DM can be very discreet, with minor symptoms, and the condition may remain undiagnosed for several years. Older people, people with obesity, lack of physical activity, hypertension and/or dyslipidaemia run an increased risk of developing this form of T2DM. Some racial/ethnic subgroups also run a higher risk and this is often associated with a strong complex and not clearly understood genetic predisposition. T2DM is the focus of this thesis.

Gestational diabetes is diabetes that is diagnosed in the second or third trimester of pregnancy, without being related to already existing T1DM or T2DM. It affected an estimated one in seven births in the world in 2017.[13] A meta-analysis of cohort studies following women with gestational diabetes between 1960-2009 reported that they had at least a seven-fold increase in the risk of developing T2DM in the future compared with those who were normoglycaemic during their pregnancies.[20]

Other specific types of diabetes account for a relatively small proportion of diabetes. This group comprises genetic defects in beta cell function or in insulin action, diseases of the exocrine pancreas, diabetes induced by drugs, infections, uncommon forms of immune-mediated diabetes and diabetes associated with other genetic syndromes.

1.1.3 Diagnostic criteria

The current diagnostic criteria for diabetes (Table 1) were issued by the WHO and the ADA.[21–23] Today, three diagnostic tests are recommended: fasting plasma glucose (FPG), two-hour postload glucose (2hPG) from an oral glucose tolerance test (OGTT) or glycated haemoglobin A1c (HbA1c). FPG is the level of blood glucose measured after at least eight hours of fasting. It reflects the hepatic glucose output during the night.[24] During an OGTT, 75 g of glucose dissolved in 200 ml water is rapidly ingested. Glucose samples are taken before (FPG) and after (2hPG) to determine how quickly it is cleared from the blood. The 2hPG reflects insulin resistance in peripheral tissues and/or reduced capacity of the pancreatic beta cells to produce insulin.[25] HbA1c represents the 'weighted average' of blood glucose during the preceding 120 days corresponding to the lifetime of the erythrocytes. Specifically, it measures the proportion of the haemoglobin which has been glycated ("coated with sugar").[26]

Regardless of method, the diagnostic thresholds are related to a level above which diabetes-induced retinopathy starts to develop.[28] The cut-off points were derived from cross-sectional studies including Pima Indians, an Egyptian study and the Third National Health and Nutrition Examination Survey examining retinopathy across different glycaemic levels.[15]

In 1985, the WHO stated that epidemiological studies should be restricted to the use of 2hPG, only because the fasting state can rarely be assured and because of the strong correlation between FPG and 2hPG.[29] Since then, the two-hour 75 g OGTT has been an international standard for T2DM diagnosis. In 1997, the ADA expert group proposed that the diagnosis of T2DM for epidemiological purposes should be based on FPG alone and did not recommend the 2hPG.[15] The goal of this recommendation was to standardise and facilitate screening for T2DM, since many people with T2DM remained undiagnosed. The ADA acknowledged that this approach would probably underestimate the prevalence of T2DM compared with the OGTT. To include subjects whose OGTT would have been conclusive for diabetes or IGT, the ADA lowered the FPG cutoff value from 7.8 mmol/L to 7 mmol/L. HbA1c, historically used for monitoring glycaemic control and to identify patients with a high risk of microvascular complications, was added as a diagnostic tool for T2DM in 2010 by the ADA[23] and adopted by the WHO in 2011.[22]

Prediabetic states, characterised by glucose values ranging between normal levels and the cut-off for diabetes, include impaired glucose tolerance (IGT = elevated postprandial blood glucose detected by an OGTT), impaired fasting glucose (IFG = elevated fasting glucose) and high-risk HbA1c according to the ADA. In 2003, the ADA lowered the cut-off point for IFG to 5.6 mmol/L, as the prediction of T2DM over a five-year period appears to increase in data analyses in the Pima Indian, Mauritius, San Antonio and Hoorn studies.[30] In the Mauritius study, for example, the incidence was about 15% for a FPG of 5.5-5.7mmol/L compared with 32% for a FPG of 6.1-6.9 mmol/L.[31] Due to the lack of evidence of benefits in terms of reducing progression to T2DM and cardiovascular events, the WHO did not adopt the lower ADA threshold for IFG.[21] Nor has the WHO adopted high-risk HbA1c, as there does not appear to be a specific level at which the risk of T2DM clearly begins.

Table 1. Comparison of the World Health Organisation (WHO) and American Diabetes Association (ADA) diagnostic criteria for dysglycaemia. All tests are to be repeated twice, except elevated random plasma glucose when symptoms are present.

Dysglycaemic category	WHO 2006[21], 2011[22]	ADA 2018[32]
Type 2 diabetes mellitus		
HbA1c (DCCT[1]/IFCC[2])	≥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)
Random plasma glucose	Symptoms + ≥11.1 mmol/L (≥200 mg/dL)	Symptoms + ≥11.1 mmol/L (≥200
Impaired glucose tolerance		
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
Impaired fasting glucose		
FPG	6.1-6.9 mmol/L (110-125 mg/dL)	5.6-6.9 mmol/L (100-125 mg/dL)
2hPG	<11 mmol/L (<200 mg/dL)	<11 mmol/L (<200 mg/dL)
High-risk HbA1c	x	5.7-6.4% (39-47 mmol/mol)

[1]Standardised to the Diabetes Control and Complications Trial (DCCT) assay.
[2]The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a new reference method that measures the concentration of only one molecular species of glycated haemoglobin A1c (HbA1c) (mmol/mol).[33] FPG= Fasting Plasma Glucose; 2hPG=2 hour Postload Glucose.

1.1.4 Symptoms and complications of dysglycaemia

Symptoms indicating diabetes include thirst, polydipsia, polyuria, weight loss, sometimes with polyphagia, and blurred vision.[22] Children with T1DM typically present with polyuria/polydipsia, while approximately one-third present with life-threatening diabetic ketoacidosis.[34] Regardless of the pathophysiology of diabetes, chronic high blood glucose levels are associated with long-term damage, dysfunction and the failure of different organs.

Microvascular complications of diabetes include retino-, nephro- and neuropathy and are closely related to glycaemic level.[35] The macrovascular complications, comprising coronary artery disease (CAD), peripheral vascular disease and ischaemic stroke, may start to develop several years before the glucose rises in people with T2DM, as illustrated in Figure 2, and the underlying mechanisms are not fully understood. In addition, recent studies suggest that heart failure is an important and probably underestimated diabetes-related complication.[36]

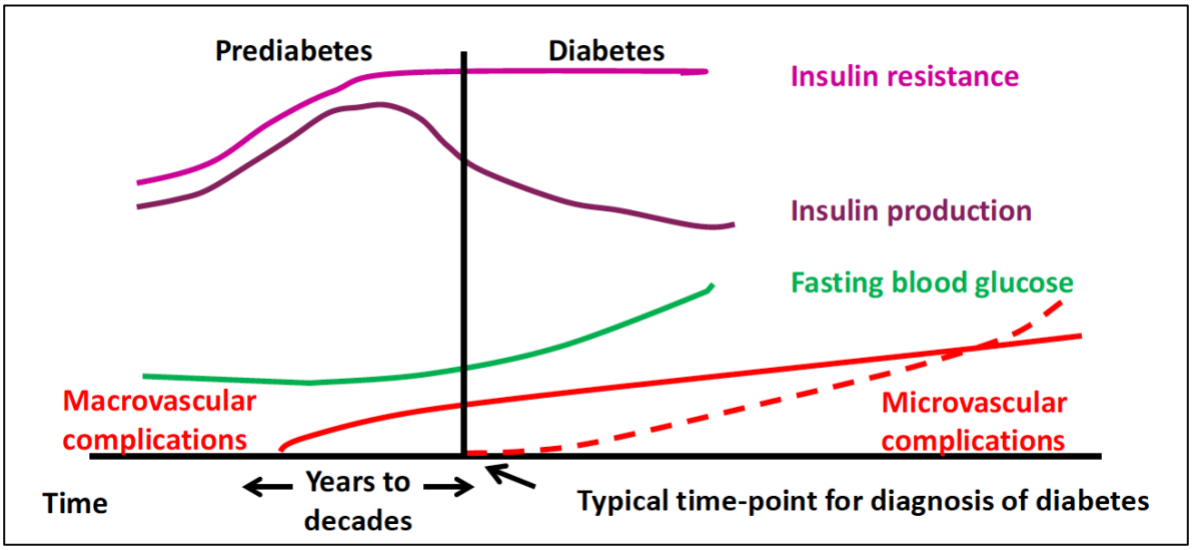


Figure 2. Progress of dysglycaemia and its relationship to macro- and microvascular complications. Adapted by permission from Laakso et al.[37]

1.1.5 Epidemiology of dysglycaemia

Diabetes is currently the seventh most common cause of death in the world.[38] The estimated care costs for people with diabetes are about 673 billon US dollars a year, corresponding to 12% of global health expenditure.[13] According to the IDF, the global prevalence of T2DM is expected to increase from 425 million adults in the 20- to 79-year age groups (8.8% of the global population) in 2017 to 629 million people (9.9% of the global population) in 2045.[13] The Global Burden of Diseases, Injuries and Risk Factors study reported that the mean FPG increased by 0.07 mmol/L per decade or more between 1980 and 2008.[39] The more recent Non-Communicable Disease Risk Factor Collaboration, including studies based on at least a FPG, 2hPG or HbA1c, reported an increasing global prevalence between 1980-2014 from an estimated 4.3% to 9.0% in men and 5.0% to 7.9% in women.[40] About 28% of this increase was estimated to relate to a true rise in the prevalence, 40% due to increased longevity in the population and 32% due to interaction between these two factors. T2DM prevalence was lowest in north- and south-western Europe, around 5-6%. The western countries in general appear to be experiencing a plateau in the incidence of T2DM. At the other extreme, T2DM prevalence was higher than 20% in Polynesia and Micronesia and around 15% in Melanesia and in the Middle East and North Africa. In these regions, there is also an increase in prevalence among younger people and at a lower body mass index (BMI), compared with western populations.

1.1.5.1 Swedish data

A sedentary lifestyle and the prevalence of obesity are increasing in Sweden.[41] Accordingly, a rise in the prevalence and incidence of T2DM could be expected, but no such clear trend has been observed in a number of studies. In a cross-sectional study from northern Sweden, the prevalence of T2DM was 5.8% and 6.5% in men and women respectively, without any clear increase between 1990 and 2009.[42] In a longitudinal study initiated in 1972 at the primary healthcare centre in Laxå, an increase in the prevalence of T2DM was observed between 1972-1988, from 2.8% and 2.6% in 1972 to 4.5% and 4.6% in 1988 in women and men respectively, but no increase was observed between 1988-2001.[43] The incidence rate for T2DM was 0.3%, without any increase between 1972-2001. In contrast, another study, based on the Swedish national drug prescription registry, reported an increasing prevalence of T2DM between 2007-2013 from 5.8% to 6.8% but with a stable incident rate of 0.4% in 2013.[44] The authors estimated that, with a constant incidence and continued improvement in relative survival, the prevalence will increase to 10.4% in 2050. Furthermore, the prevalence of diabetes among immigrants from the Middle East is approximately two times higher compared with Swedish-born subjects.[45,46] Because the numbers in this group of immigrants have increased considerably in recent years,[47] the total prevalence of diabetes in Sweden will probably increase.

1.1.6 Risk factors for dysglycaemia

1.1.6.1 Demographic risk factors

Age is an important risk factor, as approximately 50% of all patients with T2DM are older than 60 years.[13] Heredity also appears to be an important factor, but its impact seems to differ considerably between different populations and in different environments.[48] Ethnicity and migration are also reported as independent risk factors.[49] A literature review of immigrants in the Nordic countries reported an excess risk of T2DM in non-European immigrant groups, in some cases 10 times the risk of the indigenous population.[50]

1.1.6.2 Lifestyle-related risk factors

The American Nurses' Health Study, following nurses free from T2DM and CVD for 16 years, reported that those with normal body 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 of T2DM than those without these lifestyle traits.[51] Obesity was the strongest risk factor for the development of T2DM in the Nurses' Health Study. It is estimated that obesity explains more than 80% of all cases. In spite of this, several risk factors interact and T2DM is often clustered with other risk factors, including hypertension, dyslipidaemia, insulin resistance and abdominal obesity, a combination usually referred to as the 'metabolic syndrome'.[52] Importantly, a combination of two or more risk factors multiplies the risk of CVD.[53]

1.2 CARDIOVASCULAR RISK

1.2.1 Cardiovascular disease

1.2.1.1 Epidemiology of cardiovascular disease

CVD is currently the most common cause of mortality in the world.[38] According to the WHO, 17.9 million people died from CVD in 2016, accounting for 31% of all global deaths. The incidence of CVD is increasing worldwide, especially in low- and middle-income countries where an estimated 75% of CVD deaths occur. CVD is responsible for 10% of disability-adjusted life years (DALYs) lost in low- and middle-income countries and 18% in high-income countries.[54] In Europe, CVD caused 3.9 million deaths in 2017, accounting for 45% of all deaths in the region.[55] Cardiovascular mortality has declined substantially in high-income countries over the past two decades, but both the absolute number of CVD deaths and morbidity have increased, due to a combination of increased longevity and improved survival in manifest CVD.[56]

1.2.1.2 Pathophysiology of cardiovascular disease

Approximately 80% of deaths due to cardiovascular causes, such as acute myocardial infarction (AMI) or stroke, are related to atherosclerosis,[54] a chronic and systemic condition of inflammation and lipid accumulation in the arterial wall.[57] The condition is built up over decades, as illustrated in Figure 3.[58] Atherosclerosis stiffens the vessel wall and eventually results in the formation of a plaque. Plaques can produce flow-limiting stenosis that lead to tissue ischaemia or, due to fissuring, provoke thrombosis that can impede blood flow locally (Figure 3d) or embolise and lodge in distal arteries.[57] Other cardiovascular causes of morbidity and mortality include cardiomyopathies, cardiac arrhythmias, congenital heart disease and rheumatic heart disease.[54]

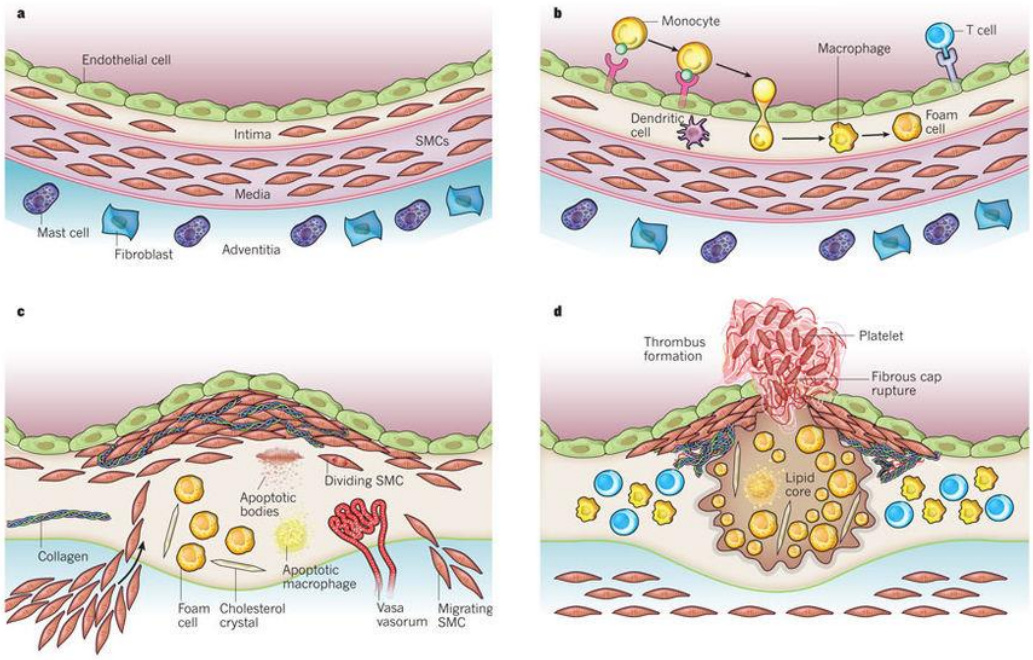


Figure 3. Stages in the development of atherosclerotic lesions (with permission from Libby P et al[58]).
a: Normal artery containing three wall layers; **b:** The initial steps of atherosclerosis characterised by monocytes adhering to the intima and migrating into the vessel wall where they transform to macrophages taking up lipids and turning into foam cells; **c:** lesion progression to an atherosclerotic plaque involving the migration of smooth-muscle cells from the media to the intima, proliferating resident, intimal smooth-muscle cells stimulating extracellular matrix synthesis and the creation of a fibrous cap. Plaque macrophages and smooth-muscle cells can die in advancing lesions and extracellular lipids derived from dying cells can accumulate in the central region of a plaque, often denoted as the lipid or necrotic core; **d:** The fracture of the fibrous cap puts blood coagulation components in contact with tissue factors, thereby triggering a thrombus formation that extends into the vessel lumen, impeding blood flow.

1.2.1.3 Risk factors for cardiovascular disease

The increase in global life expectancy during the last century naturally increases exposure to CVD.[56] In addition, trends such as industrialisation, urbanisation, the IT revolution and the use of processed (fast) food have led to a successively increasing unfavourable lifestyle made up of unhealthy dietary habits, physical inactivity and tobacco use, i.e. an accumulation of risk factors for CVD.[59] According to the WHO, the global leading risk factors for cardiovascular mortality are raised blood pressure (to which 13% of global deaths are attributed), followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and overweight and obesity (5%).[60] INTERHEART, a case-control study comparing patients with AMI and control subjects, reported that smoking, abnormal blood lipids, hypertension, T2DM, abdominal obesity and living in an unfavourable psychosocial situation increased the risk of AMI, while the consumption of fruits, vegetables, a modest amount of alcohol and regular physical activity decreased it.[61] This pattern was seen across the world in men and women of all ages. It was estimated that genetic susceptibility to AMI only explained one per cent of the population attributable risk when added to these nine factors.[61] The protective effect of alcohol as reported by the INTERHEART study is however, the subject of debate. Recently, the Global Burden of Diseases, Injuries and Risk Factors Study found some protective effects of alcohol in connection with ischaemic heart disease and T2DM among women. However, when the overall health risks associated with alcohol consumption such as the risk of cancer, injuries and communicable disease, were considered, the protective effects on ischaemic heart disease and T2DM were offset.[62]

1.2.2 The link between dysglycaemia and cardiovascular disease

T2DM increases the risk of CVD two to four times and together these two conditions account for more than half of global mortality.[59] Around 20% of patients with AMI have T2DM. Furthermore, in patients with AMI, about two thirds have previously unknown T2DM or IGT.[63] Patients with a combination of CAD and T2DM have a two times higher mortality than those without.[64] About 50% of the mortality in patients with T2DM is related to macrovascular complications.[65] According to the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) annual report, the prognosis after AMI has improved in patients both with and without T2DM, but the one-year mortality is still about 30% higher in patients with T2DM.[66] Furthermore, the presence of IGT increases the risk of future cardiovascular events in patients with AMI to an almost similar extent as newly detected T2DM.[11,12]

The exact causes behind the increased risk of CVD in patients with T2DM are not fully understood. It has been suggested that the abnormal metabolic state, such as chronic hyperglycaemia, dyslipidaemia and insulin resistance that accompanies T2DM, causes arterial dysfunction by promoting inflammatory activation, thrombosis and vasoconstriction.[67] Hyperglycaemia, dyslipidaemia and insulin resistance inhibit nitric oxide (NO; vasodilator) formation and increase the formation of reactive oxygen species (ROS).[68] In addition, hyperinsulinaemia and hyperglycaemia stimulate the production of vasoconstrictors, most importantly endothelin-1.[69]

Dyslipidaemia is present in 60-70% of patients with T2DM. It is characterised by elevated triglycerides, low high-density lipoprotein (HDL)-cholesterol and the predominance of small, dense low-density lipoprotein (LDL)-cholesterol, often without a particular increase in the absolute amount of LDL cholesterol.[70] The small, dense LDL particles are reactive and more likely to undergo oxidation,[37] which increases their uptake by smooth-muscle cells and macrophages. This promotes the formation of foam cells in the intima (Figure 3), causing a cytokine-mediated increase in inflammation and the inhibition of vasodilatory NO production, amplifying the atherosclerotic process in T2DM.[71] In addition to dyslipidaemia, more than 80% of patients with T2DM develop hypertension. Hypertension and T2DM share several common pathways involving inflammation, oxidative stress, insulin resistance and obesity.[72]

Heart failure has often been neglected as a cardiovascular complication of T2DM, but it is increasingly recognised as a common and serious complication of T2DM. Hyperglycaemia is believed to contribute to the fibrotic remodelling of the myocardium, beyond the risk of developing ischaemic heart disease and hypertension.[36]

1.2.3 The prevention of dysglycaemia and cardiovascular disease

1.2.3.1 Lifestyle intervention

Several randomised trials have reported on the importance of lifestyle intervention in patients with dysglycaemia. In the US Diabetes Prevention Programme, T2DM incidence in 3,234 people with IGT was reduced by 58% with intensive lifestyle intervention and by 31% with metformin compared with placebo after 2.8 years.[73] A 16-lesson curriculum covering diet, exercise and behaviour modification was designed to help participants achieve a 7% weight reduction. Compared with the placebo group, the incidence of T2DM was reduced by 27% in the intervention group and 18% in the metformin group during a mean follow-up of 15 years.[74] In the Finnish Diabetes Prevention Study,[75] lifestyle intervention aimed to produce a weight reduction of at least 5% through healthy diet and moderate-intensity training

sessions of 30 minutes a day or more. At follow-up after about seven years, there was a 43% relative risk reduction in the incidence of T2DM in the intervention group compared with the control group. The first RCT to show that lifestyle intervention in patients with IGT reduces future cardiovascular events was the Da Qing study. In 1986, 577 patients with IGT from primary care centres in Da Qing, China, were randomised to either a six-year period of lifestyle intervention or serving as a control group receiving standard medical care. After 23 years, the intervention group had significantly lower rates of all-cause mortality, CVD mortality and incidence of T2DM compared with the control group. A difference in CVD mortality between the intervention and control group was not seen until 12 years after study start.[76]

1.2.3.2 Glycaemic control

Glucose-lowering drugs mainly belong to insulin providers (insulin, sulphonylureas, meglitinides), incretins (GLP-1 receptor agonists, DPP-4 inhibitors), insulin sensitisers (metformin, peroxisome proliferator-activator receptor (PPAR) agonists) and glucose reabsorption inhibitors (SGLT-2 inhibitors).[77] According to international guidelines, metformin is the first-line treatment, although knowledge of its effect on cardiovascular events is limited.[78]

The goal for glycaemic control according to international guidelines has been to lower HbA1c to $\leq 7\%$ ($\leq$53 mmol/L), but this target can vary depending on individual patient profiles. This recommendation is based on the results of the Diabetes Control and Complications (DCCT) Trial from 1993, the first study to demonstrate that patients with T1DM, who reached near-normal levels of HbA1c, had a 35% to 70% reduction in the risk of the microvascular complications; neuropathy, nephropathy and retinopathy.[79] The reduction of these complications with intensive therapy persisted during the long-term follow-up of the DCCT cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study.[80] It was also noted that the intensive therapy during the DCCT had a major effect on cardiovascular outcomes, with a 58% reduction in fatal and non-fatal myocardial infarctions and stroke.[81]

Several randomised clinical trials have addressed the question of whether intensive treatment to normalise HbA1c levels can reduce the risk of CVD in patients with T2DM, but the results are inconclusive. The UK Prospective Diabetes Study (UKPDS), comparing strict with less strict glycaemic control by means of metformin or insulin-based therapy, showed a reduced relative risk of developing microvascular complications in the intensively treated group. However, the results showed only an insignificant relative risk reduction of 16% (p=0.052) for fatal/non-fatal AMI, with a mean HbA1c level of 7.0% vs. 7.9%, an insignificant 11% increase in the risk of stroke[19] and a 39% lower AMI risk (p=0.01) in a subgroup of overweight patients treated with metformin (mean HbA1c 7.4% vs. 7.9%).[82] More recent randomised trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD)[83], the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)[84] and the Veterans Affairs Diabetes Trial (VADT)[85] trials failed to show any macrovascular benefits as a result of intensive glycaemic control. In the ADVANCE trial, there was evidence of 'thresholds', with the implication that there was no significant change in the risk of macrovascular events and death below an HbA1c level of 7.0% and below 6.5% for microvascular events. The risks increased significantly above these thresholds, with a 40% higher risk of a microvascular event, a 38% higher risk of a macrovascular event and a 38% higher risk of death for each 1% increase in HbA1c (all $p < 0.0001$).

There has been a recent paradigm shift, with the last-generation glucose-lowering agents with regards to reducing cardiovascular events in patients with established T2DM and CVD or at

high risk of such disease. The SGLT-2 inhibitors empagliflozin, in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)[86], and canagliflozin, in the Canagliflozin Cardiovascular Assessment Study (CANVAS), had a significant beneficial impact on major cardiovascular events (MACE = cardiovascular death and non-fatal MI and stroke)[87], while dapagliflozin had an significant beneficial impact on heart failure hospitalisations and cardiovascular death in the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes.[88] Similar reductions in major cardiovascular outcomes were seen with the GLP-1 receptor agonists liraglutide, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)[89], semaglutide, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide (SUSTAIN-6)[90], and albiglutide, in the Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes) trials.[91] These positive results were achieved at glycaemic levels reached by other glucose-lowering drugs. They must therefore relate to so-called pleiotropic effects beyond the glucose-lowering capacity. The exact mechanisms are, however, not known and more research is needed in order to understand the results.

1.2.3.3 Multifactorial management

The ADA and the European Society of Cardiology (ESC) guidelines for the management of dysglycaemia and CVD underline the importance of multifactorial risk factor management in people with T2DM in order to reduce morbidity and mortality.[77,92] Lifestyle modification, including smoking cessation, increased physical activity, weight loss, healthy diet patterns and the avoidance of alcohol overconsumption, is the base to which pharmacological treatment may be added.

The Steno-2 Study investigated the effects of multifactorial risk-factor control by means of behaviour modification and pharmacological therapy in patients with T2DM and microalbuminuria.[93] Long-lasting reductions in the risks of death and cardiovascular events including heart failure[94] and severe renal dysfunction[95] were observed in the group exposed to strict multifactorial risk-factor control as compared with patients randomly assigned to conventional care. In a population-based study, 271,174 patients with T2DM from the Swedish National Diabetes Register were compared with 1,355,870 age- and gender-matched controls living in the same areas as the patients during a median follow-up period of 5.7 years. Patients with four defined risk factors (HbA1c, LDL cholesterol, blood pressure and smoking) within recommended treatment targets had little or no age-adjusted excess risk of death, AMI or stroke.[96] For each risk factor within target range the excess risk of outcomes decreased stepwise. The risk of hospitalisation for heart failure was, however, consistently higher among patients with T2DM than among controls. An HbA1c outside the target range was the strongest predictor of AMI and smoking was the strongest predictor of death.

1.2.3.4 Implementation of preventive measures

Despite the wealth of evidence of the need for the detection and cardiovascular prevention of patients with dysglycaemia and the feasibility of CVD prevention at population level, the implementation of and adherence to these programmes are still far from satisfactory. The ESC, together with other partners, has been issuing guidelines for CVD prevention in clinical practice since 1994. These guidelines have been updated at regular intervals, most recently in 2016.[97] The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) surveys I-V have been conducted since 1995 under the auspices of the Euro Heart Survey programmes of the ESC, with the objective of studying how well the guidelines are adhered to in clinical practice across Europe. The surveys demonstrate that large proportions of patients do not achieve the recommended targets for CVD prevention.[98] In EUROASPIRE IV, examining 6,187 patients with established CAD,

46% had no T2DM, 19% had newly diagnosed T2DM and 35% had previously known T2DM. The combined use of cardio-protective drugs was 53%, 55% and 60% in these groups. The guideline-recommended blood pressure target of < 140/90 mmHg was achieved in 68%, 61% and 54% and the corresponding LDL-cholesterol target of < 1.8 mmol/L was achieved in 16%, 18% and 28%. Among patients with known T2DM, an HbA1c of < 7.0 % was reached in 53%, while 11% had an HbA1c of > 9.0%.[99] A considerable proportion of the patients therefore failed to reach guideline-recommended treatment targets for glycaemic, blood pressure and lipid control.

In 2017, an estimated 50% of people with T2DM were undiagnosed, according to the IDF.[7] The highest proportion of people with undetected T2DM lived in Africa (69%) and the lowest in Europe (38%), North America and the Caribbean (38%).[13] About 20-30% of patients with newly detected T2DM already exhibit signs of macrovascular and/or microvascular complications at diagnosis.[100] Screening for IGT is encouraged by the fact that T2DM can be prevented or delayed in approximately 50% of patients with lifestyle and/or pharmacological interventions.[73,101,102] Furthermore, there is strong evidence that multifactorial risk-factor control reduces the risk of future micro- and macrovascular complications of T2DM.

1.3 SCREENING

1.3.1 Screening criteria

The criteria for screening adopted by the WHO originate from a report by Wilson and Jungner in 1968.[103] These criteria outline a number of conditions that should be fulfilled to make screening for a defined condition acceptable (Table 2). Through a literature overview of different criteria for screening, Andermann et al. revisited and further modified the "classic criteria" in 2008 (Table 2).[104] Several other aspects reflect changes in western medicine and society, such as the focus on evidence-based health care, the awareness of cost-effectiveness and quality assurance but also the importance of informed choice.[104] They are referred to as the "classic criteria", based mainly on the capacity of the screening tools to detect the condition early and the availability of an acceptable treatment.

Table 2. The Wilson and Jungner screening criteria modified by Andermann et al.[104]

- The condition sought should be an important health problem
- There should be an accepted treatment for patients with recognised disease
- Facilities for diagnosis and treatment should be available
- There should be a recognisable latent or early symptomatic stage
- There should be a suitable test or examination
- The test should be acceptable to the population
- The natural history of the condition, including development from latent to declared disease, should be adequately understood
- There should be an agreed policy on whom to treat as patients
- 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
- 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 recognised 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 minimise 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

1.3.2 Population screening versus opportunistic screening

Whether it is more advantageous for subjects with T2DM to be detected via an organised screening programme or be tested for T2DM when presenting to a physician for another reason, so-called "opportunistic screening", in terms of reducing the risk of morbidity and mortality, is the subject of debate.[105,106] The rationale for screening is the potential to intervene earlier in the disease course and thereby achieve improved long-term outcomes.

In a study based on a population register of a general practice in Ely, 1,705 individuals, 40 to 65 years of age, were followed for 18 years with mortality as the outcome. Patients invited for T2DM screening in intervals of five years from 1990 were compared with those in a similar population not invited for screening. Although screening resulted in cases being identified about 3 years earlier, it did not impact health outcomes.[107] In a Swedish study from the primary healthcare centre in Laxå, a diabetes register was established in 1972. Approximately 85% of the eligible population had been screened in 2001. After a median follow-up of 13.6 years, there was no reduction in total mortality or CVD outcomes in screening-detected patients with T2DM compared with those diagnosed clinically.[108] In another Swedish study, the Västerbotten Intervention Programme,[109] residents were invited for screening with an OGTT at age 30, 40, 50 and 60 years between 1992-2013. Individuals with T2DM detected via this kind of screening had a better outcome than those diagnosed through opportunistic screening after an average follow-up of 8.7 years.

The first RCT of large scale population screening for T2DM , the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION-Europe)[110], compared the effect of intensive multifactorial treatment or routine care in screening-detected people aged 40-69 years. After a mean follow-up of 5.3 years, a significant improvement in CVD risk factors was observed in the intensively treated as compared with the control group. However, there was only a non-significant decrease of 17% in the incidence of CVD mortality and morbidity. Furthermore, follow-up of the ADDITION-Cambridge[111] and the ADDITION-Denmark[112], with a median duration of 9.6 and 9.5 years respectively, did not reveal any reduced all-cause, CVD- or T2DM-related mortality associated with an invitation to screening through the primary care centres.

At the present time, large scale population screening is not recommended, as most studies have failed to show that this kind of strategy is effective in improving prognosis regarding cardiovascular events. The most recent Swedish National Guidelines[113] recommend opportunistic screening based on the results of the ADDITION studies, demonstrating that population screening did not impact mortality. Opportunistic screening is also advocated by the ESC[77], ADA[32] and IDF.[114] It is expected to be implemented at primary healthcare centres, disregarding the fact that the effectiveness of this outreach strategy has been questioned[105,112], as people at high risk of T2DM, such as those with low socio-economic status or certain ethnic minorities, may have limited access to health care or are less likely to attend routine health checks.[115–122] In spite of this, the 2018 ADA guidelines underline that testing should be carried out within a healthcare setting, due to a potential need for follow-up and treatment, and not through community outreach.[32] The essential contents of these guidelines are summarised in Table 3. They recommend screening through an informal assessment of risk factors or by means of a risk questionnaire to determine whether there is a need for a diagnostic test.

Table 3. Summary of guidelines for screening of dysglycaemia according to the American Diabetes Association (ADA), European Society for Cardiology (ESC) and International Diabetes Federation (IDF).

The ADA 2018 guidelines[32]
1) Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or (≥23 kg/m^2 in Asian Americans)) adults who have one or more of the following risk factors ▪ First-degree relative with T2DM ▪ High-risk race/ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander) ▪ History of CVD ▪ Hypertension (≥140/90 mmHg or on therapy for hypertension) ▪ HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.8 mmol/L) ▪ Women with polycystic ovary syndrome ▪ Physical inactivity ▪ Other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans) 2) Patients with prediabetes (HbA1c ≥5.7% [39 mmol/mol], IGT or IFG) should be tested yearly 3) Women diagnosed with gestational diabetes should have lifelong testing at least every three years 4) For all other patients, testing should begin at age 45 years 5) If results are normal, testing should be repeated at a minimum of three-year intervals, with consideration of more frequent testing depending on initial results and risk status 6) To test for T2DM, FPG, 2hPG and HbA1c are equally appropriate
The ESC 2013 guidelines[77]
1) People should be separated into three different populations ▪ The general population ▪ People with assumed glucose perturbations (e.g. obese, hypertensive or with T2DM in the family) ▪ Patients with CVD 2) In the general population and people with assumed abnormalities, the appropriate screening strategy is initiated with a risk questionnaire, e.g. Finnish Diabetes Risk Score (FINDRISC). In individuals with high scores, screening continues with an OGTT or FPG+HbA1c 3) In CVD patients, screening should be initiated with FPG + HbA1c. If these tests are inconclusive, an OGTT should be performed
The IDF 2017 guidelines[114]
1) Screen people with risk factors for diabetes attending your local health-care facility ▪ Risk factors for diabetes include age above 40-45 years, obesity, increased waist circumference, hypertension and family history of diabetes 2) Use a locally validated screening test, e.g. FINDRISC. If unavailable, use FPG. ▪ People with a positive screening test should proceed to a diagnostic test. If the result of that test is normal, they should be advised on healthy lifestyle changes and the diagnostic test should be repeated every year ▪ People with a negative screening test should have that test repeated at least every three years

BMI= Body Mass Index; T2DM= Type 2 diabetes mellitus; CVD= Cardiovascular Disease; HDL= High Density Lipoprotein; HbA1c= Haemoglobin A1c; IGT= Impaired Glucose Tolerance; IFG= Impaired Fasting Plasma Glucose; OGTT= Oral Glucose Tolerance Test; 2hPG= 2 hour Postload Glucose; FINDRISC= Finnish Diabetes Risk Score

1.3.3 Screening methods

1.3.3.1 The Finnish Diabetes Risk Score

To limit the cost of large-scale screening by means of glucose measurements, a widely used strategy is to use a questionnaire as the first screening tool in an attempt to identify people at high risk of developing T2DM.[123] Several risk scores have been developed, all addressing the known risk factors of T2DM. One of them, the Finnish Diabetes Risk Score (FINDRISC; Figure 4), has been tested and found to be accurate in identifying individuals at risk of future T2DM, not only in Finland[124] but in several other countries.[123] In addition, it is valuable for the detection of IGT, relates to markers of insulin resistance[125] and predicts CVD events and mortality.[126] The FINDRISC includes eight questions/items (age, BMI, waist circumference, physical activity, intake of fruit and vegetables, high blood pressure, history of high glucose value and family history of T2DM) which, in combination, provide an assessment of the risk of developing T2DM during the upcoming ten years.[127] Depending on the response to each question, a score (0-26) is set and the respondent is allocated to one of five risk categories with a sensitivity of 78%, a specificity of 77% and a predictive value of a negative test of 99%.[124] The FINDRISC provides the potential for the early diagnosis of T2DM, as people with a high and very high risk can be recommended a laboratory-based evaluation of their glycaemic state.

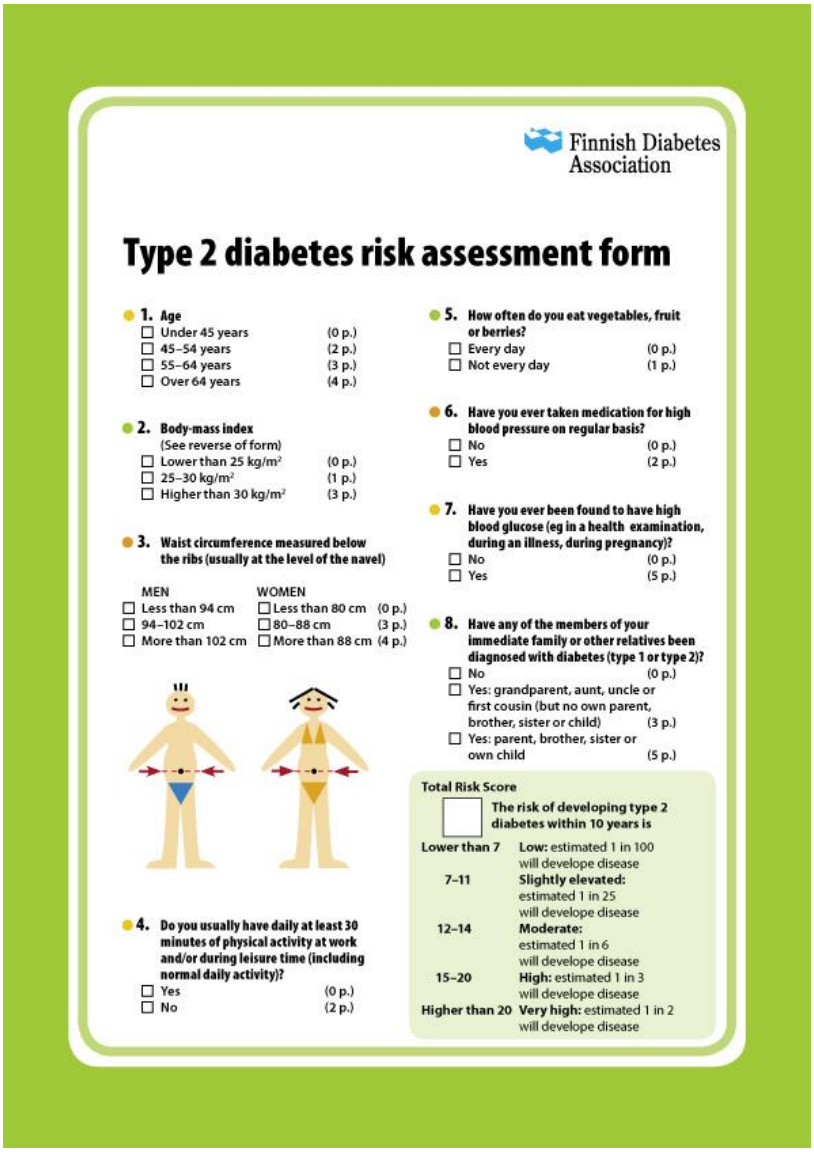


Figure 4. The Finnish Diabetes Risk Score (FINDRISC).[124]

1.3.3.2 FPG, 2hPG or HbA1c?

There is an ongoing debate regarding the diagnostic tests for dysglycaemia. As outlined in Table 4, all screening tests have advantages and disadvantages. The debate focuses mainly on the lower sensitivity of FPG and HbA1c than an OGTT. The latter test is, however, more time consuming and the reproducibility of the 2hPG has been questioned.[128,129] Guidelines from the ADA endorse all three methods for detecting T2DM as equally appropriate,[78] while the ESC guidelines recommend that screening should be initiated with FPG and/or HbA1c, followed by an OGTT if these tests are negative.[77] Furthermore, it is important to screen for IGT that is only disclosed by means of an OGTT, since it significantly increases the risk of CVD. [11,12]

Table 4. Pros and cons of dysglycaemia screening by means of haemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and 2 hour postload glucose (2hPG).[128,129]

HbA1c (glycated haemoglobin reflecting average glucose level during the last six to eight weeks)
+ Captures chronic hyperglycaemia + Fasting not needed + Greater pre-analytical stability than plasma glucose - Poor marker of important pathophysiological abnormalities featuring T2DM - Variability depending on ethnicity, which is poorly understood. - Influenced by erythrocyte turnover (e.g. haemoglobinopathies, malaria, anaemia, blood loss) - Influenced by hepatic disease, chronic kidney disease and splenomegaly - Cost higher than FPG - Delays the diagnosis of T2DM in ~60% of incident cases - Relationship to future cardiovascular events in need of clarification
FPG (lowest level of plasma glucose reflecting hepatic glucose production during the night)
+ Relatively high sensitivity for the diagnosis of T2DM + Simple and inexpensive - Overnight fasting - Influenced by a variety of conditions (e.g. stress, diet, exercise, smoking) - Pre-analytical variability (in particular due to glycolysis) - Relationship to future cardiovascular events in need of clarification
2hPG (postload glucose after 75 g glucose intake reflecting insulin resistance and/or decreased beta-cell function)
+ The only test that detects IGT + Reflects impairment of beta cell function and/or reflects insulin resistance - Overnight fasting - Influenced by a variety of conditions (e.g. stress, diet, exercise, smoking) - Pre-analytical variability (in particular due to glycolysis) - Time consuming (somewhat more than two hours) - Relationship to future cardiovascular events in need of clarification

T2DM= Type 2 Diabetes Mellitus; IGT= Impaired Glucose Tolerance

In 1998, the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study compared the ADA and WHO recommendations for epidemiological studies.[130] Data were collected from 13 populations and three occupation-based studies from eight European countries. All the studies used both a FPG and a 75 g OGTT. Of the 1,517 people with newly diagnosed T2DM, 40% met the FPG criterion only, 31% met the 2hPG criterion only, while 28% met both criteria. The use of only a FPG would have failed to

diagnose ~30% of people with T2DM. The EUROASPIRE IV survey compared the diagnostic features of HbA1c, FPG, 2hPG in 4,004 patients with CAD without previously known T2DM.[131] An OGTT identified the largest number of patients who actually had T2DM. HbA1c alone would have left 83% of those with T2DM undetected The overlap in case detection between the these three diagnostic tests were small. An important but unanswered question is whether this matters and whether there are any differences in cardiovascular outcome for people diagnosed on the basis of a 2hPG, a FPG or an HbA1c,.

The 2hPG, FPG and HbA1c seem to be equal predictors of microvascular complications of T2DM, with a threshold for a significant increase of risk with increasing glycaemia.[35] However, as of today, studies with all three of these measurements of glucose metabolism have not been large enough to compare their relative abilities to predict cardiovascular outcome.

1.3.3.3 Dysglycaemia in the range of diabetes and cardiovascular outcome

In patients with manifest T2DM, there is a greater risk of CVD with increasing dysglycaemia. In a meta-analysis based on 102 prospective studies in the Emerging Risk Factors Collaboration, FPG was non-linearly related to vascular risk. Hazard ratios (HR) were about 50% higher in people with a history of T2DM and with FPG concentrations of $\geq$ 7 mmol/L than in people with a history of T2DM but FPG of < 7 mmol/L.[132] In a study from the Swedish National Diabetes Register comprising 18,334 individuals with T2DM, of whom one-fifth had a history of CVD (the age, gender and other cardiovascular risk factors adjusted), relative risk increased for coronary heart disease by 11-13%, stroke by 8-9%, CVD by 10-11% and total mortality by 9-10% with higher baseline as well as mean updated HbA1c levels during six years of follow-up.[133]

1.3.3.4 IFG, high-risk HbA1c, IGT and cardiovascular outcome

The relationship between FPG and CVD risk in the ranges below the diagnostic threshold for T2DM has been the subject of debate. Studies have reported of a linear relationship, threshold effects, a J-shaped association or no association.[134] A definite threshold which could be used to define T2DM based on the risk of CVD has not been shown.[21] In the West of Scotland Coronary Prevention Study, FPG was measured in 6,447 men with hypercholesterolaemia but no history of CVD or T2DM. An elevated FPG level below the threshold for T2DM was a significant risk factor for future T2DM but not for CVD over 15 years of follow-up.[135] The relationship between FPG and cardiovascular events was further investigated in an analysis of 102 prospective studies including 698,782 participants by the Emerging Risk Factors Collaboration group of investigators.[132] The results showed that IFG is only modestly and non-linearly associated with the risk of CVD (HR 1.17; 95% CI 1.08-1.26 for FPG 6.1-6.9 vs. 3.9-5.6 mmol/L). The DECODE study reported a J-shaped relationship between mortality and glucose, with the lowest rates for a FPG glucose of 4.5-6.1mmol/L but with the risk increasing significantly at only $\geq$7.0 mmol/L (the threshold for T2DM diagnosis).[136] However, neither FPG nor HbA1c added significant information regarding future cardiovascular events when 2hPG was entered into the statistical model. The 2hPG, in the range of IGT or T2DM, was a significant and independent predictor of future cardiovascular events.

To summarise, different measurements of glucose metabolism may contribute independent information and appear to have different predictive values in direct comparisons. Epidemiological studies of general populations and small prospective cohort studies suggest that dysglycaemia diagnosed on the basis of a 2hPG is associated with a poorer prognosis than dysglycaemia diagnosed by means of an elevated FPG or HbA1c for both mortality and CVD. It may be that FPG, 2hPG and HbA1c reflect different glycaemic metabolic processes, thereby potentially leading to different associations with mortality and CVD, as it appears

that limited data are available on the relative value of all three of these tests in predicting the prognosis in patients following an acute coronary syndrome (ACS).

1.3.3.5 Point-of-care technique

Since the OGTT includes both a FPG and a 2hPG, accurate, user-friendly point-of-care glucose-recording techniques would save time, reduce costs and eliminate preanalytical errors, while, at the same time, providing immediately available information on the glycaemic state. This is useful and convenient for both patients and professionals. Blood glucose measurements in the 24 European countries included in EUROASPIRE IV were performed using the photometric point-of-care technique, HemoCue® Glucose 201+ System (HemoCue®, Ängelholm, Sweden). However, the accuracy of this equipment for the screening of dysglycaemia has been questioned,[137] since the conversion of whole blood to plasma glucose and adjustment for cholesterol levels may affect the result.[138] On the other hand, the hexokinase method, frequently used as a reference method in laboratory settings, has disadvantages that are not shared by HemoCue®. It is relatively large and non-portable, requires careful maintenance and interference and technical malfunctions can easily occur.[139] The storage and transportation of the samples and delays in measurement and conversion to plasma glucose values are further challenges.[140–142]

2 AIMS

The general aim of this thesis was to evaluate different screening strategies for dysglycaemia with respect to CVD. The four specific goals were to:

1) Compare the prognostic value of FPG, 2hPG and HbA1c in patients with CAD regarding future cardiovascular events and incident T2DM (**Study I**).

2) Explore the prevalence of dysglycaemia in patients treated for hypertension and/or dyslipidaemia but without CVD by means of HbA1c, FPG and 2hPG and examine whether initiating screening with the FINDRISC questionnaire would reduce the need for these blood tests (**Study II**).

3) Examine the effectiveness of different outreach strategies in identifying individuals at risk of T2DM and/or CVD in a Swedish municipality with a heterogeneous population comprising a large number of immigrants (**Study III).**

4) Compare the agreement between glucose measurements made by HemoCue® and accredited hospital laboratories in patients with CAD and unknown dysglycaemia and investigate between-site agreement comparing local hospital laboratories with a central hospital laboratory (**Study IV**).

3 MATERIAL AND METHODS

3.1 PATIENTS

This thesis used two main sources of patient data. **Studies I**, **II** and **IV**, dealing with methodological issues of importance for dysglycaemia screening, were based on the European cross-sectional multicentre EUROASPIRE IV and V surveys, providing both questionnaire data and blood samples from large numbers of patients with established CAD. **Study III**, assessing the effectiveness of different outreach strategies used when screening for T2DM, derived information from questionnaires distributed to the population of the Swedish municipality of Södertälje.

3.1.1 Studies I, II and IV – the EUROASPIRE surveys

3.1.1.1 General aspects

The ESC, in collaboration with allied societies, has developed and updated guidelines on CVD prevention at regular intervals from 1994 through 2016 (Figure 5). The implementation of these guidelines in clinical practice was evaluated by means of five cross-sectional surveys, the EUROASPIRE surveys. These surveys have been conducted since 1995 through the EURObservational Research Programme of the ESC as outlined in Figure 5.

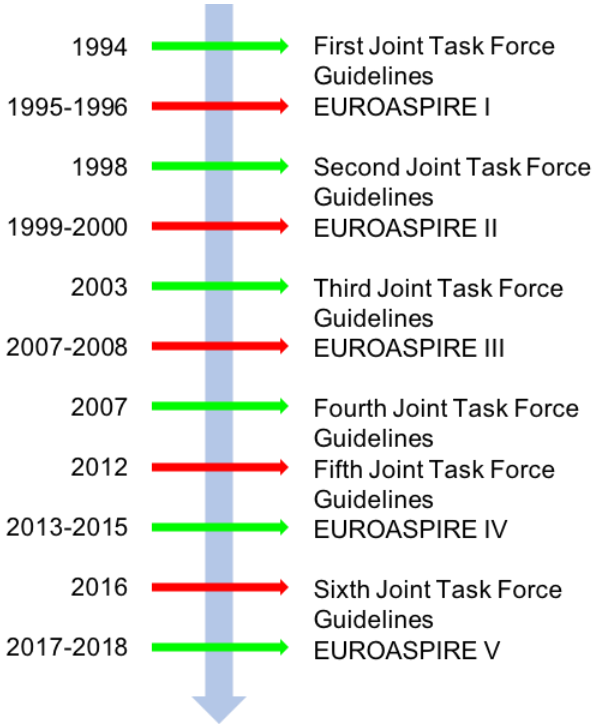


Figure 5. Joint European guidelines and EUROpean Action on Secondary and Primary prevention In order to Reduce Events (EUROASPIRE) surveys of cardiovascular disease prevention over time.

Consecutive patients (men and women ≥18-<80 years) were retrospectively identified from hospital discharge lists if they had been hospitalised for a first or recurrent CAD event six to 36 months before enrolment in the survey: (i) coronary artery bypass grafting (CABG); (ii) percutaneous coronary intervention (PCI); (iii) acute myocardial infarction (AMI) (ICD-10 121); and (iv) acute myocardial ischaemia (ICD-10 120).

Within each participating country, one or more geographical areas with a defined population were selected and all hospitals serving these populations were identified. Eligible patients were invited to attend a study visit. The invitation procedure varied between countries, according to local privacy rules and the advice of local ethical committees.

EUROASPIRE IV and V included a primary care arm investigating individuals free from any manifestations of CVD but at increased cardiovascular risk as they had hypertension, dyslipidaemia or T2DM. Patients were identified from the records at general practices selected in each of the participating countries according to the structure of the local health services. The primary care arm recruited men and women aged ≥ 18-< 80 years without atherosclerotic disease, who had been prescribed one or more of the following treatments: (i) blood pressure-lowering and/or (ii) lipid-lowering and/or (iii) glucose-lowering (diet and/or oral drugs and/or insulin) since ≥ 6 months to < 3 years prior to the time of the interview.

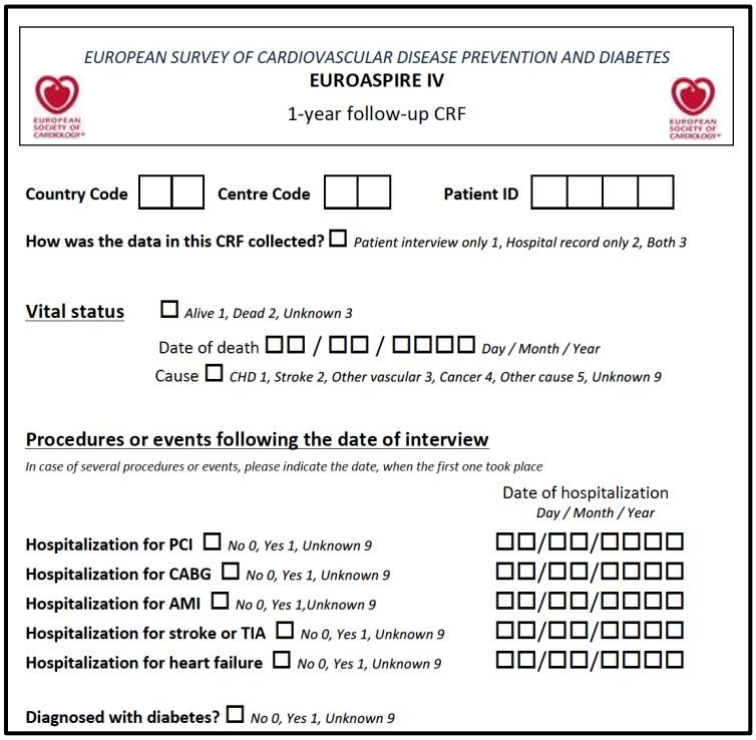
Centrally trained research staff reviewed patient medical records and interviewed and examined the patients by means of standardised methods, entering the retrieved data into an electronic central database. Demographic details, smoking status, history of obesity, hypertension, dyslipidaemia, glucose metabolism and medication were obtained from medical records. Self-reported information on lifestyle, including dietary habits and physical activity, other risk factor management and medication, were obtained at interview. On that occasion, the following investigations were performed: height, weight, waist circumference, blood pressure, blood lipids, FPG and HbA1c in all participants and postload glucose (OGTT) in participants without a history of T2DM. The case record forms were translated into all the languages of participating countries and the self-reported questionnaires were validated versions for each country.

3.1.1.2 Patients in Study I

EUROASPIRE IV was conducted at 79 centres in 24 European countries between May 2012 and April 2013. A total of 16,426 medical records were scrutinised and 7,998 (49%) patients with CAD attended the interview. The diagnostic capacity of FPG, 2hPG and HbA1c was investigated by Gyberg et al.[131] in 4,004 patients without a history of T2DM for whom full information was available on all three tests. The patient cohort (n=3,775) in **Study I** is based on a follow-up of the 4,004 patients studied by Gyberg et al.[131]

3.1.1.1 Follow-up data in Study I

All EUROASPIRE IV centres were asked to complete a single-page follow-up questionnaire (Figure 6) for all interviewed participants. To be eligible for Study I, the information had to cover ≥ 12 months in ≥ 90% of the patients from the respective centres. Cardiovascular death was recorded as death from CAD, stroke and other vascular diseases. Non-cardiovascular death was recorded as death from cancer or other causes. Deaths without any reported cause were classified as "without known cause". Non-fatal events were recorded as hospitalisation for PCI, CABG, AMI, stroke/transient ischaemic attack (TIA) and heart failure. Follow-up information was obtained from patient interviews, medical records, external registries or databases (mortality registries, municipal records and archives) or, if needed, by contacting relatives or a family doctor. Information was requested on vital status and, in the event of mortality, date and cause of death. Information was also obtained on T2DM diagnosed since the baseline investigation. The information on follow-up was based on self-reported information from the patients in 63%, from hospital records in 27%, from external databases in 7% and from a patient's family member or the family doctor in 3%. Of a total of 4,004 patients without any history of diabetes at the baseline investigation, screening for dysglycaemia with an OGTT and HbA1c revealed that 1,161 (29%) of them had previously unrecognised T2DM (*FPG ≥ 7 mmol/L or 2hPG ≥ 11.1 mmol/L or HbA1c ≥ 6.5%*)[131] and they were excluded from the analysis for incident T2DM at follow-up. During the original screening, 1,079 of these patients had T2DM and 2,696 were free from T2DM. Of these 2,697 patients, information on incident T2DM was available in 2,609 (97%) at follow-up.



EUROPEAN SURVEY OF CARDIOVASCULAR DISEASE PREVENTION AND DIABETES

EUROASPIRE IV

1-year follow-up CRF

Country Code ☐☐ Centre Code ☐☐ Patient ID ☐☐☐☐

How was the data in this CRF collected? ☐ *Patient interview only 1, Hospital record only 2, Both 3*

Vital status ☐ *Alive 1, Dead 2, Unknown 3*

Date of death ☐☐ / ☐☐ / ☐☐☐☐ *Day / Month / Year*

Cause ☐ *CHD 1, Stroke 2, Other vascular 3, Cancer 4, Other cause 5, Unknown 9*

Procedures or events following the date of interview

In case of several procedures or events, please indicate the date, when the first one took place

	Date of hospitalization *Day / Month / Year*
Hospitalization for PCI ☐ *No 0, Yes 1, Unknown 9*	☐☐/☐☐/☐☐☐☐
Hospitalization for CABG ☐ *No 0, Yes 1, Unknown 9*	☐☐/☐☐/☐☐☐☐
Hospitalization for AMI ☐ *No 0, Yes 1,Unknown 9*	☐☐/☐☐/☐☐☐☐
Hospitalization for stroke or TIA ☐ *No 0, Yes 1, Unknown 9*	☐☐/☐☐/☐☐☐☐
Hospitalization for heart failure ☐ *No 0, Yes 1, Unknown 9*	☐☐/☐☐/☐☐☐☐

Diagnosed with diabetes? ☐ *No 0, Yes 1, Unknown 9*

Figure 6. Follow-up questionnaire of the EUROpean Action on Secondary and Primary prevention In order to Reduce Events (EUROASPIRE) IV patients.

3.1.1.3 Patients in Study II

In the primary care arm of EUROASPIRE IV, 4,579 patients were identified between January 2014 and April 2015 from practice records in 14 European regions. A total of 3,212 of these patients, free from previously known dysglycaemia, were being treated for hypertension and/or dyslipidaemia. Information from the FINDRISC, the OGTT and HbA1c was missing in some of them, leaving 2,395 who constituted the population in **Study II**.

3.1.1.4 Patients in Study IV

Study IV comprised 87 patients with CAD subjected to an OGTT at three hospitals under the auspices of EUROASPIRE V: Karolinska University Hospital, Solna, Sweden, and Kings Mill Hospital and Milton Keynes University Hospital in the UK.

3.1.1.5 Laboratory measurements and investigations in Studies I, II and IV

All laboratory analyses, apart from glucose measurements with the HemoCue® equipment, were performed at the central core laboratory for the EUROASPIRE surveys (Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland). *Total and HDL cholesterol and triglycerides* were analysed in serum and *LDL* cholesterol was calculated according to Friedewald's formula.[143] *Venous blood* was drawn in a fasting state (≥10 hours) into a tube containing clot activator (Venosafe, Terumo Europe, Leuven, Belgium) for lipid assays and into a potassium ethylenediaminetetraacetic acid (EDTA) tube for HbA1c assay. *HbA1c* was analysed in whole blood using an immunoturbidimetric method and expressed in mmol/mol, according to IFCC, and %, according to DCCT. *The OGTT* was performed using 75 grams of anhydrous glucose in 200 ml of water in the morning after ≥ 10 hours of fasting, as described by the WHO.[21] Blood for FPG was drawn before the glucose intake with a dip safe from the EDTA tube in which the HbA1c was collected. Samples for 2hPG were drawn from whole venous blood using an EDTA tube. *Plasma glucose* was analysed locally with a photometric point-of-care technique (HemoCue® Glucose 201+ in EUROASPIRE IV and HemoCue® Glucose 201RT in EUROASPIRE V; HemoCue®, Ängelholm, Sweden).

In **Study IV,** venous blood sampling in an EDTA tube and a fluoride/citrate plasma tube was performed immediately before and one (1hPG) and two hours (2hPG) after the glucose load. Glucose analysis with HemoCue® was performed from the EDTA tubes within 10 minutes following sampling. Venous blood samples collected in the fluoride/citrate plasma tubes were sent to the participating local hospital laboratories directly after the postload glucose sampling. They were analysed three to five hours after sampling with their standard methods. To study potential between-site variability in plasma glucose analyses, samples of whole blood collected in fluoride/citrate tubes were sent frozen to the central laboratory in Helsinki. These samples were stored at -70°C pending analysis.

Height (kg) and weight (cm) were recorded in light indoor clothes without shoes (Scales 701 and Measuring stick model 220; SECA Medical Measuring Systems and Scales, Birmingham, UK). *Waist circumference* was measured using a metal tape applied horizontally at the point midway on 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.[144] *Blood pressure* was recorded in a sitting position with an automatic sphygmomanometer (Omron M6; OMRON Corporation, Kyoto, Japan). *Physical activity* was assessed by means of the International Physical Activity Questionnaire (IPAQ; IPAQ core group, Karolinska Institutet, Stockholm, Sweden). *Anxiety and depression scores* were estimated using the Hospital Anxiety and Depression Scale (HADS) questionnaires.

Smoking status, in addition to self-reported data, was verified by the concentration of breath carbon monoxide using a smoker analyser (Bedfont Scientific, Model Micro+).
The FINDRISC questionnaire[127] (as described on page 21, Figure 4) was integrated as part of the interview conducted by the research staff in **Study II**.

3.1.1.6 Definitions
Dysglycaemia, according to the ADA and the WHO, was defined as outlined in Table 1.[21–23] *Overweight* was defined as a BMI of 25.0-29.9 kg/m^2 and *obesity* as a BMI of ≥ 30 kg/ m^2. *Central obesity* was defined as a waist circumference of ≥ 88 cm for women and ≥ 102 cm for men.[144] *Blood pressure* was defined as elevated if systolic blood pressure (SBP) was ≥ 140 mmHg and/or diastolic blood pressure (DBP) was ≥ 90 mmHg. *Smoking* was defined as self-reported smoking or exhaled carbon monoxide of >10 ppm (in those who reported that they had stopped smoking).[146] *The physical activity target* was defined as vigorous physical activity outside work for ≥ 20 minutes at least once/week. *The educational level* was defined as low if only primary school or less had been completed.

3.1.2 Study III – pilot project in the Municipality of Södertälje

3.1.2.1 General information
The Forum for Health Development (Forum för Välfärd; http://www.forumforvalfard.se), launched in 2013, is a politically independent platform consisting of representatives with knowledge and experience from academia, industry, the health-care sector, government and trade unions. One of its initial projects was to show how the prevention of T2DM and/or CVD at population level could be approached. For this purpose, an alliance was created with researchers at the Cardiology Unit, Department of Medicine at Karolinska Institutet, and it resulted in Study III.

Using a community outreach, all the inhabitants of the Municipality of Södertälje aged 18-65 years (n ~51,000) without known T2DM and/or CVD were encouraged to complete the FINDRISC questionnaire during six weeks in May-June 2014. The questionnaire was translated into the most common languages in the municipality and was launched as an

internet-based survey in Swedish, English, Finnish, Turkish, Assyrian/Syrian and Arabic and in a paper version in Swedish and Arabic.

Responders scoring ≥ 15 indicating a high risk of future T2DM and thereby CVD and > 20 indicating a very high risk of future T2DM and thereby CVD were automatically informed about their risk profile and the importance of a healthy lifestyle. In addition, they were encouraged to visit a primary healthcare centre for further clinical management or to attend a temporary laboratory unit for blood glucose measurements. All the data collected through either the paper- or internet-based version of the FINDRISC questionnaire were administered at Karolinska Institutet. Blood glucose measurements at the two sites set up for the purpose of the study were clinically assessed at Karolinska Institutet, with written information mailed to the participant, including advice on further need for care.

3.1.2.2 Outreach strategies

Workplaces: an e-mail with information about the survey and a link to the survey was sent to the employees at Södertälje County, the Scania Ltd car plant and Södertälje Hospital. For the employees at the AstraZeneca Ltd pharma company, information was posted on the intranet. It was estimated that 9,883 employees living in Södertälje County were contacted.

Syrian Orthodox churches: at the St Afrem, St Tomas, St Gabriel and St Jacob Syrian Orthodox churches, physicians speaking Syrian and Arabic, supported by medical students, nursing students and board members of the church, encouraged the church visitors to complete the FINDRISC after Sunday worship. The number of questionnaires that were distributed were counted by the physicians and amounted to 1,060.

Crowded public places: medical students and nursing students were stationed at public places to encourage people to complete the FINDRISC. At football matches, the speaker informed the spectators about the survey. The number of people reached could only be estimated for the football matches based on the number of tickets sold, which was 7,500.

Primary care centres: the FINDRISC was on display in the waiting room at eight primary care centres in Södertälje. The respondents were instructed to return the questionnaires in a post box. In addition, at one primary care centre, the FINDRISC was collected either by the receptionist or by a doctor or nurse during the appointment. The estimate of the total number of people reached was based on a medical data register with information on the weekly number of visits per primary care centre and was ~6,300.

Pharmacies: three of the pharmacies in Södertälje were supplied with the questionnaires. If requested, a pharmacist helped the customer to complete the survey. According to data on the number of visitors provided by the pharmacy managers, the total number people reached was ~7,000.

Mass media: articles about the survey were published in the local daily press A Syrian-speaking physician and a representative from the Forum for Health Development participated in a one-hour programme about health on the Syrian TV channel, Syroyo. It was not possible to estimate the total number of individuals reached through these channels.

Social media: a Facebook site was created to distribute information about the survey, which was also spread on Twitter. Posts regarding the survey were targeted at the inhabitants of Södertälje in the 20- to 65-year age group, through Facebook. It was not possible to estimate the total number reached by this communication channel.

Mail: 10,000 invitational letters with a link to the survey were sent from the "Forum för Välfärd" to randomly selected inhabitants. In addition, another 985 letters were sent with letterheads representing Södertälje Hospital and 985 letters representing "Forum för Välfärd and the Swedish Heart Lung Foundation", with the incentive of a donation to charity.

3.1.2.3 Cost analysis

The cost of outreach through a channel was based on the categories of costs as presented in Table 5, divided by the number of outreached respondents at high or very high risk. The costs of the operational and research team were not included. The cost of processing the channels was estimated based on the normal salary of a research nurse. Processing the channels included meetings with the collaborating organisations, educating/informing the students and physicians at different channels about the study design and their tasks and having meetings on the progress of the project.

Table 5. Cost categories for outreach through different communication channels. The costs of the operational and research teams are not included.

Developing online questionnaires
Permits *- From the police for attending public places* *- Renting public space* *- Records from the Swedish National Register of Addresses*
Material *-Graphic design* *-Printing questionnaires* *-Printing information brochures* *-Stamps* *-T-shirts* *-Banners* *-Measuring tapes* *-Weighing scales*
Advertisements
Personnel *– Students staffing the channels* *– Students for transfer of questionnaire data to Excel sheets* *– Physicians staffing the channels* *– Material transport*
Processing channels

3.1.2.4 Definitions

The *place of birth* was defined as "born in Sweden", "born in another Nordic country", "born in another European country, excluding Nordic countries" and "born outside Europe". *Educational level* was defined as primary school (grade 1-9), high school (grade 10-12) and post-secondary education (e.g. college or university). The level of *employmen*t was categorised as full time, part time, self-employed, student, unemployed or on sick leave (including both part-time and full-time sick leave).

3.2 STATISTICAL ANALYSES

3.2.1 Studies I and II

Distributions of the baseline characteristics of patients were summarised using means, standard deviations and proportions. Included and excluded patients were compared according to Mann-Whitney (continuous variables) and chi-square tests (categorical variables). HRs for the primary and secondary outcomes, their 95% confidence intervals and statistical significances were estimated using the Cox proportional hazards model. To allow regional variation in the form of the underlying hazard function, Cox regression models were stratified by country. First, HRs and their statistical significance were adjusted for age and gender. To study the independent prognostic role of different dysglycaemia markers, variables that are known cardiovascular risk factors (educational level, current smoking, BMI, systolic blood pressure, LDL cholesterol, statin use, level of physical activity and Hospital Anxiety and Depression Scale score) were regarded as potential confounders and hence added to the model as covariates. The adjusted multivariate Cox regression model was used to show the impact on the risk of cardiovascular events when the 2hPG increased by one unit.

In supplementary analyses of data from **Study I,** a comparable continuous model was provided, also including FPG and HbA1c. FPG was added as a quadratic and cubic effect in the Cox model to see whether there was a curvilinear association. Furthermore, all models were screened for potential multicollinearity and inflation in standard errors of beta coefficients was searched for when gradually creating the multivariate models. In addition, pairwise Pearson correlation coefficients between glycaemic parameters were studied.

Study II was supplemented with an analysis including area under the receiver operating characteristic curve (AUC) that shows the discriminative power of the FINDRISC, FPG and HbA1c combined in seven different ways for the prediction of T2DM. All the statistical analyses in **Studies I-II** were undertaken using SAS statistical software (release 9.3 and 9.4) at the Department of Public Health, Ghent University, Belgium.

3.2.2 Study III

No statistical analyses were undertaken in **Study III** due to the nature of this study in which descriptive analyses were judged to be sufficient.

3.2.3 Study IV

In **Study IV,** descriptive statistics are presented as the median and interquartile ranges (Q1; Q3) and the mean. The correlation between the two methods was calculated according to Spearman using Excel. The Bland-Altman method was used to plot the bias (the difference between the HemoCue® and hospital laboratory measurements, the HemoCue® and the central hospital laboratory and the local hospital laboratories and the central hospital laboratory) against the corresponding glucose mean.[147] Surveillance error grid analysis was performed for HemoCue® compared with local hospital laboratory measurements, according to the methodology described by Klonoff et al.,[148] using a Microsoft Excel™ VBA macro program (Microsoft Corporation, Redmond, WA, USA).[149] The surveillance error grid displays clinical risks on a continuous colour-coded scale relevant to the clinical practice as perceived by T2DM experts.

The International Organisation for Standardisation (ISO) have issued criteria for how accurate glucose meters should be for use by people with diabetes. The current ISO 15197:2013 accuracy criteria require that ≥ 95% of meter results fall within ± 0.83 mmol/L or ± 15% of the laboratory reference result at blood glucose concentrations of < 5.6 mmol/L and ≥ 5.6 mmol/L respectively.[150] A comparison of the surveillance error grid with ISO

15197:2013 using computer-simulated data pairs with realistic error distribution has suggested that a device with ≤ 3% errors outside the surveillance error grid no-risk "green" zone would meet the ISO requirements of ≤ 5% data pairs outside the 0.83 mmol/L 15% standard limits, while higher percentages outside the surveillance no-risk zone would indicate non-compliance with the standard.[149]

3.3 ETHICAL CONSIDERATIONS

All studies comply with the Declaration of Helsinki. The separate protocols were approved by the Regional Ethical Review Board in Stockholm. The responsible national co-ordinators ascertained that requirements for ethical approval were adhered to in each country participating in the EUROASPIRE surveys. Written and oral informed consent was obtained prior to enrolment. Participation in all studies was voluntary and anonymous.

4 RESULTS

4.1 THE PROGNOSTIC VALUE OF FPG, HBA1C AND 2HPG (STUDY I)

4.1.1 Cardiovascular events

4.1.1.1 Original analyses

After a median follow-up period of 2.03 years, complete information, including all three glycaemic tests, was available in 3,775 (94.3%) of the 4,004 patients investigated at baseline. The clinical characteristics of included and excluded (n=229) patients are presented in Table 6. The excluded patients were slightly younger, smoked more often, were less physically active, had higher HADS Anxiety and Depression scores, lower systolic blood pressure, a higher LDL-cholesterol and FPG. Their median age was 64.5 years. Only 9.2% of the patients were younger than 50 years and 1.2% were younger than 40 years.

Table 6. Baseline characteristics of the patients with complete and incomplete follow-up data respectively. The presented data are proportions (% = no/no of observations x 100), unless otherwise stated.

Variable	Follow-up data available (n=3,775)	Follow-up data incomplete (n=229)	p =
Recruiting event			
CABG	11.1 (419/3775)	12.2 (28/229)	0.15
PCI	55.2 (2083/3775)	48.9 (112/229)	
AMI	23.2 (877/3775)	29.3 (67/229)	
Ischaemia	10.5 (396/3775)	9.6 (22/229)	
Age at interview (years; SD)	63.8 (9.69)	60.8 (11.0)	<0.0001
Gender (females)	23.6 (891/3775)	22.3 (51/229)	0.69
Time since hospital discharge (years)	1.5 (0.69)	1.5 (0.73)	0.52
Low educational level	16.8 (632/3750)	20.7 (47/227)	0.15
Current smoking	15.3 (578/3775)	22.3 (51/229)	0.007
Regular physical activity	45.0 (1563/3471)	29.5 (62/210)	<0.0001
BMI (kg/m²)	28.6 (4.3)	28.2 (4.6)	0.10
Obesity	33.1 (1249/3771)	29.0 (66/228)	0.22
Central obesity	54.6 (2041/3737)	56.7 (122/215)	0.57
Blood pressure (mm Hg)			
Systolic	132.5 (18.8)	128.4 (17.5)	0.002
Diastolic	78.3 (10.8)	78.9 (10.8)	0.38
Cholesterol (mmol/L)			
Total	4.5 (1.09)	4.8 (1.01)	0.15
LDL	2.6 (0.91)	2.7 (0.89)	0.04
Plasma glucose			
Fasting (mmol/L)	6.4 (0.9)*	5.8 (0.46)	0.003
2h postload (mmol/L)	7.9 (2.71)*	6.3 (0.97)	0.58
HbA1c (%)	5.7 (0.42)*	8.1 (2.59)	0.22
HADS Anxiety score	5.2 (3.81)	6.3 (4.31)	0.0008
HADS Depression score	4.4 (3.53)	5.0 (3.82)	0.04
Pharmacological treatment			
Antiplatelet	93.2 (3504/3761)	94.7 (215/227)	0.42
Lipid lowering	85.9 (3231/3761)	83.2 (189/227)	0.28
Beta-blockers	81.9 (3080/3761)	80.2 (182/227)	0.54
ACE inhibitors	58.8 (2212/3761)	54.2 (123/227)	0.19
ARB	15.9 (599/3761)	16.3 (37/227)	0.85
ACE inhibitors or ARB	74.2 (2790/3761)	69.2 (157/227)	0.10
Diuretics	24.5 (920/3761)	26.4 (60/227)	0.52

*These values differ from those in the published manuscripts since they have been corrected but the correction did not influence the main results. CABG= Coronary Artery By-pass Graft; PCI= Percutaneous Coronary Intervention; AMI=Acute Myocardial Infarction; BMI=Body Mass Index; LDL=Low Density Lipoprotein; HbA1c= Haemoglobin A1c; ACE=Angiotensin Converting Enzyme; ARB=Angiotensin Receptor Blocker

The primary, composite cardiovascular endpoint (first of cardiovascular death, myocardial infarction, stroke or hospitalisation for heart failure) occurred in 246/3,775 (6.5%) patients. The 2hPG indicating IGT or T2DM (i.e. dichotomised as < 7.8 vs. ≥ 7.8 mmol/L) was a statistically significant predictor of the primary composite endpoint (the first occurrence of one of the following cardiovascular events: cardiovascular death, hospitalisation for AMI, stroke/TIA or for heart failure). New onset of DM constituted the secondary endpoint) with an adjusted HR of 1.38 (95% CI 1.07-1.78; p=0.01), as presented in Figure 7. Neither FPG nor HbA1c predicted the primary outcome. There was no U- or J-shaped relationship between FPG and the primary endpoint. Adding FPG as a quadratic (or even cubic) effect in the Cox model did not reveal any curvilinear association (p=0.27 for the quadratic term).

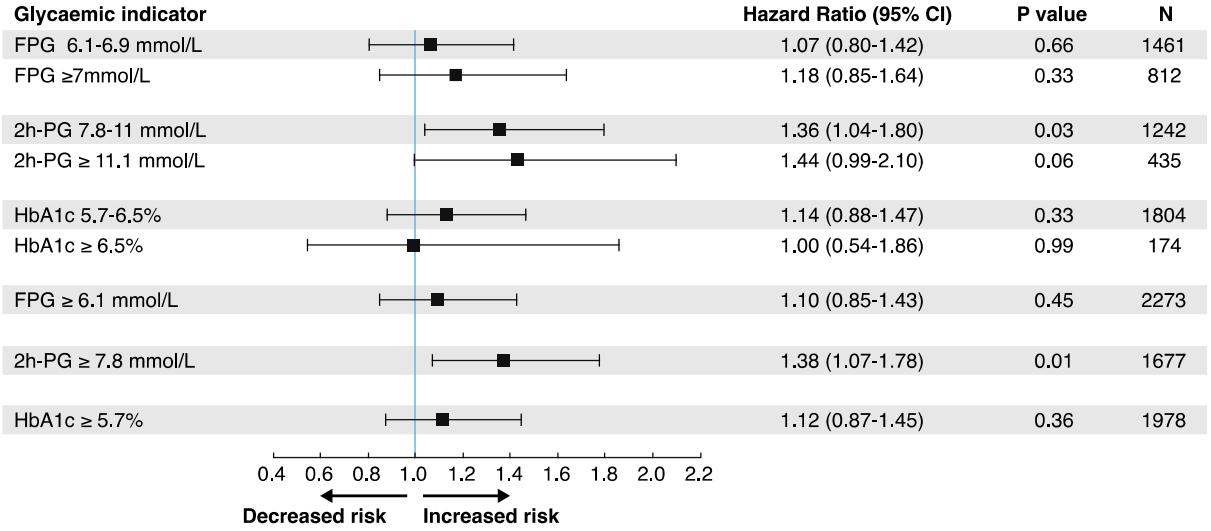


Figure 7. Prognostic value of fasting plasma glucose (FPG), 2h postload glucose (2hPG) and haemoglobin A1c (HbA1c) for the primary, composite endpoint (the first occurrence of one of the following cardiovascular events: cardiovascular death, hospitalisation for acute myocardial infarction, stroke/transient ischaemic attack or for heart failure) in 3,775 patients with coronary artery disease free of type 2 diabetes mellitus at baseline. Hazard ratio (95% confidence interval) and p-value, adjusted for age and sex.

In the adjusted (age, sex, educational level, current smoking, BMI, systolic blood pressure, LDL-cholesterol, statin use, level of physical activity and HADS anxiety and depression score) multivariate Cox regression model, an increment of 1 mmol/L in 2hPG increased the primary event risk by 6% (HR 1.06; 95%CI 1.01-1.13; p=0.03) independently of the level of HbA1c and FPG. The corresponding HR for an increase of 1 SD (2.7 mmol/L) in 2hPG was 1.18 (95%CI 1.01-1.38; p=0.03).

4.1.1.2 Supplementary analyses

In a supplementary analysis, the mean (SD) for FPG at baseline was 6.4 (0.90) mmol/L, 2hPG 7.9 (2.71) mmol/L and HbA1c 5.7% (0.42). These values have been corrected and differ from those in the published manuscript **(Study I)**. This correction did not influence the results.

When FPG and HbA1c were studied in the comparable continuous model, the risk of the primary composite endpoint did not increase significantly for an increment of FPG by 1 mmol/L (HR 1.01; 95%CI 0.85-1.21; p=0.87) or by 1 SD (0.9 mmol/L) (HR 1.01; 95%CI 0.87-1.19; p=0.87). Likewise, an increment in HbA1c of 1% (HR 0.83; 95%CI 0.57-1.21; p=0.33) or of 1 SD (0.42%) (HR 0.92; 95%CI 0.79-1.08; p=0.33) did not increase the risk of the primary cardiovascular endpoint.

All models were screened for potential multicollinearity. No inflation in standard errors of beta-coefficients was detected when gradually building the multivariate models. The pairwise Pearson correlation coefficients (*r*) were low between the glycaemic parameters: 0.38 between FPG and 2hPG, 0.39 between FPG and HbA1c and 0.47 between 2hPG and HbA1c.

4.1.2 Incident T2DM

At the time of follow-up, information on incident T2DM was available in 2,609 (97%) of the participants, who were free from T2DM at baseline. At that time, 78 (3%) of them had developed T2DM. As outlined in Figure 8, FPG between 6.1-6.9 mmol/L was not predictive, while both HbA1c between 5.7-6.4% and 2hPG between 7.8-11.0 mmol/L were significant predictors.

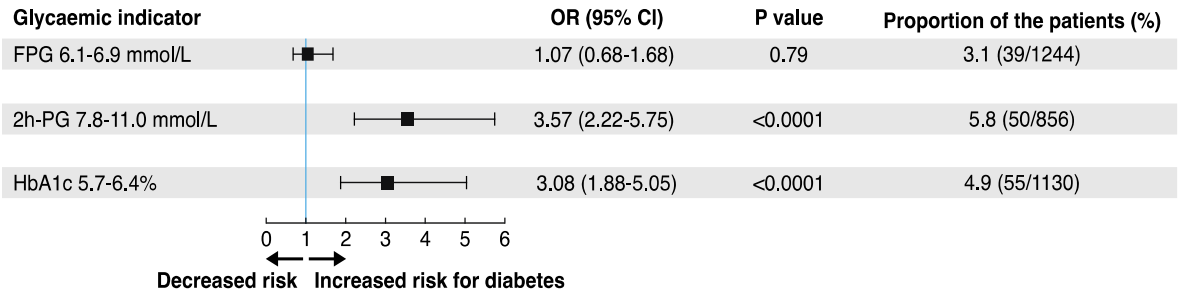


Figure 8. The capacity of fasting plasma glucose (FPG), 2h postload glucose (2hPG) and haemoglobin A1c (HbA1c) to predict incident type 2 diabetes mellitus in 2,609 patients without this disease at the baseline investigation. Odds ratio (95% confidence interval) and P-value adjusted for age and sex.

4.2 DYSGLYCAEMIA IN PATIENTS TREATED FOR HYPERTENSION AND/OR DYSLIPIDAEMIA (STUDY II)

The clinical characteristics of included (n=2,395) and excluded (n=817) patients are presented in Table 7. Those excluded from the analysis were more often smokers, less physically active and had a lower educational level, higher diastolic blood pressure, FPG and HbA1c and were more frequently using lipid-lowering and calcium channel blockers. Of the 2,395 included patients, 85% were using antihypertensive medication and another 153 patients had blood pressures in the hypertensive range. As a result, 89% of the population had hypertension at the time of examination.

Table 7. Pertinent characteristics of included and excluded patients. **Significance of the difference between groups, adjusted for age and sex; **N=177; ****N=167; ****N=668.*

Variable	Included	Excluded	p-value*
Age (years; mean ±SD)	58.1 (7.8)	57.9 (11.7)	0.71
Female gender (%, n)	60.8 (1457/2395)	57.8 (472/817)	0.13
BMI (kg/m^2; mean±SD)	29.4 (5.0)	29.3 (4.7)	0.38
Obesity (%, n)	40.8 (976/2395)	39.4 (318/808)	0.52
Central obesity (%, n)	60.7 (1452/2393)	60.6 (477/787)	0.81
Smoking (%, n)			
Current	16.0 (382/2395)	19.7 (161/817)	0.03
Past	26.2 (628/2395)	24.8 (203/817)	0.27
Hypertension (%, n)	49.1 (1175/2392)	52.1 (420/806)	0.19
Blood pressure (mm Hg; mean±SD)			
Systolic	138.6 (17.9)	139.6 (18.3)	0.20
Diastolic	82.8 (10.3)	84.5 (10.7)	0.0002
Cholesterol (mmol/L; mean±SD)			
Total	5.63 (1.19)	5.60 (1.18)	0.63
HDL	1.31 (0.32)	1.30 (0.34)	0.29
LDL	3.58 (1.03)	3.54 (1.01)	0.52
Triglycerides (mean±SD)	1.66 (1.02)	1.73 (1.19)	0.56
Plasma glucose (mmol/L; mean±SD)			
Fasting	6.24 (0.91)	6.40 (0.83)**	0.02
2h postload	7.34 (2.28)	7.62 (2.26)***	0.13
HbA1c (%)	5.67 (0.50)	5.75 (0.67)****	0.0003
Pharmacological treatment (%, n)			
Aspirin/antiplatelets	27.8 (665/2391)	25.0 (204/815)	0.14
Lipid-lowering	31.0 (741/2391)	39.1 (318/814)	<0.0001
Beta-blockers	30.5 (730/2392)	31.5 (256/813)	0.53
ACE inhibitors	48.2 (1153/2392)	49.0 (399/814)	0.71
AT-II receptor blockers	18.9 (452/2392)	19.8 (161/813)	0.56
Calcium channel blockers	22.4 (535/2392)	26.3 (214/814)	0.03
Diuretics	29.4 (703/2391)	31.5 (257/815)	0.21
Low educational level (%, n)	10.5 (250/2382)	14.7 (120/816)	0.002
Low/moderate physical activity (%, n)	55.4 (1295/2337)	61.5 (487/792)	0.001

BMI=Body Mass Index; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; HbA1c=Haemoglobin A1c; ACE=Angiotensin Converting Enzyme; AT-II= Angiotensin II

4.2.1 Prevalence of dysglycaemia in patients treated for hypertension and/or dyslipidaemia

According to the OGTT, 934 (39%) had previously undetected dysglycaemia (T2DM 19%, IGT 20%). The OGTT identified 92% of patients with T2DM, FPG + HbA1c 90%, FPG 80%, 2hPG 29% and HbA1c 22% (Figure 9). There was little (8%) overlap between all three methods.

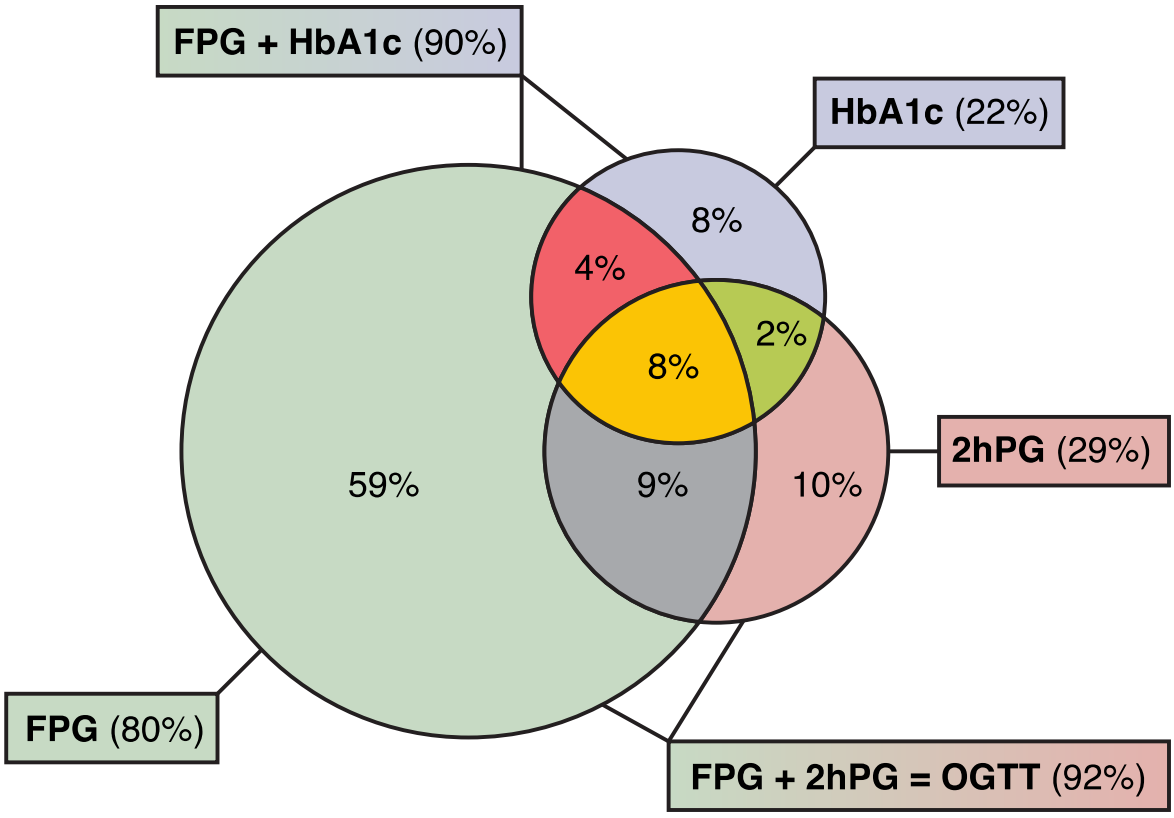


Figure 9. Proportions and their overlap between screening with fasting plasma glucose (FPG) ≥ 7 mmol/L, 2h postload glucose (2hPG) ≥ 11.1 mmol/L, haemoglobin A1c (HbA1c) ≥ 6.5%/48 mmol/mol and combinations commonly used in clinical practice (FPG + HbA1c and FPG + 2hPG) in the 492 patients with newly detected type 2 diabetes mellitus.

4.2.2 Dysglycaemia in relation to the FINDRISC categories

Of patients who, according to the FINDRISC, had a low, moderate or slightly elevated risk, 20, 34 and 41% had dysglycaemia (IGT or T2DM) respectively and, of those in the high and very high-risk category, 49 and 71% had dysglycaemia (IGT or T2DM) respectively (Figure 10).

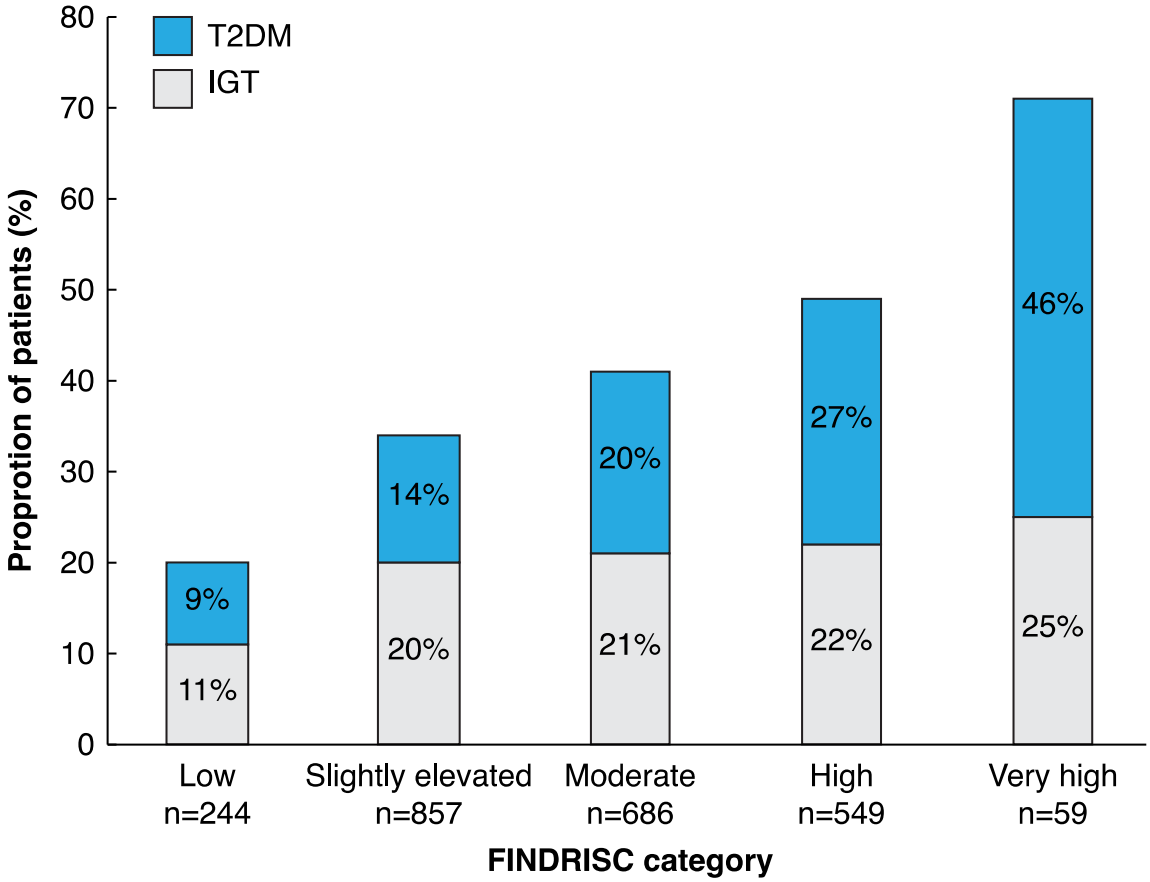


Figure 10. Proportion of patients treated with antihypertensive and/or lipid-lowering drugs with newly detected dysglycaemia (type 2 diabetes mellitus [T2DM] and impaired glucose tolerance [IGT]) according to the oral glucose tolerance test (OGTT) in each of the Finnish Diabetes Risk Score (FINDRISC) categories. The total number of patients in each FINDRISC category is indicated below each bar.

4.2.2.1 Supplementary analyses

In the supplementary analyses of its discriminative value, the FINDRISC was of some value in predicting T2DM (AUC 0.672) (Table 8). This was not, however, convincing, beyond what was achieved with a FPG (AUC 0.811) or an HbA1c (AUC 0.836) alone.

Table 8. Discriminative power of the Finnish Diabetes Risk Score (FINDRISC), fasting plasma glucose (FPG), 2h postload glucose (2hPG) and haemoglobin A1c (HbA1c) in 2,395 patients.

Model (including age and sex)	**Likelihood ratio χ^2 statistics (degree of freedom)**	**Area under the curve** (AUC; range 0-1, the higher the better)
FINDRISC	51.5 (3)	0.672
FPG	225.9 (3)	0.811
HbA1c	186.8 (3)	0.836
FINDRISC + FPG	235.5 (4)	0.819
FINDRISC + HbA1c	204.6 (4)	0.835
HbA1c + FPG	296.2 (4)	0.862
FINDRISC + HbA1c + FPG	302.5 (5)	0.865

4.3 EFFECTIVENESS OF DIFFERENT OUTREACH STRATEGIES (STUDY III)

The total number of respondents to the FINDRISC questionnaire through the different communication channels was 4,412, of whom 372 (7%) had high/very high risk scores. As illustrated in Figure 11 A and B, the highest response rate to the FINDRISC was obtained through workplaces (27%) and the largest proportion of respondents at high/very high risk through the Syrian Orthodox churches (18%).

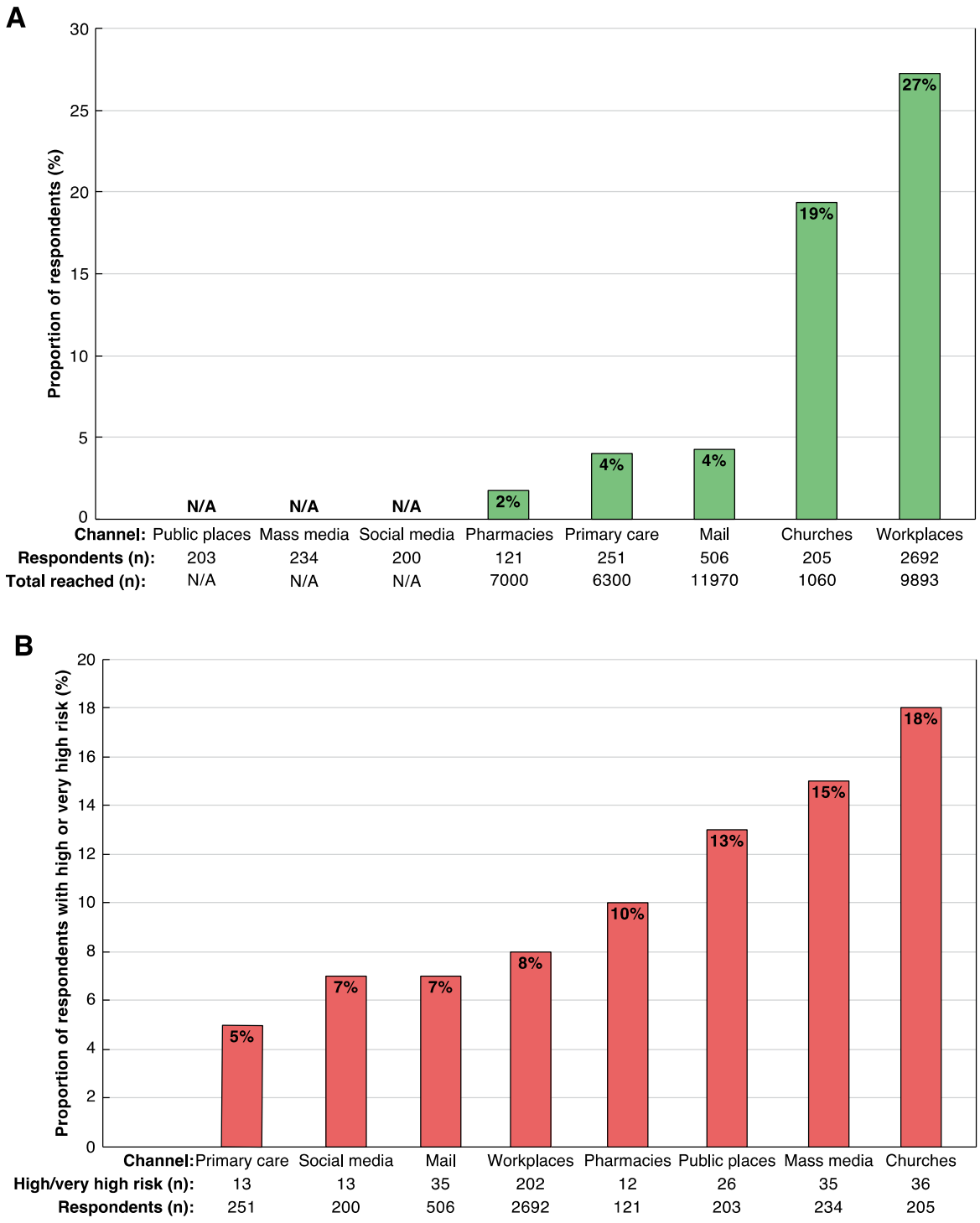


Figure 11. Proportion of respondents
A. To the Finnish Diabetes Risk Score (FINDRISC) reached through different communication channels
B. At high or very high risk of future type 2 diabetes mellitus, according to the FINDRISC questionnaire, identified by different communication channels

The proportion reached through primary care centres was 4%, of whom 5% were at elevated risk. The respondents reached through workplaces were mainly born in Sweden and 53% had post-secondary education compared with those reached via the Syrian Orthodox churches, who were mainly born outside Europe and had a lower education (Table 9). Crowded public places reached a total of 203 respondents, mass media 234 and social media 200 respectively (proportions not known).

Table 9. Characteristics of the respondents reached through different communication channels. The presented data are n (%), unless otherwise stated.

	Respondents n	Females n (%)	Mean age	Respondent sborn outside Europe n (%)	Respondents with post-secondary education n (%)	Smokers n (%)	Respondents in full-time employment n (%)
Pharmacies	121	85 (70)	44	18 (15)	57 (47)	20 (17)	70 (58)
Workplaces	2692	1931 (72)	46	291 (11)	1427 (53)	290 (11)	2323 (86)
Primary care	251	169 (67)	45	51 (20)	103 (41)	44 (18)	162 (65)
Churches	205	92 (45)	50	178 (87)	65 (32)	37 (18)	90 (44)
Crowded places	203	105 (52)	44	128 (63)	100 (49)	47 (23)	87 (43)
Mail	506	310 (61)	45	94 (19)	255 ((50)	48 (9)	295 (58)
Mass media	234	184 (79)	51	16 (7)	132 (56)	27 (12)	173 (74)
Social media	200	132 (66)	41	21 (11)	79 (40)	32 (16)	124 (62)
Total	4412	3008 (68)	46	797 (18)	2218 (50)	545 (12)	3324 (75)

The average cost of identifying a person at elevated risk was €70. The cost of identifying a person at elevated risk was €104 via the Syrian Orthodox church compared with €8 through workplaces and €112 through primary care centres (Figure 12).

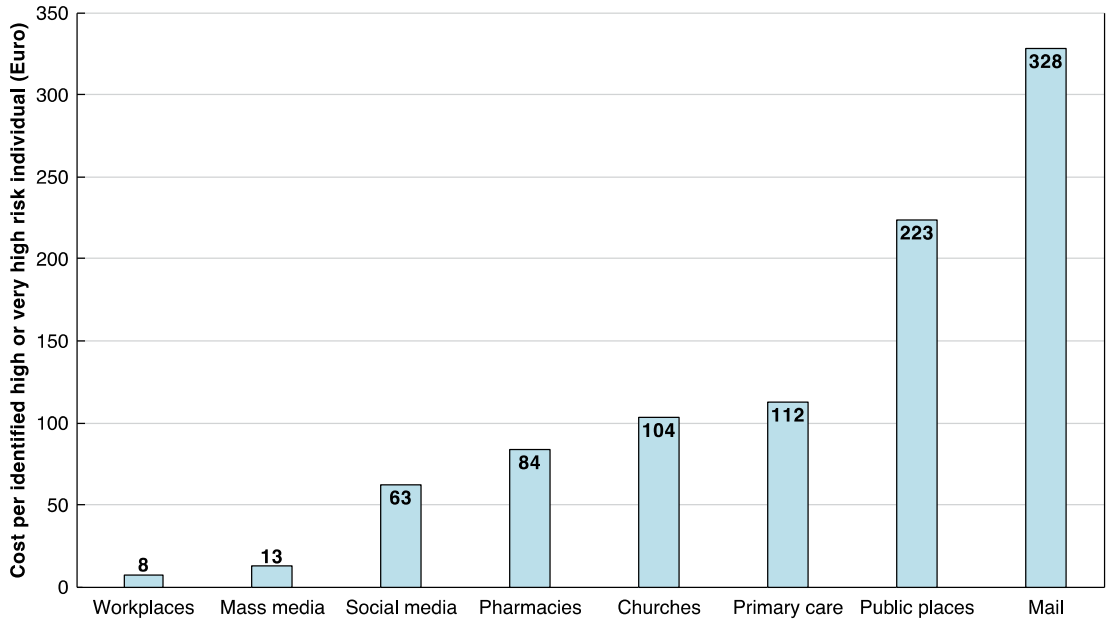


Figure 12. The estimated cost in euros (€) of identifying an individual at high/very high risk of future type 2 diabetes mellitus according to the Finnish Diabetes Risk Score (FINDRISC) by communication channel. The estimated cost of crowded public places only included football matches.

4.4 THE ACCURACY OF POINT-OF-CARE EQUIPMENT IN SCREENING FOR DYSGLYCAEMIA (STUDY IV)

Two hundred and fourteen pairs of plasma glucose values were analysed from 87 patients, of which 85 were in the fasting state, 57 at 1hPG and 72 at 2hPG using HemoCue® monitors and local hospital laboratories. The median fasting glucose level was 6.2 mmol/L and the interquartile ranges Q1 and Q3 were 5.6 and 6.9 with HemoCue® compared with 5.8 mmol/L (5.3; 6.4) at the local hospital laboratories. The corresponding values for the median 2hPG were 7.0 mmol/L (6.2; 8.5) with HemoCue® and 6.8 (5.7; 8.8) at the local hospital laboratories. The two methods correlated (FPG r=0.94 and 2hPG r=0.96; p<0.05). The correlations between glucose values obtained at the local hospital laboratories and the central laboratory were *r*=0.93 for FPG and 1.0 for 2hPG respectively. The plot according to the Bland-Altman method showed small differences between HemoCue® and the local hospital laboratory method (Figure 13).

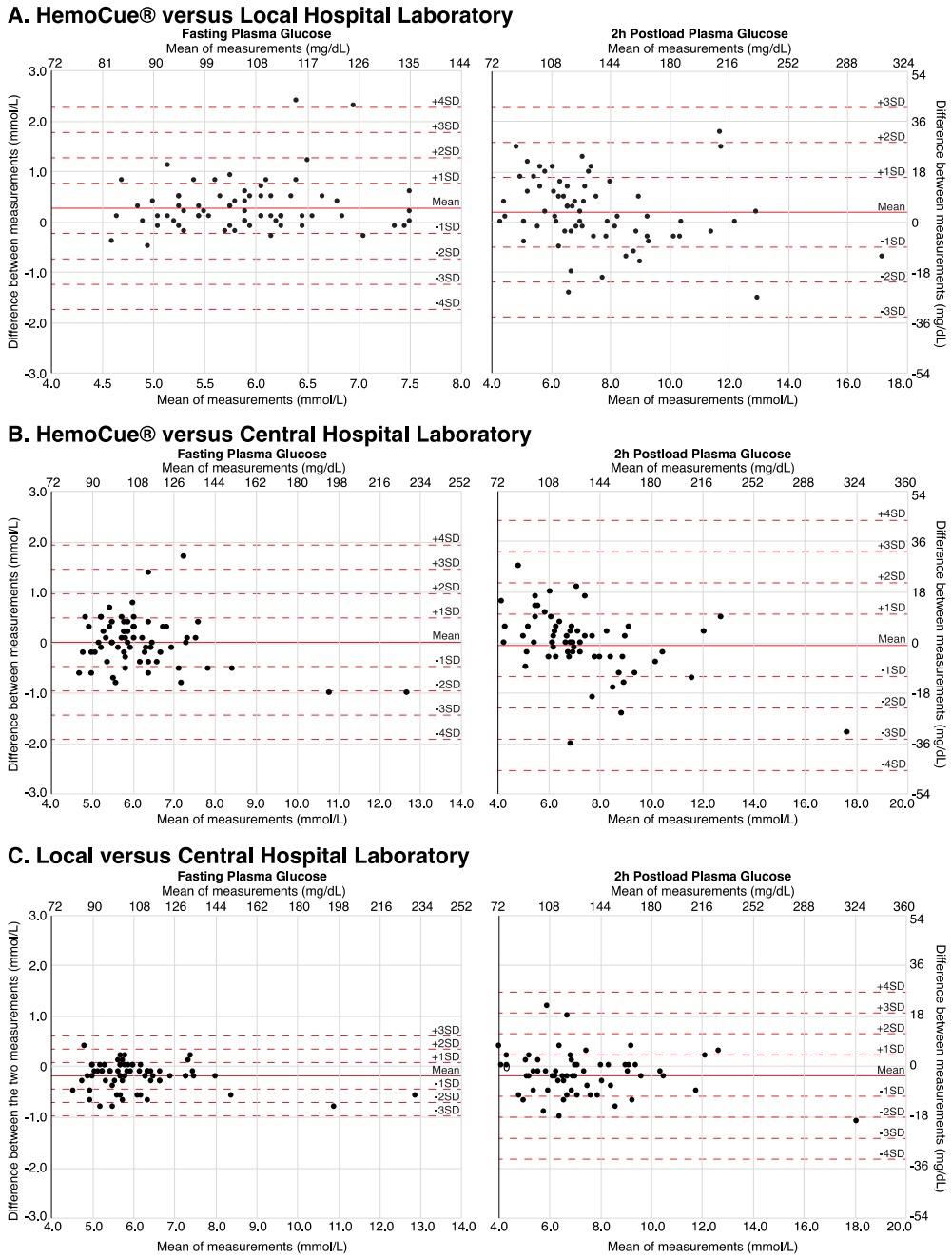


Figure 13. Plot according to Bland-Altman expressing the difference between A) the HemoCue® and hospital laboratory measurements; B) HemoCue® and the central hospital laboratory; and C) the local hospital laboratories and the central hospital laboratory.

In the surveillance error grid, 98.6% of the values were in the deep green zone, indicating no risk, while the remaining values (1.4%) were within the light green zone, indicating "slight, lower risk" for hypo- or hyperglycaemia with Hemocue® when compared with the reference method at the local laboratory (Figure 14).

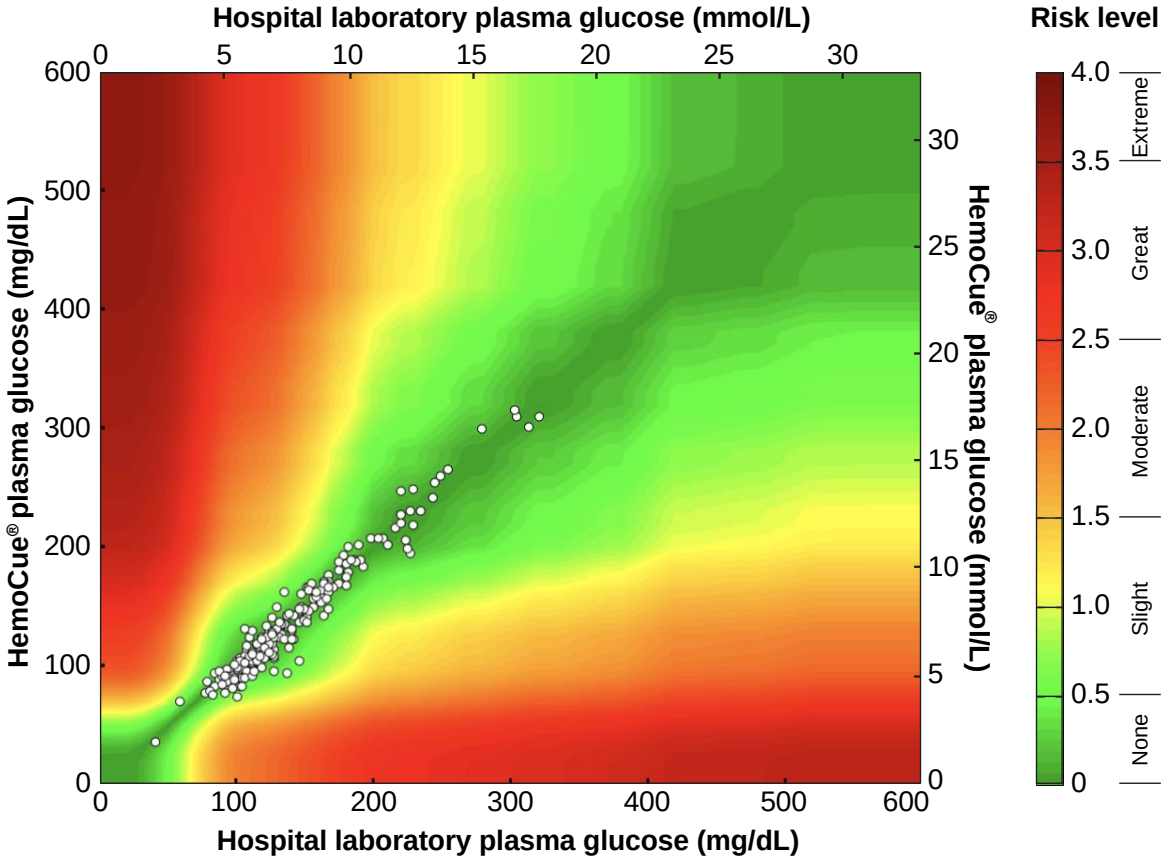


Figure 14. Surveillance error grid analysis for HemoCue® and the local hospital laboratories. The y-axis depicts the HemoCue® readings and the x-axis the local laboratory glucose measurements. The colour-coded risk zone definition is according to Klonoff et al.[148] The degree of risk for hypo- or hyperglycaemia is coded from 0 (none) to 4 (extreme).

5 DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS

1) An OGTT has the best diagnostic capacity of different diagnostic tests for dysglycaemia in patients with CAD.[131] The main finding of the present investigation (**Study I**) was that the 2hPG, but not the FPG or HbA1c, was a significant predictor of future cardiovascular events. The implication is that the 2hPG obtained by an OGTT captures aspects of dysglycaemia (detection rate and prognostic information) of relevance to the development of CAD that is underestimated by both the FPG and HbA1c.

2) There is evidence that underlines the need for the early detection of dysglycaemia to prevent or postpone its complications. A large group of particular interest in this respect is people free from CVD but with known hypertension and/or dyslipidaemia in whom the presence of dysglycaemia raises the cardiovascular risk substantially. The present investigation (**Study II**) revealed that a large proportion of these patients, 39%, had previously unknown dysglycaemia. The use of a simple questionnaire, the FINDRISC, applied to reduce the demand for blood testing turned out to be inadequate in this population.

3) The investigation of the effectiveness of unconventional outreach strategies on the commonly advocated opportunistic screening via primary care centres in a population with a high proportion of immigrants (**Study III**) revealed that the highest response rate was obtained through workplaces and the largest proportion of individuals at high risk were identified through the Syrian Orthodox churches. The cost of identifying a high-risk person varied greatly, depending on the outreach strategy. The implication is that the choice of outreach strategy affects the participation rate, the risk group that can be targeted and screening costs.

4) The accuracy of point-of-care glucose measurements has been questioned as compared with accredited hospital laboratories. The HemoCue® point-of-care system did, however, correlate well with laboratory measurements and can be considered accurate for dysglycaemia screening (**Study IV**).

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Strengths

The materials and methods upon which this project is based have several strengths. The EUROASPIRE database used in **Studies I**, **II** and **IV** is unique, combining data retrieved from medical records with face-to-face interviews based on internationally validated questionnaires and examinations by trained personnel using the same protocol, standardised equipment and including central laboratory measurements. All three standard methods for glucose measurements, the FPG, 2hPg and HbA1c, were measured.

Loss to follow-up is a particular problem associated with cohort studies. However, only 6% of the patients in **Study I** were lost to follow-up, which must be regarded as a great strength, even though the follow-up period was relatively short.

To investigate the effectiveness of different outreach strategies in a heterogeneous population, a multichannel screening approach was initiated in **Study III**. This was based on the assumption that large-scale screening for T2DM could be improved by the choice of outreach strategy accounting for the characteristics of the targeted population.

The glucose values collected in **Study IV** were not only compared between the point-of-care equipment and the local hospital laboratory, but all tests were also validated at a central, core laboratory.

5.2.2 Limitations

5.2.2.1 Selection bias

Selection bias may affect the external validity, i.e. the generalisability, of a study to other populations. The populations in **Studies I-II** are all subjected to the influence of what is labelled as *self-selection* because the centres volunteered to participate in the EUROASPIRE surveys. These centres may have a particular interest in cardiovascular prevention and may not be representative of other centres in the same country or across Europe. If anything, it is therefore likely that the standard of care is higher at these centres than that provided to patients in everyday clinical practice.

The patient material in **Study I** consisted predominantly of men, which could affect the generalisability of the results to women. The results do, however, originate from a population typical of daily clinical practice and are valid from that perspective.

In **Study I,** the age ranged between 18-80 years (mean=64). The distribution was thus skewed, with only 9.2% of the patients younger than 50 years. Younger patients, who develop dysglycaemia and CAD, may differ from older subjects. However, excluding patients younger than 50 years did not alter the main results.

In **Study III,** individuals who completed the FINDRISC voluntarily may be more health conscious than those who did not attend screening. People who are more health-conscious may run a lower risk of developing T2DM. In contrast, some of the participants may have been particularly concerned about their risk of T2DM, e.g. due to a family history of the disease. These biases should counteract each other, but, as none of them was quantified, the net bias remains unknown.

Another selection bias may be introduced in surveys with low participation rates, as there may be important differences between participants and those who abstained from participation. In EUROASPIRE IV, only 49% of consecutive patients with established CAD identified from medical records attended the interview.[151] This may reflect low participation in epidemiological research in general,[152] but it could also be due to restrictions imposed by national and European laws on how often and through which channels the patients can be contacted. In some countries, patients can only be contacted via mail, while personal contacts are prohibited. Nevertheless, the low participation rate introduces a potential bias, as non-participants are more likely to have unhealthy lifestyles and poorer risk-factor control.[152] The present findings would then, if anything, underestimate the true prevalence of dysglycaemia and its impact on future cardiovascular events. Likewise, the true prevalence of dysglycaemia in **Study II** may also be higher, as patients who were excluded due to missing data had higher blood pressure levels and glycaemic variables.

In **Study III,** Södertälje was chosen as a community that could be used to study immigrant-dense populations. The results from this city, with approximately 39% immigrants, cannot therefore be immediately generalised to other communities. Moreover, and in the absence of a formal comparison between pertinent characteristics of the Syrian and the total population of Södertälje, the cohort is not representative of the entire municipality. In spite of this, **Study III** contributes a very important message, namely that it is important to consider the characteristics of the screened population when choosing the most efficient outreach strategies and that a "universal" screening programme may not be effective.

5.2.2.2 Information bias

The majority of incident T2DM were self-reported diabetes in **Study I** and the FINDRISC questionnaire was self-administered in **Studies II** and **III**. One concern when it comes to self-reported data relates to *recall bias***,** a systematic error that occurs when participants do not recall previous events or experiences accurately or omit details for other reasons. Recall bias can threaten the internal validity and credibility of a study.[153] Validation studies report a specificity of > 90% for self-reported T2DM and a sensitivity of 60-70%.[154–156] One study reported that patients tended to minimise their dysglycaemia, believing that they had "borderline T2DM", although they were classified as having T2DM in their medical records.[156] In these studies, sensitivities of self-reported data for other cardiovascular risk factors were almost similar to that of T2DM. Based on these studies, it can be assumed that the self-reported incident T2DM in **Study I** may represent an underestimation of the true prevalence of dysglycaemia. Furthermore, since a large number of patients at baseline in **Study I** had undiagnosed T2DM, reflecting the low screening rate by health-care providers, it is likely that many patients remained undetected during the follow-up period. Another uncertainty that arises from not reassessing the patients' glycaemic status at follow-up in **Study I** is that glycaemic status tends to change over time. This may be important, as the prognostic value of glycaemic indicators regarding future cardiovascular events may reflect patients whose glycaemic status deteriorates, but it may be less critical in those who return towards a better glycaemic status. However, Wallander et al. investigated a population of patients with ACS using an OGTT at hospital discharge and after three and twelve months. The vast majority, 93%, originally classified as having T2DM, still had dysglycaemia 12 months later.[157] Returning towards normal glucose metabolism was very uncommon.

One further limitation in **Studies I-II** is that, as in almost all similar epidemiological studies, dysglycaemia was based on a single glucose recording rather than, as recommended by the WHO for a clinical diagnosis, repeated measurements.

5.2.2.3 Dichotomising glucose

Glucose, a continuous variable, was dichotomised in **Study I** according to the diagnostic criteria issued by the ADA and the WHO. This kind of dichotomisation may be regarded as a simplification, losing information on any changes in the effect of the measured variable within the different intervals.[158] The reason for dichotomising patients into having either normal values or dysglycaemia was to mirror clinical practice, where the diagnosis of dysglycaemia is based on certain cut-off levels. Dichotomisation may also be a good strategy to present data in a way that is easier to interpret and present. However, looking at the three glycaemic parameters in a continuous Cox regression model, the 2hPG was still the only test that was able significantly to predict the primary composite endpoint. Since some previous studies have reported on a non-linear relationship between FPG and CVD, the model was tested for a U- or J-shaped relationship between FPG and the primary endpoint, without any significant relationship being found. In addition, adding FPG as a quadratic (or even cubic) effect in the Cox regression model did not reveal a curvilinear association. However, such analysis may lack statistical power in **Study I.**

5.2.2.4 Collinearity in multiple regression models

One advantage of multivariate regression analysis is that, by including as many covariates as possible, the model allows us to argue that the primary predictor matters, after attempting to control for all the important variables that could possibly affect the outcome. The pitfall is the increasing risk of including variables that are correlated or act as an intermediate step in a casual pathway. It may be that two "independent" variables are so strongly correlated to one another that they are collinear. Two variables are perfectly collinear if there is an exact linear relationship between them, meaning mathematically a

correlation coefficient r equal to 1 or −1. However, studying correlations only among *pairs* of predictors is limiting. Although the r between any two X variables may be small, three independent variables may be highly correlated as a group. When two or more variables are correlated, we may have the problem of multicollinearity.[159] One serious consequence of multicollinearity is that the standard error of the regression coefficient estimators are inflated, which makes some variables statistically insignificant when they should be significant. In **Study I,** the models were screened for multicollinearity which did not appear to be a concern as both the pairwise correlation coefficients were low between the glycaemic indicators and no inflation was found in the regression coefficients when building the multivariate models. However, multicollinearity is a matter of degree and the pattern of covariation between the predictor variables will determine, to some extent, which becomes significant in the final Cox regression model. In practice, multicollinearity is an important issue, particularly in clinical work, where there may be multiple standard measurements of the severity of disease.

5.3 SPECIFIC FINDINGS IN PERSPECTIVE

5.3.1 Prognostic implications of indicators of dysglycaemia

The 2hPG, but not FPG or HbA1c, added prognostic information regarding future cardiovascular events in **Study I,** which is in line with the findings in several previous studies, as outlined below.

The population-based DECODE and Collaborative analysis of Diagnostic criteria in Asia (DECODA) studies, comprising people of different ethnicities with and without known CVD, observed that the 2hPG was a better predictor of all-cause mortality and future cardiovascular events than FPG.[136,160] The 2hPG was compared with HbA1c in two studies that were part of DECODE. Both tests predicted all-cause mortality, but neither FPG nor HbA1c added significant information if 2hPG was entered into the statistical model.[161] In the observational Framingham Offspring Study in people with treated T2DM free from CVD, FPG, 2hPG and HbA1c tests were individually significant predictors of CVD during a four-year period, but the 2hPG was the only test that remained independently predictive of CVD when all the tests were modelled together.[162] In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study of 10,026 people without diagnosed T2DM and any history of CVD, the 2hPG and FPG, but not HbA1c, were significant predictors of all-cause mortality, while all the tests were significant predictors of CVD mortality.[163] There was a linear relationship for 2hPG and HbA1c and cardiovascular risk and a J-shaped relationship for FPG. In a population-based cohort study from Germany, IFG and "high-risk" HbA1c were not significantly associated with incident cardiovascular events after adjustment for conventional cardiovascular risk factors. In contrast, strong associations with cardiovascular events persisted after adjustment among individuals with manifest T2DM, regardless of how they were diagnosed.[164]

The Atherosclerosis Risk in Communities Study reported that people with "high-risk" HbA1c run an increased risk of developing T2DM and CVD independent of FPG[165], but a postload glucose was not included in this study. The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk)[166] reported that HbA1c significantly predicted all-cause mortality and cardiovascular events, even below the threshold for the diagnosis of T2DM and independent of age and classic cardiovascular risk factors. However, neither a FPG nor a 2hPG was analysed in this model. In a cohort of 8,365 individuals aged 50-74 years, adding IFG or high-risk HbA1c to the Systematic Coronary Risk Evaluation (SCORE) model did not improve cardiovascular risk prediction in individuals without T2DM during an eight-year follow-up.[167] To summarise, it appears that the 2hPG is a stronger predictor of cardiovascular outcomes in population-based studies.

In patient populations with CAD, the Silent Diabetes Study compared the prognostic capacity of HbA1c with that of an OGTT in 1,015 patients without previously known T2DM undergoing coronary angiography. The 2hPG was closely related to the severity of CAD and future mortality during a three-year period and in this respect superior to FPG, whereas there was no association with HbA1c.[168] In a retrospective study of 1,056 patients with acute coronary events without known T2DM, FPG and 2hPG were measured pre-discharge. The 2hPG but not the FPG predicted future ACS during a period of 41 months. The 2hPG also improved the predictability of the Global Registry of Acute Coronary Events (GRACE) risk score.[169] Unfortunately, HbA1c was not included in this study. In the present study, 2hPG indicating IGT (n=1,242) was significantly associated with the primary endpoint, while the 2hPG indicating T2DM (n=435) showed a similar trend with borderline statistical significance, probably due to the lack of power, given the results of previous studies. Evidence is accumulating that it is more important to find out whether CAD patients have dysglycaemia, defined as either IGT or T2DM, than to classify them as having either IGT or T2DM.[11,170] The latter is an arbitrary division that was introduced to distinguish people with dysglycaemia who had T2DM from those who ran a high risk of developing T2DM.[171]

The present study adds new information by incorporating hospitalisation for heart failure in the primary endpoint, which traditionally only includes cardiovascular death, non-fatal MI and stroke. Heart failure emerges as a common and very serious complication of T2DM in the setting of CAD.[172] The importance of heart failure is further underlined by the results of recent trials with the SGLT-2 inhibitors empagliflozin[86], canagliflozin[173] and dapagliflozin[174] in patients with T2DM and established cardiovascular disease or at high cardiovascular risk. SGLT-2 inhibition was associated with a reduction in cardiovascular mortality, which was driven by a decrease in hospitalisation for heart failure.

5.3.2 Screening for dysglycaemia in high-risk patients

In **Study II**, patients free from CVD but on treatment for hypertension and/or dyslipidaemia had a surprisingly high prevalence of dysglycaemia, which was relatively high even in the lower FINDRISC categories. Using the FINDRISC as an initial screening step to select high-risk individuals for further blood glucose testing was therefore not helpful. The most reasonable explanation for this poor discriminatory ability is the high prevalence of dysglycaemia in the population in **Study II** compared with the general Finnish population in which the FINDRISC was developed.[124]

The FPG was the single best test for detecting T2DM, but the use of FPG is limited as it is unable to detect IGT. The combination of FPG and 2hPG via an OGTT identified 92% of those with T2DM and the 2hPG another 20% with IGT. The superiority of this combination corresponds to the outcome of a previous study from EUROASPIRE IV on the glycaemic screening of patients with established CAD.[131] "High-risk" HbA1c classified the majority (72%) of the present population as having glucose perturbations. It is reasonable to suppose that this proportion is too high. At the same time, HbA1c underestimates the prevalence of previously undiagnosed diabetes. Furthermore, "high-risk" HbA1c is reported to be less sensitive than IFG and IGT when it comes to detecting individuals with insulin resistance and beta cell dysfunction.[175]

The present findings gain support from previous experience. In the Impaired Glucose Tolerance and Long-Term Outcomes Observational (IGLOO) study, based on 1,377 Mediterranean participants without known CVD but with one or more cardiovascular risk factors,[176] the prevalence of screening-detected dysglycaemia was 37% (IGT 11%; T2DM 17%). A similar proportion, 41%, was reported by the Atherosclerosis Risk in Communities Study[177] screening 8,286 middle-aged American participants, of whom many had

hypertension, dyslipidaemia and/or central obesity, with an OGTT. Further, 14% had screening-detected T2DM in a cross-sectional population-based study from Kuwait, in which more than half the participants were overweight or obese but without any history of CVD.[178]

Since hypertension is a component of the FINDRISC, it can be argued that it is inappropriate to use this questionnaire in patients with hypertension. One way to investigate whether it matters would be to study a subgroup with only dyslipidaemia. Unfortunately, this was impossible, as 89% of the present study population were either being treated with blood pressure-lowering drugs or were found to have hypertension when investigated. Furthermore, statin use may increase the risk of T2DM, as well as β-blockers and possibly calcium channel blockers.[179] However, patients on statins had a lower proportion of dysglycaemia and there were no significant differences for β-blockers or calcium channel blockers between patients with and without dysglycaemia.

One alternative, limiting the need for an OGTT to 62% of the present population (those with IFG), would be to start screening with a FPG and continue with an OGTT only in patients not fulfilling the criteria for T2DM. With a strategy of this kind, 18% of patients with IGT would be missed. It has to be debated whether this is acceptable. It may be argued that patients under treatment for hypertension and/or hyperlipidaemia should have received lifestyle advice, the cornerstone of dysglycaemia management, so that the detection of IGT would not add more to their management. The present data show that primary care patients on treatment for hypertension and/or dyslipidaemia, in addition to undetected dysglycaemia, had a high prevalence of obesity, smoking and low levels of physical activity.[180] These findings indicate that patients at risk of future cardiovascular events without established CVD require better risk-factor management, given the results of the Steno-2 Study[94] and the reports from the Swedish National Diabetes Register showing that multifactorial management is imperative in reducing the risk of cardiovascular events.[96] In the report from the Swedish National Diabetes Register of patients with T2DM with or without established CVD, the excess risk of outcomes decreased stepwise for each risk factor within target. Patients with optimal risk-factor control had little or no age-adjusted excess risk of death, AMI or stroke.[96] Furthermore, it was also found that levels of HbA1c, systolic blood pressure and LDL cholesterol lower than the recommended target levels were associated with a reduced risk of outcomes. As regards IGT, experiences from the Da Qing study[76], the US Diabetes Prevention Program[101] and the Finnish Diabetes Prevention study[181] demonstrate that an improved lifestyle can significantly reduce the development of overt T2DM during prolonged periods of follow-up. Moreover, micro- and macrovascular complications, including cardiovascular and total mortality, were reduced in the Da Qing study. In patients with T2DM, glucose-lowering drugs can be initiated if lifestyle improvements prove not to be sufficient.

5.3.3 Implementation of screening

Study II shows that screening for dysglycaemia in people with a high proportion of IGT or T2DM is far from optimal, despite the fact that the addition of dysglycaemia to other risk factors substantially increases the future risk of cardiovascular events including mortality.[53]

The current guidelines recommend the opportunistic screening of individuals at risk of T2DM and screening is expected to be implemented in the primary health care setting. In **Study III,** it was evident that, in the specific population of Södertälje Municipality, several unconventional approaches were more beneficial in terms of the participation rate, the proportion of identified high-risk individuals and cost effectiveness. Södertälje Municipality was regarded as an appropriate setting for a study of different screening strategies, as its population consists of both immigrants and Swedish-born people, people with a different socio-economic status and the location of well-established workplaces in the industrial and

health-care sectors. The largest proportion of respondents was obtained through workplaces. It was, however, through co-operation with the Syrian Orthodox church that the largest proportion of individuals at high/very high risk, who were notably presumed to be unlikely to participate in a risk assessment, could be reached. The majority of these respondents were born outside Europe and had a lower level of education and a higher rate of unemployment. These factors may have contributed to differences in health awareness, understanding of the health-care system and limited opportunities to pay for the cost of lifestyle or medical care.[182]

The experiences in **Study III** are not unique. In a Swedish community-based mass screening for atrial fibrillation performed in 2010-2012, participation was low in Södertälje, with many immigrants and a high incidence of ischaemic stroke.[118] Similarly, areas with a low mean income and a high proportion of immigrants had lower participation rates in screening for aortic aneurysms compared with areas with higher socio-economic status.[183] In Tower Hamlets, a deprived borough in the East End of London with a large minority ethnic population, breast cancer screening uptake was 60% in the white population compared with a much lower uptake among women from Pakistan (40%) and Bangladesh (37%). A multi-channel approach through a strong partnership between community organisations, primary health-care centres and public health, with campaigns targeted at Pakistani and Bangladeshi women, increased the total screening uptake from approximately 45% to 63% in three years.[120] Attempts have been made in Afro-American communities to introduce health information by approaching churches, barbershops, beauty salons and other community-based organisations to reach people in deprived areas for the screening of cardiovascular risk factors and breast and cervical cancer. These settings, which are accessible to all communities and are frequently visited, have offered important opportunities for both the reach and the reinforcement of health messages.[116,184–194]

Considering that ADDITION-Cambridge[111] and ADDITION-Denmark[112], did not reveal any reduced all-cause, CVD- or T2DM-related mortality associated with an invitation to screening through the primary care centres, population-based screening for T2DM is the subject of debate. However, ADDITION used only a single mailed invitation, with no reminders to non-respondents and only the primary care centres as an outreach strategy. Only 10% of all people with newly diagnosed T2DM in the ADDITION primary care centres were actually identified through the screening programme. **Study III** strongly supports the assumption that screening in other settings and through different outreach strategies may be more effective and could have yielded a different result. Another explanation is that many individuals in the control group of the ADDITION studies were diagnosed through opportunistic screening. Studies from high-income countries indicate an increase over time in laboratory testing for T2DM in the absence of any formal screening programmes or recommendations.[195]

Studies I and II underline that there is a significant gap between what is currently known about dysglycaemia prevention and screening and what is commonly practised. This screening inertia is difficult to understand in the light of several studies reporting that non-pharmacological interventions in people with IGT are cost effective to reduce the risk of T2DM.[196] A study from the US demonstrated, by using a simulation model, that a national community-based lifestyle programme (based on the US Diabetes Prevention Programme)[73] could delay or prevent T2DM in high-risk individuals and save USD 5.7 billion in 25 years.[197] A Swedish study of individuals with IGT using the Finnish Diabetes Prevention Study programme as a base also reported that lifestyle intervention would be highly cost effective to prevent progression of IGT to T2DM.[198]

5.3.4 Glucose measurement using the point-of-care technique

In **Study IV,** glucose measurements using the HemoCue® point-of-care system corresponded well to the glucose levels obtained at the hospital laboratories from a practical, screening perspective. There were small individual differences between the HemoCue® and the hospital laboratory methods, as the surveillance error grid showed a high level of accuracy with almost all values located in the "no-risk" zone. The Bland-Altman plot indicated a tendency towards higher FPG measurements according to HemoCue® compared with hospital laboratory measurements.

In a study by Stork et al., a total of 500 paired glucose values were obtained from 24 volunteers participating in a hyperinsulinaemic glucose clamp study and analysed by both HemoCue® and approved laboratory standards.[139] In line with the results of the present investigation, the agreement between the two methods was very strong. Other studies reported on consistently higher blood glucose, especially in the hypoglycaemic range, with HemoCue®, but also on lower values than with laboratory glucose.[199] When several point-of-care glucometers, including HemoCue®, were compared with standard laboratory procedures for the diagnosis of T2DM and IGT in 168 individuals undergoing an OGTT, the glucometers were less reliable than the laboratory procedures, especially in the fasting state.[200] These results may, however, have been affected by the use of capillary blood samples with the glucometers, considering that glucose concentrations are reported as higher in capillary blood than venous blood, especially in the postprandial state.[201,202] Several other factors may confound comparisons of glucose measurements with point-of-care and central laboratory methods. First, there is no universal agreement on a reference method for glucose determination, even though the hexokinase method is one of the most common.[140–142] Secondly, a discrepancy between two paired measurements by two devices does not necessarily mean that the tested method is inferior to the reference method.

Since glucose is unstable in whole blood, it is important that samples are analysed without delay. HemoCue® analyses whole blood immediately following blood sampling, which prevents glycolysis, which is the most frequent and important source of pre-analytical error with laboratory measurement. If sample transportation to and handling at the laboratory is delayed, the measured plasma glucose may become lower than the actual level. In the present study, this possibility was at least partially overcome by inhibiting the potential of glycolysis by using fluoride/citrate tubes.[203] In spite of this, glycolysis may have contributed, to some extent, to the fact that some patients had higher glucose with HemoCue® than when measured at the laboratory. The conversion of whole blood to plasma glucose and adjustments for cholesterol levels may also have affected the accuracy of HemoCue®.[138]

The point-of-care technique has the advantage of providing an immediate analysis of the FPG. Furthermore, before establishing a diagnosis in the clinical setting, these patients would have been subjected to renewed testing of their glucose, since the diagnosis of T2DM requires two positive tests. To summarise, the HemoCue® point-of-care system should be regarded as a convenient and accurate method for glucose measurement. The acceptance of point-of-care glucose measurement would simplify and thereby improve patient management that is currently far from satisfactory, as regards dysglycaemia screening.

5.4 ETHICAL CONSIDERATIONS

Risk assessment and the screening of individuals for dysglycaemia raises several ethical questions. In 1968, Wilson at the Ministry of Health in the United Kingdom and Jungner at Sahlgrenska University Hospital in Gothenburg wrote *"in theory, screening is an admirable method of combating disease ... [but] in practice, there are snags"*.[103] The concern about

screening emerged from the problem that disease detection may be simple, but providing adequate therapy to those with newly detected disease and avoiding harm to those not in need of treatment can be far from easy.

Looking at the Wilson-Jungner criteria, T2DM satisfies many of the criteria established for screening programmes. It has a long asymptomatic period during which serious complications can develop, there are simple validated questionnaires and reliable diagnostic tests and interventions for glucose, blood pressure and lipids are effective.[97,98] However, large-scale population screening programmes, such as those that have been established for colon and breast cancer, have not been proven to be cost effective for T2DM. If screening through outreach strategies other than the primary care centres were shown to be cost effective and the impressive effects of SGLT2 inhibitors and GLP-1 receptor analogues on cardiovascular outcomes in people with T2DM at high cardiovascular risk also apply to those at lower cardiovascular risk, screening for dysglycaemia in a broader perspective could perhaps be justified. The cost of large-scale screening with a simple questionnaire appears to be reasonably small when performed through effective channels. However, risk questionnaires may not always be accurate, as observed in **Study II**. Risk scores attempt to estimate the combined effects of several risk factors. They may, however, not be capable of analysing interaction effects in any detail, thereby making the estimates approximate. Furthermore, the risk of a population might also be under- or overestimated, since the prevalence of disease can change over time, making a once valid test inaccurate. One example of this is SCORE for assessing the 10-year risk of CVD based on conventional risk factors. The high-risk SCORE version was recommended for Central and Eastern Europe and the former Soviet Union. When the performance of SCORE was examined, it was observed that the high-risk version of SCORE underestimated the risk substantially in Russia, with an increase in CVD mortality, but, at the same time, it overestimated the risk in countries in which CVD mortality had declined.[207,208]

Seen from a population perspective, screening for a "mass disease" provides information on the direction of change in important factors for public health on which interventions can be based. However, there is a preventive paradox according to Geoffrey Rose, "*a preventive measure that brings large benefits to the community offers little to each participating individual*".[209] A mass approach, like that in **Study III**, may reduce morbidity at population level but may cause anxiety and stress in individuals. In **Study II,** many patients were classified as having high-risk HbA1c without any available evidence that this was of any benefit to these patients in terms of treatment or prognosis. However, looking at the psychological aspect of screening in T2DM, its impact appears to be limited.[210] For example, in a substudy of the ADDITION (Cambridge) trial, no clinically relevant differences were found for anxiety, depression, T2DM-specific worry and self-rated health between the screening attenders and the control participants.[211] In a qualitative interview study of 23 participants in the ADDITION (Cambridge) trial,[212] T2DM screening in order to detect the disease at an early stage was perceived as a good thing. However, on a personal level, the participants tended to not pay attention to their risk. Most participants with IFG or IGT struggled to understand the implications of these conditions and were not intending to change their lifestyles. This may partly be due to lack of understanding and management protocols for patients with IGT by health care providers as reported by a qualitative study of general practitioners in England.[213]

In **Study III,** individuals who were given the opportunity to have their blood glucose measured at the temporary lab units did not show up, despite being informed about their elevated risk according to the FINDRISC. One explanation may be that these individuals did not take the risk of having T2DM seriously, as concluded in the ADDITION trial, or that

they did not assimilate the information they were given. This is clearly worrying and raises the question "Is risk assessment justified if individuals at risk do not undergo further evaluation?". However, it may be that high-risk individuals chose to seek their primary care centres for further evaluation. Further information on this was not, however, available.

5.5 FUTURE DIRECTIONS

This project has shown that the three diagnostic tests for dysglycaemia differ in their diagnostic and prognostic capacities. These observations beg the question: do patients with dysglycaemia captured uniquely by the FPG, HbA1c or 2hPG tests differ in terms of underlying pathophysiology and future complications? Studies are needed to examine whether, for example, individuals diagnosed solely on the basis of HbA1c differ from those diagnosed only by a 2hPG when it comes to underlying mechanisms and complications. One hypothesis is that these two groups of patients display different levels of insulin resistance. This prediction could be tested by measuring markers of insulin resistance and inflammation in individuals diagnosed on the basis of different tests. Furthermore, intervention studies with, for example, SGLT2 inhibitors or GLP-1 receptor agonists of individuals diagnosed on the basis of FPG, 2hPG or HbA1c may shed light on the clinical relevance of these tests.

In a recent study from Sweden, five clusters of patients with adult-onset diabetes, who would traditionally be categorised as T1DM, T2DM or LADA, were identified.[214] These five clusters consisted of severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes. Severe autoimmune diabetes overlapped with T1DM and LADA but severe insulin-deficient diabetes and severe insulin-resistant diabetes, represented two new types of diabetes masked within T2DM according to the present classification of diabetes. Individuals with severe insulin-resistant diabetes displayed a substantially increased risk of kidney complications while individuals with severe insulin-deficient diabetes had the highest risk of retinopathy. Individuals with severe insulin-resistant diabetes and mild age-related diabetes seemed to have higher risk of coronary events. However, the differences in coronary events between the clusters were not significant when adjusted for age and sex. The findings in this PhD project are therefore compatible with recent evidence showing that T2DM is a heterogeneous disease. Our findings may help to identify T2DM subgroups with an increased risk of complications, bringing us one step closer to individualised medicine in which treatment is tailored to each patient's individual need and risk profile.

Study I did not have the power to look into single cardiovascular outcomes rather than a composite endpoint. The prognostic value of the screening tests may differ with regard to different cardiovascular outcomes, which would be interesting to investigate in more detail in future, larger samples. Moreover, the need to find simple screening strategies remains an important goal. It would be valuable to validate the time-saving algorithm based on the use of one hour postload glucose from an OGTT in patients at high risk of future cardiovascular events that was suggested based on EUROASPIRE IV patient data.[215]

The populations in **Studies I** and **II** at risk of future cardiovascular events need better risk factor control. Today, there is a substantial gap between guideline recommendations and daily practice. In future studies, we need to examine how optimally to implement existing knowledge on the prevention of dysglycaemia and CVD in clinical practice. The findings of **Study III** indicate that unconventional outreach strategies may be effective, e.g. through churches, employers and social media, in place of the conventional primary care setting. However, it remains to be shown whether these unconventional outreach strategies will also

be effective in providing lifestyle interventions in individuals at elevated risk of dysglycaemia.

Many individuals with an elevated risk of dysglycaemia are believed not to have undergone further investigation in **Study III**, even though they were offered medical assistance. It is not only an interesting but also a very important topic for future studies to explain why these individuals were not interested in following up their questionnaire results. At the same time, novel strategies for motivating high-risk individuals to attend screening should be examined.

6 CONCLUSIONS

1) When comparing the prognostic capacity of FPG, HbA1c and 2hPG regarding future cardiovascular events in patients with CAD, the 2hPG was the only test that provided independent prognostic information. An OGTT should therefore be performed in patients with a high risk of future cardiovascular events.

2) The prevalence of previously undetected dysglycaemia was high in patients treated for hypertension and/or dyslipidaemia but without established CVD. The use of the FINDRISC questionnaire did not reduce the demand for blood testing. Screening in this population should be initiated with at least a FPG.

3) The choice of outreach strategy was important to reach high/very high risk groups for T2DM and for screening costs in the immigrant-dense, thereby heterogeneous, population of the Municipality of Södertälje. Future screening programmes should carefully consider their choice of outreach strategies in relation to the characteristics of the screened population.

4) The HemoCue® point-of-care system is accurate for dysglycaemia screening and its use saves time when performing an OGTT.

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