Karolinska Institutet, Department of Medicine Solna
Cardiology Unit, Karolinska University Hospital
Stockholm, Sweden

DYSGLYCAEMIA AND CARDIOVASCULAR DISEASE

Aspects on screening, management, and prognosis

Giulia Ferrannini

Stockholm 2023

Cover art by Anna Ferrannini, 2022
All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet
Printed by Universitetsservice US-AB

ISBN number 978-91-8016-587-7

DYSGLYCAEMIA AND CARDIOVASCULAR DISEASE

Aspects on screening, management, and prognosis

By
Giulia Ferrannini

Thesis for a doctoral degree (PhD)

Principal Supervisor:

Associate professor Linda Garcia Mellbin
Department of Medicine, Solna
Division of Cardiology
Karolinska Institutet

Co-supervisors:

Professor Lars Rydén
Department of Medicine, Solna
Division of Cardiology
Karolinska Institutet

Professor Anna Norhammar
Department of Medicine, Solna
Division of Cardiology
Karolinska Institutet

Viveca Gyberg MD PhD
Department of Medicine, Solna
Division of Cardiology
Karolinska Institutet

Opponent:

Professor DMSc, Chief Physician Peter Haulund Gaede
Department of Cardiology and Endocrinology
Næstved, Slagelse and Ringsted Hospitals
University of Southern Denmark

Examination Board:

Professor Mikael Rydén
Department of Medicine H7 Endocrinology and Diabetes
Karolinska Institutet

Associate Professor Nina Johnston
Uppsala Clinical Research Center
Uppsala University

Associate Professor Sofia Carlsson
Department for Environmental Medicine
Karolinska Institutet

To my family

List of Contents

Abstract

Background: Dysglycaemia, in this thesis defined as impaired glucose tolerance (IGT) or type 2 diabetes (T2DM), is a major risk factor for cardiovascular disease (CVD). International guidelines recommend screening for dysglycaemia and target-driven lifestyle and pharmacological management in people with high cardiovascular (CV) risk or established CVD for both men and women. New glucose-lowering drugs with proven CV benefit are now available.

Aims: The overall aim of this doctoral thesis was to investigate the screening and management of patients with CVD or at high CV risk including gender differences and implementation of new cardioprotective glucose-lowering drugs by studying:
- the prevalence of dysglycaemia according to different screening tools in patients without known diabetes (**Study I**) and by gender (**Study II**);
- the value of new screening methods for dysglycaemia in these patients (**Study III** and **IV**);
- the management of such patients as regards lifestyle habits, use of cardioprotective drugs, and treatment target attainment (**Study I**) including possible gender disparities (**Study II**);
- gender differences in prognosis (**Study II**);
- whether cardioprotection of the glucagon-like peptide-1 receptor agonist dulaglutide is dependent on metformin (**Study V**).

Methods: **Studies I, II, III** and **IV** were based on the population from the EUROASPIRE V cross-sectional survey; **Study II** included data from EUROASPIRE IV and V. Both surveys included patients with established coronary artery disease recruited across Europe at least six months prior to the investigation. Data on clinical history, life-style advice and pharmacological treatment was based on validated questionnaires and standardised blood tests at a study visit. **Study V** is based on patients with T2DM at high CV risk from the randomised controlled trial REWIND.

Results: *Prevalence and screening for dysglycaemia*: In **Study I**, 29% of the study population had dysglycaemia detected by screening, with 70% of them being identified by a two-hour postload glucose value (2hPG) during an oral glucose tolerance test (OGTT). **Study II** found that more women than men had IGT and more men had T2DM.
Study III validated a diagnostic algorithm for T2DM based on the assessment of a one-hour postload glucose value (1hPG) during the OGTT, shortening the time needed for glycaemic classification in 79% of them. In **Study IV**, the diagnostic performance of different insulin resistance indexes was unsatisfactory compared with the yield of an OGTT.
Management: **Study I** showed that multifactorial management after the coronary event was unsatisfactory, with poor adherence to recommended treatment targets for blood pressure, lipids and glycaemic control and a high prevalence of obesity, persistent smoking and limited physical activity. **Study II** highlighted how this management was particularly inadequate in women, possibly contributing to a worse prognosis compared with men in those with known T2DM. **Study V** found that CV protection with dulaglutide seems to be present irrespective of metformin treatment at baseline.

Conclusions: There is a compelling need for implementation of screening for dysglycaemia in patients with CAD, and the OGTT should be the preferred method because it identifies more patients with dysglycaemia, which otherwise would be missed. Time might be mature to introduce an algorithm based on the 1hPG value to identify T2DM. Its prognostic implications should however be further investigated. Multifactorial management of these patients is in demand of a substantial improvement, especially in women, where deficient care may be associated with worse prognosis. The use of new glucose-lowering agents with cardiovascular efficacy should be prioritised regardless of background glucose-lowering therapy.

Sammanfattning

Bakgrund: Dysglykemi, i denna avhandling definierad som nedsatt glukostolerans (IGT) eller typ 2 diabetes (T2DM), är en allvarlig riskfaktor för hjärt-kärlsjukdom (CVD). Internationella riktlinjer rekommenderar screening för dysglykemi och målstyrd livsstil och farmakologisk behandling hos personer med hög kardiovaskulär (CV) risk eller etablerad CVD, både män och kvinnor. Nya glukossänkande läkemedel med bevisad CV-fördel finns nu tillgängliga.

Mål: Huvudsyfte med denna doktorsavhandling var att undersöka screening och hantering av patienter med hjärt-kärlsjukdom eller hög CV risk, inklusive könsskillnader och implementering av nya kardioprotektiva glukossänkande läkemedel genom att studera:
- prevalensen av dysglykemi enligt olika screeningverktyg hos patienter utan känd diabetes (**Studie I**) och efter kön (**Studie II**);
- värdet av nya screeningmetoder för dysglykemi hos dessa patienter (**Studie III** och **IV**);
- omhändertagandet av sådana patienter genom livsstilsvanor, användning av hjärtskyddande läkemedel och måluppfyllelse för behandling (**Studie I**) inklusive möjliga könsskillnader (**Studie II**);
- könsskillnader i prognos (**Studie II**);
- huruvida hjärtskydd av GLP-1 RA dulaglutid är beroende av metformin-behandling (**Studie V**).

Metoder: **Studierna I**, **II**, **III** och **IV** baserades på populationen från den europeiska multicenterstudien EUROASPIRE V; **Studie II** inkluderade data från både EUROASPIRE IV och V. Båda undersökningarna inkluderade patienter med etablerad kranskärlssjukdom som rekryterats över hela Europa minst sex månader före undersökningen. Data om anamnesen, livsstilsråd och farmakologisk behandling baserades på validerade frågeformulär och standardiserade blodprov vid ett studiebesök. **Studie V** är baserad på patienter med T2DM med hög CV risk från REWIND randomiserade studien.

Resultat: *Prevalens och screening för dysglykemi*: I **Studie I** hade 29% av studiepopulationen dysglykemi upptäckt genom screening, varvid 70 % av dem identifierades med ett två timmars glukosvärde efter belastning (2hPG) under ett oralt glukostoleranstest (OGTT). **Studie II** visade att fler kvinnor än män hade IGT och fler män hade T2DM.
Studie III validerade en diagnostisk algoritm för T2DM baserad på bedömningen av ett glukosvärde efter en timme efter belastning (1hPG) under OGTT, vilket förkortade den tid som behövs för glykemisk klassificering hos 79 % av dem. I **Studie IV** var den diagnostiska prestandan för olika insulinresistensindex bristfällig jämfört med utbytet av en OGTT.
Hantering: **Studie I** visade att multifaktoriell behandling efter kranskärlshändelsen var otillfredsställande, med dålig efterlevnad av rekommenderade behandlingsmål för blodtryck, lipider och glykemisk kontroll och en hög förekomst av fetma, ihållande rökning och begränsad fysisk aktivitet. **Studie II** visade på hur denna behandling var särskilt otillräcklig hos kvinnor, vilket möjligen bidrog till en sämre prognos jämfört med män hos de med känd T2DM. **Studie V** fann att CV skydd med dulaglutid verkar finnas oavsett metforminbehandling vid baslinjen.

Slutsatser: Det finns ett övertygande behov av implementering av screening för dysglykemi hos patienter med CAD, och OGTT bör vara den föredragna metoden eftersom den identifierar fler patienter med dysglykemi, som annars skulle missas. Tiden kan vara mogen för att introducera en algoritm baserad på 1hPG-värdet för att identifiera T2DM. Dess prognostiska implikationer bör emellertid undersökas ytterligare. Multifaktoriell behandling av dessa patienter kräver en avsevärd förbättring, särskilt hos kvinnor, där bristfällig vård kan leda till sämre prognos. Användningen av nya glukossänkande medel med kardiovaskulär effekt bör prioriteras oavsett bakgrundsterapi för glukossänkande behandling.

Sommario

Introduzione: La disglicemia, in questa tesi definita come ridotta tolleranza al glucosio (IGT) o diabete di tipo 2 (T2DM), è un importante fattore di rischio per le malattie cardiovascolari (CVD). Le linee guida internazionali raccomandano lo screening per la disglicemia, le modifiche allo stile di vita e la gestione farmacologica nelle persone con alto rischio cardiovascolare (CV) o CVD accertata sia per gli uomini che per le donne. Sono ora disponibili nuovi farmaci ipoglicemizzanti con comprovati benefici cardiovascolari.

Obiettivi: L'obiettivo generale di questa tesi di dottorato è quello di indagare lo screening e la gestione dei pazienti con CVD o ad alto rischio CV, comprese le differenze di genere e l'implementazione di nuovi farmaci ipoglicemizzanti cardioprotettivi studiando:
- la prevalenza della disglicemia secondo diversi strumenti di screening in pazienti senza diabete noto (**Studio I**) e per genere (**Studio II**);
- il valore di nuovi metodi di screening per la disglicemia in questi pazienti (**Studio III** e **IV**);
- la gestione di tali pazienti per quanto riguarda le abitudini di vita, l'uso di farmaci cardioprotettivi, e raggiungimento degli obiettivi terapeutici (**Studio I**) incluse possibili disparità di genere (**Studio II**);
- differenze di genere nella prognosi (**Studio II**);
- se la cardioprotezione del glucagon-like peptide-1 receptor agonist dulaglutide dipende dalla metformina (**Studio V**).

Metodi: gli **Studi I**, **II**, **III** e **IV** erano basati sulla popolazione dello studio europeo multicentrico EUROASPIRE V; lo **Studio II** includeva i dati di EUROASPIRE IV e V. Entrambi gli studi includevano pazienti con malattia coronarica accertata reclutati in tutta Europa almeno sei mesi prima dell'inclusione. Le informazioni sulla storia clinica, i consigli sullo stile di vita e il trattamento farmacologico erano basati su esami del sangue standardizzati e questionari convalidati. Lo **Studio V** si basa su pazienti con T2DM ad alto rischio CV del trial randomizzato controllato REWIND.

Risultati: *Prevalenza e screening per la disglicemia*: nello **Studio I**, il 29% della popolazione in studio presentava disglicemia rilevata dallo screening, con il 70% di essi identificato da un valore glicemico postcarico di due ore (2hPG) durante un test di tolleranza al glucosio orale (OGTT). Lo **Studio II** ha scoperto che più donne che uomini avevano IGT e più uomini avevano T2DM.
Lo **Studio III** ha convalidato un algoritmo diagnostico per il T2DM basato sulla valutazione di un valore glicemico postcarico di un'ora (1hPG) durante l'OGTT, accorciando il tempo necessario per la classificazione dello stato glicemico nel 79% di essi. Nello **Studio IV**, la performance diagnostica di diversi indici di insulinoresistenza era inferiore rispetto alla resa di un OGTT.
Gestione: lo **Studio I** ha mostrato che la gestione multifattoriale dopo l'evento coronarico era insoddisfacente, con scarsa aderenza agli obiettivi terapeutici raccomandati per la pressione arteriosa, i lipidi e il controllo glicemico e un'elevata prevalenza di obesità, persistenza dell'abitudine al fumo e attività fisica limitata. Lo **Studio II** ha evidenziato come questa gestione fosse particolarmente inadeguata nelle donne, contribuendo potenzialmente a una prognosi peggiore rispetto agli uomini nei pazienti con T2DM noto. Lo **Studio V** ha rilevato che la protezione CV con dulaglutide sembra essere presente indipendentemente dal trattamento con metformina al basale.

Conclusioni: C'è una necessità impellente di implementare lo screening per la disglicemia nei pazienti con CAD, e l'OGTT dovrebbe essere il metodo di scelta perché identifica più pazienti con disglicemia, che altrimenti rimarrebbero non identificati. Il tempo potrebbe essere maturo per introdurre un algoritmo basato sul valore 1hPG per identificare il T2DM, ma le sue implicazioni prognostiche dovrebbero essere ulteriormente studiate. La gestione multifattoriale di questi pazienti richiede un sostanziale miglioramento, specialmente nelle donne, dove una cura carente può portare a una prognosi peggiore. L'uso di nuovi agenti ipoglicemizzanti con efficacia cardiovascolare dovrebbe essere prioritario indipendentemente dalla terapia ipoglicemizzante di base.

LIST OF SCIENTIFIC PAPERS

I

Ferrannini G, de Bacquer D, De Backer G, Kotseva K, Mellbin L, Wood D, Rydén L. On behalf of the EUROASPIRE V collaborators.

Screening for glucose perturbations and risk factor management in dysglycaemic patients with coronary artery disease - a persistent challenge in need of substantial improvement. A report from EUROASPIRE V.

Diabetes Care. 2020 Apr; 43(4):726-733.

II

Ferrannini G, De Bacquer D, Vynckier P, De Backer G, Gyberg V, Kotseva K, Mellbin L, Norhammar A, Tuomilehto J, Wood D, Rydén L; EUROASPIRE IV & V Investigators.

Gender differences in screening for glucose perturbations, cardiovascular risk factor management and prognosis in patients with dysglycaemia and coronary artery disease: results from the ESC-EORP EUROASPIRE surveys.

Cardiovascular Diabetology. 2021 Feb; 20(1):38.

III

Ferrannini G, De Bacquer D, Gyberg V, De Backer G, Kotseva K, Mellbin LG, Risebrink R, Tuomilehto J, Wood D, Rydén L.

Saving time by replacing the standardised two-hour oral glucose tolerance test with a one-hour test. Validation of a new screening algorithm in patients with coronary artery disease from the ESC-EORP EUROASPIRE V registry.

Diabetes Research and Clinical Practice. 2022 Jan; 183:109156.

IV

Ferrannini G, De Bacquer D, Erlund I, Gyberg V, Kotseva K, Mellbin L, Norhammar A, Schnell O, Tuomilehto J, Vihervaara T, Wood D, Rydén L.

Measures of insulin resistance as a screening tool for dysglycaemia in patients with coronary artery disease. A report from EUROASPIRE V.

Diabetes Care 2022; 45: 2111-2117

V

Ferrannini G, Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Dyal L, Lakshmanan M, Mellbin L, Probstfield J, Riddle MC, Shaw JE, Avezum A, Basile JN, Cushman WC, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Pais P, Pīrāgs V, Pogosova N, Raubenheimer PJ, Sheu WH-H, Rydén L.

Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. A subgroup analysis of the REWIND Trial.

European Heart Journal 2021; 42: 2565-2573.

These studies will be referred to as **Study I, II, III, IV, V**.

List of Abbreviations

1hPG: One-hour postload glucose
2hPG: Two-hour postload glucose
3P-MACE: three-point major adverse cardiovascular events
ADA: American Diabetes Association
ACCORD: Action to Control Cardiovascular Risk in Diabetes
ADVANCE: Action and Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ARIC: Atherosclerosis Risk in Communities
AUC: area under the curve
BARI 2D: Bypass Angioplasty Investigation Revascularization 2 Diabetes
CABG: coronary artery bypass graft
CAD: coronary artery disease
CI: confidence interval
CVD: cardiovascular disease
CVOT: cardiovascular outcome trials
DALY: Disability Adjusted Life Years
DCCT: Diabetes Control and Complications trial
DIGAMI: Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction
DPP-4i: Dipeptidyl peptidase-4 inhibitors
eGFR: estimated glomerular filtration rate
ESC: European Society of Cardiology
EMA: European Medicines Agency
EUROASPIRE: European Action on Secondary and Primary Prevention by Intervention to Reduce Events
FDA: Food and Drug Administration
FPG: fasting plasma glucose
GENFIEV: Genetics, PHYsiopathology, and Evolution of Type 2 diabetes
GLP-1 RA: glucagon-like peptide-1 receptor agonists
GRACE: Global Registry of Acute Coronary Events
HbA1c: glycated haemoglobin A1c
HDL-C: high density lipoprotein cholesterol
HR: Hazard Ratio
ICD-10: International Classification of Diseases number 10
IRIS: Insulin Resistance Intervention in Stroke
MONICA: MONItoring of Trends and Determinants in CArdiovascular Disease
LDL-C: low-density lipoprotein cholesterol
OGTT: oral glucose tolerance test
OR: Odds Ratio
ORIGIN: Outcome Reduction with an Initial Glargine Intervention
PCI: percutaneous coronary intervention
PROactive: PROspective pioglitAzone Clinical Trial In macroVascular Events
ROC: receiver operating characteristic
SD: standard deviation
SGLT2i: sodium-glucose co-transporter 2 inhibitors
STABILITY: STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY
T1DM/T2DM: Type 1 diabetes/Type 2 diabetes
TECOS: Trial Evaluating Cardiovascular Outcomes with sitagliptin
UKPDS: UK Prospective Diabetes Study
WHO: World Health Organization

1. INTRODUCTION

1.1 Historical background

1.1.1 Diabetes mellitus

The earliest reference to diabetes is probably in Eber´s Papyrus (1552 BCE) where the Egyptian physician Hesy-Ra refers to a disease which *"..eliminates urine which is too plentiful*" (1). The Charaka Samhita and the Sushruta Samitha (600-500 BCE), the two foundational texts of the ancient Indian Ayurveda, describe a condition associated with polyuria and sweet urine, therefore naming the condition "madhumeda", which means "honey urine" (**Figure 1**) (2).

Figure 1. On the left, a monument dedicated to Charaka Maharishi, the author of the Charaka Samhita, in Haridwar, India; on the right, text of the Sushruta Samhita written on palm leaves found in Nepal in the 12th-13th Century (Los Angeles County Museum of Art). From Wikipedia.

The word "diabetes", which comes from Latin *diabētēs*, originates from Ancient Greek *διαβήτης* (*diabētēs*), literally "a passer through", was introduced by Aretaeus of Cappadocia (1st century CE) (2). Two different phenotypes, corresponding to type 1 and type 2 diabetes mellitus respectively, were identified by the Persian philosopher-scientist Avicenna (980–1037). He described the first as present in young and lean patients and the second as more common in older and overweight people (3). It was the English physician Thomas Willis (1621–1675) who coined the term *mellitus*, giving the disease its contemporary name (3). In 1869, the German pathologist Paul Langerhans (1847–1888) was the first to describe "*islands of clear cells*" throughout the pancreas, that stained differently than the surrounding tissue. Langerhans did not suggest a function for these areas and erroneously hypothesized that they might be lymph nodes (4). The French physician Étienne Lancereaux was the first to suggest that diabetes mellitus was a disease of the pancreatic islets, a hypothesis subsequently confirmed by Oskar Minkowski (1858–1931), Josef von Mering (1849–1908) and Gustave-Édouard Laguesse (1861–1927) (3, 5). However, no treatment for diabetes was available until the beginning of the 20th century.

1.1.2 The discovery of insulin

2021 marked 100 years from the discovery of insulin, which in 1923 was awarded the Nobel Prize in Physiology or Medicine to the Canadian scientists Frederick Grant Banting (1891–

1941) and John James Richard MacLeod (1876–1935), working at the University of Toronto (**Figure 2**).

Figure 2. The Nobel Diploma and medal received by Frederick Banting and John MacLeod (By courtesy of the Thomas Fisher Rare Book Library, University of Toronto).

This award was a subject of controversy already at the time of its announcement. Banting decided to share the prize money with the medical student Charles Herbert Best (1899–1978) and MacLeod shared his part with the biochemist James Collip (1892–1965), who had participated in the purification of the pancreatic extract, called "isletin" (3, 6). Another debated point regards who performed the first insulin extraction. In 1916 the Romanian physiologist Nicolae Constantin Paulescu (1869–1931) had already developed a pancreatic extract which normalized blood glucose when injected in pancreatectomized dogs. His work was indeed cited by Banting and McLeod, although misquoted (6, 7). Paulescu was neither nominated nor mentioned in the investigation behind the decision to award the Canadian researchers with the Nobel prize (3).

The demand on insulin increased rapidly following the first successful reports on treatment of patients with (type 1) diabetes. The Toronto team soon became unable to meet the requests and, although initially refusing to profit from their discovery, they finally reached an agreement with Eli Lilly & Co. of Indianapolis (6). Banting, Best and Collip patented their insulin extract and transferred all rights to the University of Toronto for one Canadian dollar with the request that the income should be used to fund new research (6).

Despite the controversy, the discovery of insulin is a great example of groundbreaking medical research aimed at knowledge and patient benefit and not profit. During the last century this small peptide hormone has given life back to millions of patients (6).

1.1.3 Development of other glucose-lowering drugs

After insulin, other glucose-lowering drugs were developed, with different mechanisms of action (**Figure 3**) (8).

Traditional drugs include:

- Sulphonylureas, increasing insulin release from the pancreas.
- Biguanides, including metformin, decreasing blood glucose levels by multiple mechanisms, not fully understood. Among them metformin acts by decreasing hepatic

gluconeogenesis and intestinal glucose absorption and by increasing peripheral glucose uptake and utilization (9).
- Alpha-glucosidase inhibitors slowing glucose absorption in the gastrointestinal tract by delaying the degradation of complex carbohydrates.
- Thiazolidinediones, acting on adipose tissue by binding the peroxisome proliferator-activated receptors (PPAR) and decreasing circulating fatty acids.

Novel classes of glucose-lowering agents are:

- Glucagon-like peptide-1 receptor agonists, (GLP-1 RAs), stimulating insulin secretion, inhibiting glucagon release and slowing gastric emptying (8).
- Dipeptidyl peptidase-4 inhibitors (DPP-4i), blocking the action of the enzyme that is responsible for the rapid degradation of GLP-1 and gastric inhibitory peptide (8).
- Sodium-glucose co-transporter 2 inhibitors (SGLT2i), inhibiting glucose reabsorption in the kidneys, leading to increased urinary glucose excretion (10).

The research on the development of new glucose-lowering drugs is constantly evolving, trying to identify novel targets and mechanisms and develop new molecules (11).

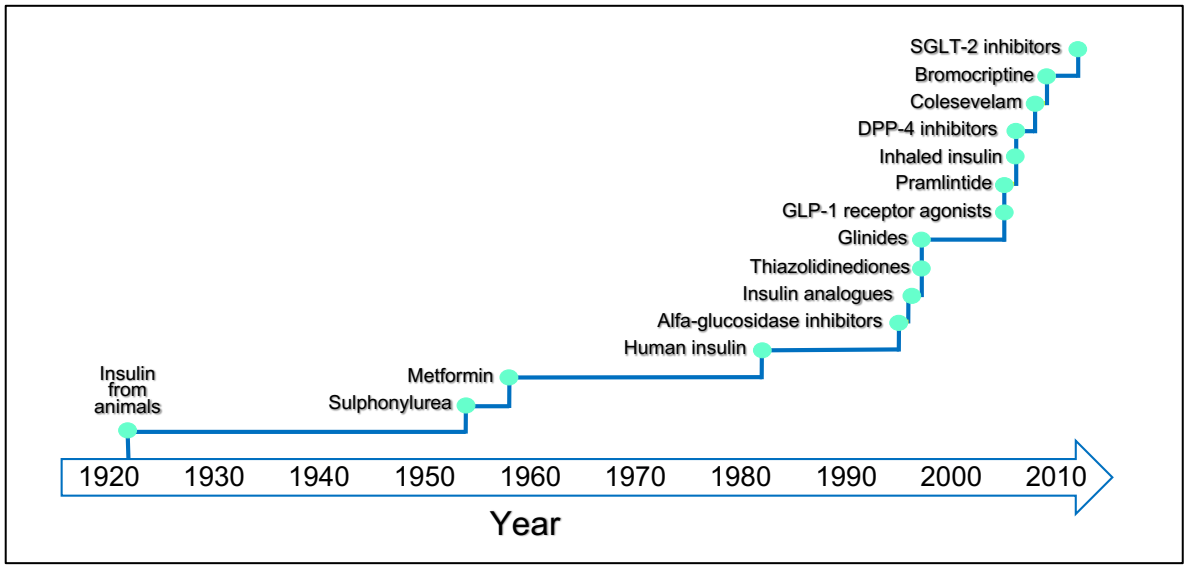


Figure 3. Introduction of medications for treating type 2 diabetes over time. The rate has accelerated over the last 20 years. Animal insulin and inhaled insulin are essentially no longer available as therapeutics.
Modified from Kahn et al (ref 8) with permission from Elsevier.
DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon like peptide-1; SGLT2: sodium-glucose co-transporter 2.

1.1.4 Diabetes as a risk factor for cardiovascular disease

The vascular complications of diabetes were unknown until insulin was introduced in clinical practice. Prior to this, the disease killed those afflicted before they had time to develop complications. Hyperglycemia was not referred to as a common feature of acute myocardial infarction in patients presenting with chest pain until the 1930s (12). Early observations linking diabetes to coronary heart disease came from studies on myocardial infarction performed in Malmö, Sweden, comprising 2,063 patients hospitalized between 1935 and 1954. It was noted that the prevalence of diabetes was approximately five times higher in patients with myocardial infarction than in the general population (13, 14). Root and colleagues reported on the "excessive development of coronary disease" in patients with diabetes in 1939. In 1948, the Framingham Heart Study was initiated, aiming at identifying cardiovascular risk factors. In

1979, diabetes was reported as a major risk factor for several forms of cardiovascular disease (CVD) including congestive heart failure, coronary artery disease (CAD), stroke, intermittent claudication, and cardiovascular death (15). Similar observations came from other research groups in the 1960s-70s (16, 17). Originally, it had been assumed that elevated glucose observed in patients with myocardial infarction was a manifestation of stress, but with accumulating knowledge it became clear that the glycaemic perturbation may be an important reason for vascular complications, and with this insight it was hypothesized that glycaemic control may protect from such complications.

A clinical trial demonstrating the possible superiority of glucose-lowering treatment on vascular complications felt compelling, and the University Group Diabetes Program was started in 1961 in the United States (18). Unfortunately, this study appeared to demonstrate an excess cardiovascular mortality with tolbutamide and excess all-cause mortality with phenformin, leading to widespread criticism and its premature termination (19). Despite the ensuing atmosphere of uncertainty, Robert Turner and colleagues set up the United Kingdom Prospective Diabetes Study (UKPDS) in Oxford in 1977. They randomized patients with newly diagnosed T2DM to diet, sulphonylureas, insulin or metformin (in obese patients only); subsequently, the trial also included randomization to acarbose (20, 21). The pivotal results of UKPDS, presented in 1998 at the European Society for the Study of Diabetes meeting in Barcelona, showed that intensive glycaemic control reduced complications related to diabetes, although not statistically significant as regards macrovascular complications (22-26). At the same time, the Diabetes Disease and Complications trial (DCCT), conducted in patients with type 1 diabetes, reported on a decrease of microvascular complications, including retinopathy, nephropathy and neuropathy, after intensive insulin-based glucose control (27). Successively, the long-term follow-up of DCCT showed a reduction of macrovascular events in the intensively treated group (28).

Since then, clinical trials testing glucose-lowering agents in patients with diabetes from a cardiovascular perspective flourished. In recent years they were conceived as cardiovascular outcome trials in high-risk populations, leading to striking results and benefit to patients by some of the studied agents, as will be further elaborated in paragraph 1.9 (29).

1.2 Definitions and classification of diabetes

Diabetes is a chronic condition characterized by hyperglycaemia due to decreased insulin secretion in the beta-cells of the pancreas, and/or impaired utilization, caused by insulin resistance (30).

According to the American Diabetes Association (ADA) diabetes is classified as follows (31):

- Type 1 diabetes (T1DM): due to autoimmune destruction of pancreatic beta-cells, with absolute insulin deficiency.
- Type 2 diabetes (T2DM): due to loss of beta-cell function, often because of insulin resistance; accounts for over 90% of all diabetes.
- Specific types of diabetes due to other causes, including monogenic syndromes, drug-induced, and chemical-induced diabetes.
- Gestational diabetes, diagnosed in the second or third trimester of pregnancy, not previously diagnosed.

Diabetes causes both acute and chronic pathological conditions. The first are represented by comas (i.e., diabetic ketoacidosis coma, hyperosmolar coma and hypoglycaemic coma). The

latter are macro- and microvascular complications. Macrovascular complications comprise CAD, ischaemic stroke and peripheral artery disease, whereas microvascular complications include retinopathy, nephropathy and neuropathy. The association between diabetes and microvascular complications is definitional and dependent on hyperglycaemia and glycaemic control. Although still important, the association between glycaemic control and macrovascular complications is seemingly more complex, since very tight control does not impact future CVD as strongly (32).

1.3 Diagnosis of glucose perturbations

1.3.1 International diagnostic criteria

According to the diagnostic criteria issued by the World Health Organization (WHO) and the ADA, diabetes can be diagnosed based on three different tools: fasting plasma glucose (FPG), two-hour postload glucose (2hPG) and glycated haemoglobin A1c (HbA1c) (**Table 1**) (33, 34). 2hPG levels are those obtained after a standardised 75-g oral glucose tolerance test (OGTT). The cutoff levels for the diagnosis of diabetes were originally related to prevalent retinopathy in large cross-sectional reports (35).

The onset of T2DM is relatively slow and metabolic abnormalities leading to overt diabetes are usually present years before the cutoff point for establishing the diagnosis. Therefore, conditions referred to as prediabetes have been defined, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), as reported in Table 1. The two conditions can be present simultaneously, and it is estimated that approximately 30-40% of those with known IFG also have IGT if subjected to an OGTT (36). These two conditions should, however, be considered as distinct. Insulin secretion is more severely impaired in IGT than in IFG, and insulin resistance is predominant in the liver in IFG and in the muscle in IGT (37).

All three screening tools can be used in clinical practice, although with important specifications. In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus stated that the FPG criteria should be used in epidemiological studies because of superior standardization and availability (38). On the other hand, in such report it is underlined that the absence of an OGTT leads to a significant underestimation of the real proportion of people with diabetes (38).

HbA1c reflects the average levels of plasma glucose during the previous 12 weeks. Its measurement does not require fasting or any other preparation. The UKPDS and DCCT established the linear relationship between HbA1c and microvascular complications both in T1DM (27) and T2DM (22). These features have made it the standard tool for glycaemic control assessment in people with established diabetes. HbA1c was adopted as a diagnostic tool for T2DM by the ADA in 2010 and by the WHO in 2011 (38, 39). However, WHO underlines that HbA1c measurement might be unreliable in many physiological and pathological conditions (40). In light of these considerations, and since several of the aforementioned conditions may be more prevalent in countries where the availability of HbA1c is problematic, the WHO advises policy-makers to ensure that accurate blood glucose measurement is largely available before the introduction of HbA1c measurement for screening purposes (41).

Table 1. Definition of glycaemic categories according to the World Health Organization and the American Diabetes Association (33, 34).

Diagnostic tool	**World Health Organization** Cutoff level		**American Diabetes Association** Cutoff level	
HbA1c	% (DCCT)	mmol/mol (IFCC)	% (DCCT)	mmol/mol (IFCC)
High-risk of diabetes	-	-	5.7 – 6.4	39 – 47
Diabetes	≥ 6.5	≥ 48	≥ 6.5	≥ 48
Plasma glucose (venous)	mmol/L	mg/dL	mmol/L	mg/dL
Normoglycemic				
FPG*	< 6.1	< 110	< 6.1	< 110
2hPG	< 7.8	< 140	< 7.8	< 140
IFG				
FPG*	6.1 – 6.9	110 – 125	5.6 – 6.9	100 – 125
2hPG	< 7.8	< 140	< 7.8	< 140
IGT				
FPG*	< 7.0	< 126	-	-
2hPG	7.8–11.0	140 – 199	140 – 199	7.8 – 11.0
Diabetes				
FPG*	≥ 7.0	≥ 126	≥ 7.0	≥ 126
2hPG	≥ 11.1	≥ 200	≥ 11.1	≥ 200
Random**	-	-	≥ 11.1	≥ 200

* Fasting is defined as no caloric intake for at least 8 hours
** In combination with classic symptoms of diabetes including polyuria, polydipsia, and unexplained weight loss

2hPG: two-hour postload glucose; DCCT: diabetes control and complications trial; HbA1c: glycated haemoglobin; FPG: fasting plasma glucose; IFCC: International Federation of Clinical Chemistry and laboratory Medicine; IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

According to the Noncommunicable disease Risk Factor Collaboration report, HbA1c ≥ 6.5% (48 mmol/mol) has a lower sensitivity for the diagnosis of T2DM compared with FPG ≥ 7 mmol/L or 2hPG ≥ 11 mmol/L (42-44). Results from the Diabetes Prevention Program highlight the lack of overlap between traditional screening methods among participants with newly diagnosed T2DM. Only 26% of those diagnosed by FPG or 2hPG had a HbA1c ≥ 6.5% (48 mmol/mol), and 55% of those with an HbA1c ≥ 6.5% (48 mmol/mol) had a current or previous diagnosis of T2DM by FPG or 2hPG (45).

In this thesis "dysglycaemia" is defined as T2DM or IGT, i.e., not including IFG in this definition. The reasons are that, despite both IFG and IGT carrying an increased risk for developing T2DM, current evidence on preventive measures only relates to IGT (30, 46). Moreover, as explored later in this section, IGT might be of greater significance than isolated IFG in people at high cardiovascular risk or with established CVD. The ADA has suggested the "high-risk" HbA1c levels as an alternative (39 – 47 mmol/mol, **Table 1**), but this seems also insufficient in disclosing all patients with IGT (44).

1.3.2 Role of one-hour postload glucose value

An elevated one-hour postload glucose value (1hPG) is not an official diagnostic criterion for T2DM, although it is used for the diagnosis of gestational diabetes (34). There is a strong interest in including it as a diagnostic criterion for prediabetes considering quite robust

evidence for its value (47). A 1hPG value > 8.6 mmol/L (155 mg/dL) during the OGTT has been suggested to correctly identify individuals with high risk of progression to T2DM in the Botnia study, in the Malmö Prevention Project and in the Genetics, PHYsiopathology, and Evolution of Type 2 diabetes (GENFIEV) study (48-50). 1hPG thresholds for the diagnosis of T2DM have been reported in Chinese patients (51) and Native Americans (52). In a meta-analysis of more than 35,000 individuals Ahuja et al. showed that an 1hPG ≥ 11.6 mmol/L detects individuals with a 2hPG level diagnostic of diabetes (≥ 11.1 mmol/L) with high sensitivity and specificity, although with a high rate of false positives (55%) indicating a need for further validation in other cohorts (53).

1.4 Epidemiology

1.4.1 Dysglycaemia

The prevalence of diabetes has dramatically increased, climbing from position number 13 in 2000 to position number seven in 2019 among the leading causes of loss of Disability Adjusted Life Years (DALYs) in adults (54). In the European Region, diabetes in responsible for the loss of nearly nine million DALYs, without substantial difference between men and women (54). According to the most recent estimates by the International Diabetes Federation (2021), 537 million adults (20-79 years old) were living with diabetes in 2021, a number that is projected to rise to 784 million by 2045 (30). Most of this increase will occur in low- and middle-income countries, mainly due to population growth and ageing (30). The prevalence of diabetes is slightly higher in men than women, 10.8% vs. 10.2%, corresponding to 17.7 million more affected men than women. In addition, 541 million people were estimated to have IGT in 2021 (30). Diabetes-related mortality is estimated to account for 12.2% of global deaths, with one third (approximately 2.2 million) occurring in people below the age of 60 yeras, i.e. in working age (30). The global health expenditure due to diabetes was 966 billion USD in 2021, with a predicted increase of 316% over 15 years (30). The highest diabetes-related costs are in the North American and Caribbean regions, followed by Europe (189 billion USD). The latter region has the lowest proportion of diabetes-related health expenditure among all WHO regions, 8.6% (30).

1.4.2 Cardiovascular disease

CVD manifestations, comprising coronary, cerebral and peripheral artery disease, are the main causes of death and DALYs in most countries. In absolute terms, ischaemic heart disease is the main global killer, responsible for 16% of mortality while stroke comes second, accounting for 11% of deaths (55). Overall, 17.9 million people died from CVD in 2019 (55).

The worldwide prevalence of CVD is growing mainly due to increased longevity and decreasing mortality for myocardial infarction (55). In addition, modern lifestyles encompassing an unhealthy diet, physical inactivity, tobacco use and excessive alcohol consumption lead to the accumulation of intermediate cardiovascular risk factors, i.e. raised blood pressure, blood glucose, blood lipids and overweight and obesity (56). These “traditional” risk factors were identified in the Framingham Heart Study and reiterated by findings in the WHO project MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) (15, 57).

The INTERHEART study, a large case-control study of patients with acute myocardial infarction from 52 countries in all continents, reported that an abnormal lipid profile, smoking,

hypertension, diabetes, abdominal obesity, psychosocial deprivation, alcohol, a low consumption of fruits and vegetables, and lack of regular physical activity account for the largest part of the risk, in both sexes, at all ages and in all regions (58). Still, these risk factors do not explain all atherosclerotic cardiovascular events, which may occur despite a satisfactory risk factor control, indicating that there are elements of importance besides those already known (59-62). Thus, there is a need for additional knowledge of the pathophysiology behind the development of CVD, not the least in people with dysglycaemia (62-64). Among known contributors to CVD risk in dysglycaemia are insulin resistance, dyslipidaemia, vascular wall stress, endothelial dysfunction and platelet hyperaggregability (65). However, other factors related to cardiometabolic health, so far less explored, might as well be of importance (65, 66).

1.5 The link between dysglycaemia and cardiovascular disease

1.5.1 The role of glycaemic control

Dysglycaemia is among the main cardiovascular risk factors, conferring a two to four times higher risk for CVD (67). The presence of dysglycaemia increases morbidity and mortality considerably in patients with CAD. Diabetes was independently associated with a two-fold increase in the risk of CAD (Hazard ratio (HR) 2.00 (95% confidence interval (95%CI) 1.83–2.19) in a large meta-analysis from the Emerging Risk Factor Collaboration (68). Similarly, T2DM was significantly associated with non-fatal myocardial infarction (HR 1.54, 95% CI 1.42 – 1.67) in a study including more than 1.9 million individuals (69).

The pathophysiology behind the relationship between dysglycaemia and CVD is based on strong foundations encompassing a multitude of genetic, epigenetic, cell-signalling, metabolic and inflammatory mechanisms (70). Hyperglycaemia leads to dysfunctional epigenetic and post-translational modifications of the vascular architecture, accumulations of toxic glycation end-products ("glucotoxicity") and augmented inflammation via release of adipocytokines which are ultimately associated with an increased risk of CVD (71-73). Still, as opposed to microvascular complications, glycaemic control alone is not able to achieve a significant reduction of macrovascular complications in patients with T2DM.

As already stated, strict glycaemic control did not significantly reduce the risk of myocardial infarction in UKPDS, although there was a benefit as regards the risk of myocardial infarction in a subgroup of obese patients treated with metformin (23). The Action and Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, lowering the average HbA1c to 6.5% (47.5 mmol/mol) did not have any beneficial effect on macrovascular outcomes in high-risk patients with T2DM (74). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, targeting a HbA1c level below 6% (42.1 mmol/mol), reported on a significant increase in deaths in the intensively treated group and no significant decrease of macrovascular events, which was the reason for the premature closure of the trial (75). In the Veterans Affairs Diabetes Trial intensive glycaemic control did not reduce cardiovascular events, at the expense of significantly more hypoglycaemic episodes (76). Finally, in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, early institution of insulin glargine had a neutral effect on cardiovascular outcomes but increased the risk for hypoglycaemia and caused a modest increase of body weight (77). In contrast, intensified insulin treatment decreased mortality in patients with diabetes who suffered an acute myocardial infarction in the first Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial (78, 79). However, the DIGAMI 2 trial, investigating different insulin treatment regimens, failed to confirm these

findings and did not find any benefits as regards the incidence of reinfarctions and stroke, possibly because of important differences in the trial populations and since the targeted glucose level was not achieved in the intensively treated group (80).

It can be concluded that, despite the importance of dysglycaemia as cardiovascular risk factor, targeting a strict glycaemic control has not been proven sufficient in preventing future macrovascular events or mortality in established diabetes.

1.5.2 Insulin resistance, beta-cell function and cardiovascular disease

Disturbances of glucose homeostasis in people with dysglycaemia relate to an impairment of beta-cell function and a decreased sensitivity to insulin (insulin resistance) (81). Accordingly, decreased pancreatic insulin production and insulin resistance in peripheral tissues can be considered as hallmarks of disturbed glucose homeostasis, developing at an early stage of the disease (**Figure 4**) (82).

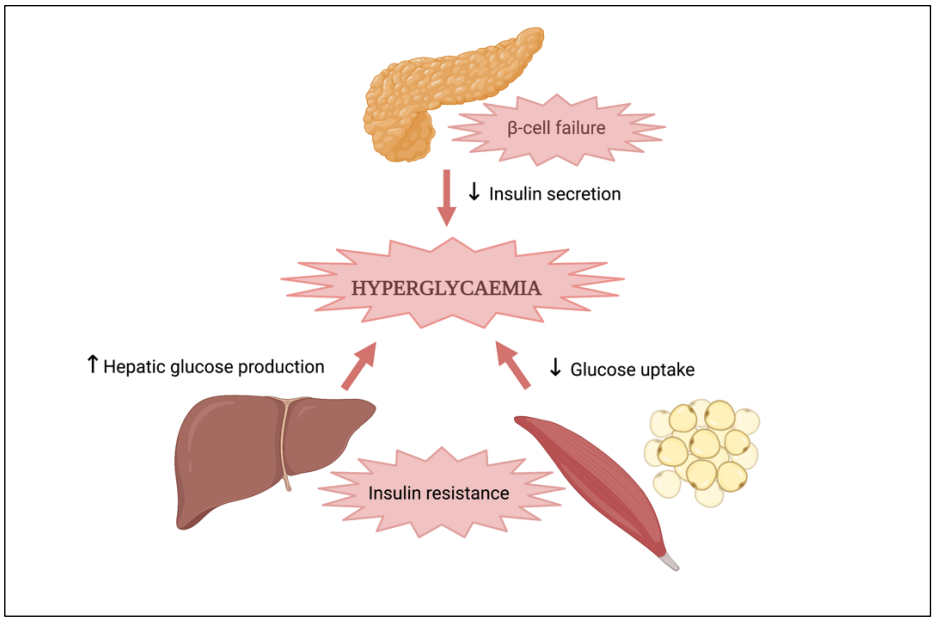


Figure 4. Impaired beta-cell function (reduced insulin secretion), increased hepatic glucose production and peripheral insulin resistance (reduced glucose uptake in muscle and adipose tissue) leading to hyperglycaemia. By Ferrannini G. Created with BioRender.com.

Insulin resistance has been suggested as an important link between dysglycaemia and CVD (82-84). In support of this hypothesis there is an established association between insulin resistance and multiple cardiovascular risk factors i.e. hypertension, dyslipidaemia, endothelial dysfunction, increased inflammatory activity and enhanced thrombogenesis (84-88).

It has been assumed that improving insulin sensitivity by means of lifestyle and pharmacological interventions is beneficial. This assumption gained support from the Diabetes Prevention Program, which randomised overweight patients with elevated FPG and IGT (but not diabetes) to either metformin, a lifestyle-modification programme or placebo (89). In both treatment arms the incidence of the primary outcome, i.e. diabetes, was significantly lower than in the placebo arm. In the Finnish Diabetes Study, T2DM was prevented in overweight people with IGT by a combination of increased physical activity and diet (90). In the Da Qing study, a six-year lifestyle intervention programme (based on diet, exercise or both) in Chinese people

with IGT reduced the incidence of diabetes and subsequently cardiovascular and all-cause mortality (91). In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial pioglitazone, a PPARγ-agonist with potent insulin sensitizing effects, significantly reduced the composite of all-cause mortality, non-fatal myocardial infarction and stroke in patients with T2DM (92). Moreover, in insulin-resistant patients without diabetes in the Insulin Resistance Intervention in Stroke (IRIS) trial, there was a 25% reduction of the risk of ischaemic stroke in patients randomized to pioglitazone vs. placebo (93). The results were consistent in patients with prediabetes (defined, according to ADA, as "high risk" HbA1c and/or IFG) (94).

The HOMA index

The gold standards for insulin resistance assessment are the euglycaemic and hyperglycaemic clamp techniques, which allow direct quantification of glucose uptake and beta-cell response (95). Despite their high sensitivity, reproducibility and independency from confounders, the clamp techniques are complex and generate discomfort to patients, which makes them unsuitable for large samples studies. As a consequence, a number of surrogate measures for insulin resistance have been proposed (96). Among them, the homeostasis model assessment (HOMA) index is widely used (97). By means of fasting glucose and insulin levels, the HOMA can predict both insulin resistance and beta cell function, based on the assumption that a simple feedback loop mechanism between the endocrine pancreas and the liver is mostly responsible for such levels (98, 99) (**Figure 5**).

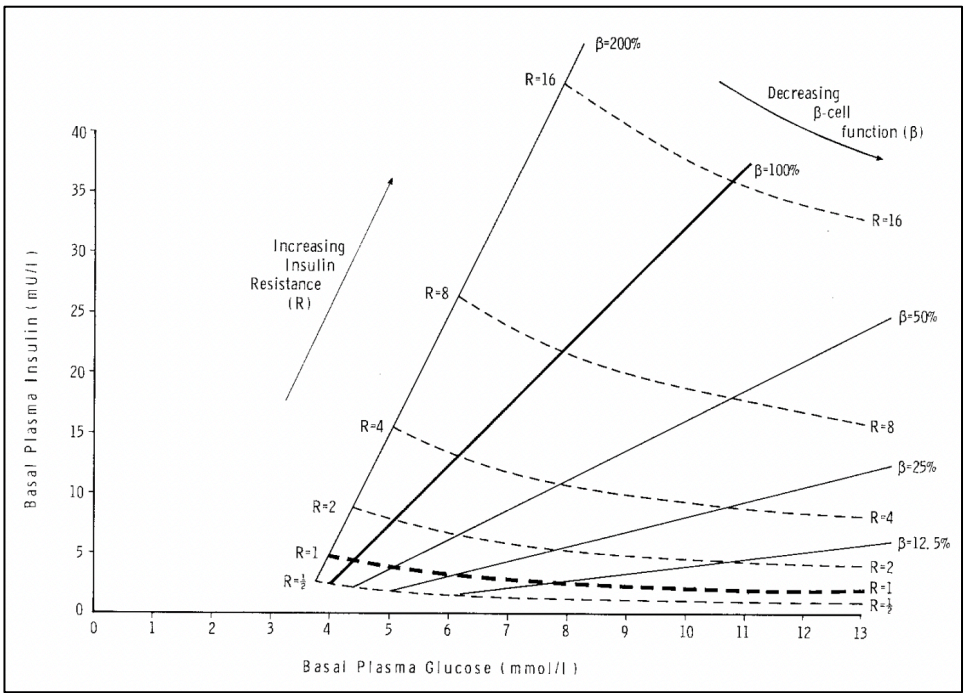


Figure 5. Basal homeostasis model assessment (HOMA). The grid depicts the predicted beta-cell and insulin resistance levels for each plasma glucose and insulin value.
For example, a person with a fasting plasma glucose of 11 mmol/L and a fasting plasma insulin of 18 mUI/L has a 50% reduction of their beta-cell function and is eight times more resistant than a person with normal insulin sensitivity, corresponding to an HOMA index of almost 9 (normal value around 3).
Reproduced from Matthews et al (ref 97) with permission from Springer Nature.

In other words, for any level of basal glucose and insulin concentrations, the model predicts insulin resistance and beta-cell function. It is therefore able to differentiate between the two

main characteristics of T2DM (97). Importantly, HOMA mirrors the main feature of diabetes, hyperglycaemia, as a function of both beta-cell function and insulin resistance, therefore reflecting their interplay (100). The HOMA index is considered an adequate measure of insulin resistance in clinical and epidemiological studies and is nearly as informative as other, more complex surrogates based on clamp techniques (96, 101, 102). The loss of accuracy compared with the clamp techniques is compensated for by the possibility to perform cost-effective analyses of large samples (101).

Insulin resistance measured as HOMA index is associated with CVD (103, 104). This index seems unaffected by glucose metabolism at the basal investigation. As an example, the age-gender- and ethnicity adjusted risk for cardiovascular events in the San Antonio Heart Study (n=187 patients followed eight years) increased by increasing quintiles of the HOMA index but was independent of the glucose level at study start (105). The Verona Diabetes Complications Study concluded that HOMA index is an independent risk marker for cardiovascular disease (fatal and non-fatal CAD, cerebrovascular and peripheral arterial disease) in people with T2DM (106). Whether HOMA index may cover the increased risk seen in patients with IGT has not been explored in any detail.

C-peptide

Another indicator of beta cell function is fasting C-peptide, a proinsulin cleavage product (107). Since its half-life is longer, its clearance from the peripheral circulation constant and there is no cross-reactivity with exogenous insulin, C-peptide measurement is preferable to estimates of insulin when the intention is to assess beta-cell function (108). C-peptide has been investigated as an independent atherogenic risk factor (109). Experimental, clinical, and epidemiological investigations of the relation between C-peptide and cardiovascular complications among patients with known T2DM has produced diverging results (110-113). In patients without previously known T2DM undergoing elective coronary angiography, Marx and colleagues reported an independent association of C-peptide levels with all cause and cardiovascular mortality and with the severity of CAD (114, 115). In a population with normal glucose metabolism from the Canary Islands, there was an association between the C-peptide levels, CAD and myocardial infarction among people (113). In an Indian cohort of patients with metabolic syndrome, C-peptide correlated with CAD severity (116). These findings suggest a role of C-peptide as predictor of cardiovascular events in people with normal glucose tolerance, IGT and newly detected T2DM. However, people with long-standing T2DM should be excluded when assessing C-peptide levels, because they change over the course of the disease with a high interindividual variability and are altered by glucose-lowering drugs. Moreover, a long duration of T2DM by itself confers an increased cardiovascular risk, thus being an additional potential confounder.

1.6 Screening for dysglycaemia in patients with cardiovascular disease

Despite its negative effect on cardiovascular morbidity and mortality, dysglycaemia remains unrecognized in a substantial proportion of patients with established CVD. In the Glucose in Acute Myocardial Infarction (GAMI) study, about two thirds of patients with acute myocardial infarction without previously known glucose perturbation had dysglycaemia (117). This finding was subsequently confirmed in the Euro Heart Survey, comprising 3,362 patients with a recent myocardial infarction or stable CAD, all without known dysglycaemia. Among them an OGTT revealed that 49% were dysglycaemic (118). The China Heart Survey, conducted according to the same protocol, confirmed these findings (119). Therefore, international guidelines for the management of patients with CVD recommend screening for glucose

perturbations to disclose and treat previously undetected dysglycaemia in such populations (34, 56, 120-122).

There is an ongoing debate on which screening test is most accurate not only for the detection of glucose perturbations, but also for providing prognostic information in patients with CAD (40, 123-125). Some studies support the use of HbA1c considering its correlation with CVD, all-cause mortality and coronary atherosclerosis, both in people with and without known diabetes (126-132). On the other hand, the OGTT has been proposed as being more informative on future cardiovascular risk in dysglycaemic patients (44). The assessment of 2hPG by means of OGTT discloses more dysglycaemic patients than FPG and HbA1c, not the least because, by definition, it is the only test to diagnose IGT (40). Several studies have observed that 2hPG ≥ 7.8 mmol/L might be associated with worse prognosis in patients with established CAD (133-136) and might be superior to HbA1c (137, 138). In the fourth European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) cross sectional survey, conducted in 2012-2013, 2hPG was superior to FPG and HbA1c in providing prognostic information (139).

1.7 Management of dysglycaemic patients with cardiovascular disease

According to international guidelines, as those issued by ADA and the European Society of Cardiology (ESC), patients with T2DM should receive a multifactorial risk management to reduce cardiovascular morbidity and mortality (56, 122). Therefore, the identification of traditional cardiovascular risk factors, i.e. elevated LDL-C, low high density lipoprotein cholesterol (HDL-C), hypertension, hyperglycaemia, overweight and smoking, is key to guideline-recommended prevention, especially in patients with dysglycaemia, as it allows a tempestive initiation of lifestyle adjustment and evidence-based pharmacological treatment.

The observational study Euro Heart Survey is seemingly the first to report on a favorable effect of a comprehensive, evidence-based pharmacological treatment, including renin-angiotensin-aldosterone system inhibitors, betablockers, statins, oral antiplatelet therapy and early revascularization, on one-year mortality, myocardial infarction and stroke in CAD patients with T2DM (140). The first randomized controlled trial to demonstrate the beneficial impact of multifactorial management in patients with T2DM at high cardiovascular risk by a combination of lifestyle interventions and pharmacological treatment was the Intensified Multifactorial Intervention in Patients with type 2 diabetes and Microalbuminuria (STENO 2) trial (141). These reports were more recently supported by observational analyses in the Swedish Diabetes Registry: patients with T2DM who achieved the recommended target of five risk factors (HbA1c < 7.0% or < 53 mmol/mol, blood pressure < 140/80 mmHg, absence of albuminuria, no smoking and low-density lipoprotein cholesterol (LDL-C) < 2.5 mmol/L or < 97 mg/dL) had little or no excess risk of death, myocardial infarction and stroke compared with controls without diabetes of corresponding ages (142).

Despite such findings supporting the pursuit of a comprehensive, multitargeted strategy, real world data picture a substantial need for improvement in clinical practice, since recommended risk factor control is generally insufficiently achieved and screening for dysglycaemia poorly practiced (44, 143, 144). In particular, the EUROASPIRE cross-sectional survey have depicted the implementation of European guidelines in Europe since 1995, by comparing diagnostic and therapeutic strategies to guideline-directed standards of care (145-147).

1.8 Gender aspects

1.8.1 Gender and sex differences in coronary artery disease and cardiovascular pharmacotherapy

Despite the terms "sex" and "gender" still being used interchangeably, growing evidence support the distinction of these two dimensions in clinical research (148). Sex describes biological features differing between females and males, including chromosomes, epigenetics, gene expression, sex hormones and their regulation, and anatomy. Gender refers to social, cultural and behavioral factors influencing the role and perception of women and men in society (**Figure 6**) (149). Sex and gender dimensions are not dichotomic parameters, and a large spectrum of identities should be considered, reflecting the multiple interactions between these two dimensions (149).

Ischaemic heart disease accounts for approximately 110 million loss of DALYs in men and 70 million in women (55). CAD has historically been considered a disease of the male sex, but it remains underdiagnosed and undertreated in women. During the last decades, CAD mortality has indeed remained higher among women than in men (150). A crucial point is the difference between sex and gender influences: although female sex might be biologically protected from CVD because of the hormonal asset, cardiovascular health has been broadly neglected in women because of social, cultural and environmental factors (151) (**Figure 6**).

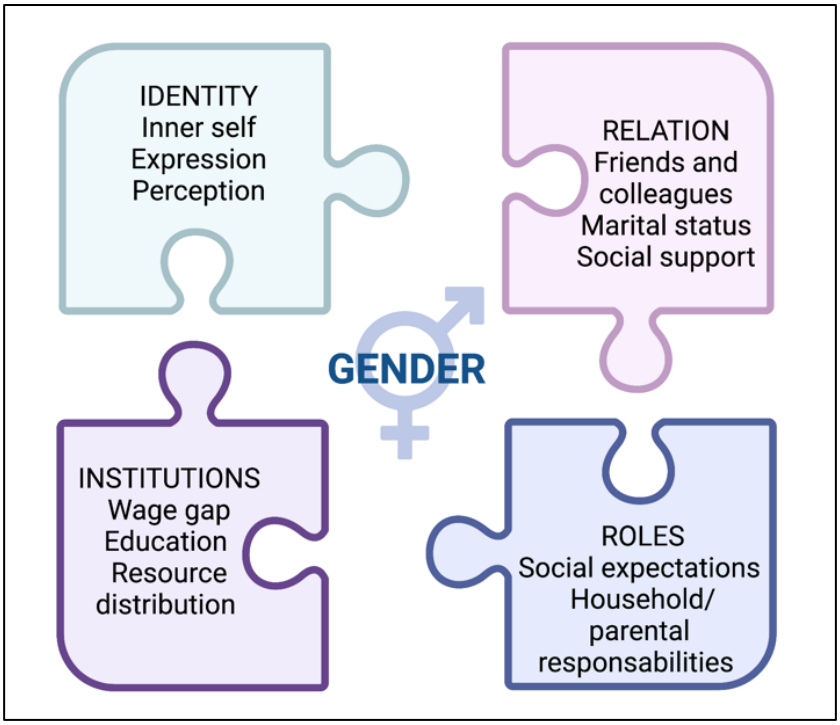


Figure 6. Gender dimensions.
By Ferrannini G. Created with BioRender.com.

This may be an explanation to a latency of approximately ten years as regards the clinical presentation of CAD in women, but when it occurs, women have a higher burden of cardiovascular risk factors (except for smoking). Moreover, women suffer a higher incidence of unstable angina and heart failure at presentation (58, 152). Women with acute myocardial infarction have more in-hospital complications and a higher short-term mortality compared with men (152, 153).

Besides the protection conferred by the presence of oestrogens in females, there are sex-specific conditions which might increase cardiovascular risk in women, e.g. polycystic ovary syndrome, premature menopause, gestational diabetes and pre-eclampsia (154). Moreover, sex modifies the pharmacokinetics of drugs in T2DM. Oral absorption of glucose-lowering medications might be more impaired in females because of prolonged gastrointestinal emptying time and higher gastric pH (155). The absorption after subcutaneous injection of insulin or GLP-1 RA might differ in females because of more marked redistribution of the blood flow in muscular and adipose tissues (155). Albumin glycosylation is more enhanced in males with T2DM and in postmenopausal women, possibly impairing the protein binding of sulphonylureas (155). Consequently, drug effects can be remarkably different (**Table 2**). Furthermore, women tend to be more exposed to adverse drug reactions. Examples are dry cough with angiotensin converting enzyme inhibitor treatment and QT prolongation with sulphonylureas (155-158).

Despite the evidence on sex- and gender-related differences, clinical trials in cardiovascular medicine have always included more men than women (159). The European Heart Health Strategy (EuroHeart) project of the ESC and the European Heart Network, co-funded by the European Commission, advocated better representation of women in clinical trials (160).

Table 2. Sex-related differences in pharmacokinetic parameters of cardiovascular drugs. Adapted from Tamargo et al (156)

Drug class	Outcomes in females vs. males
Insulin	Less hypoglycaemic episodes in longstanding T2DM
Sulphonylureas	Less glucose-lowering effect Higher risk of QT interval prolongation
Metformin	Higher incidence of adverse gastrointestinal drug effects and lactic acidosis
Thiazolidinediones	Higher plasma levels Higher incidence of hypoglycaemia, weight gain and oedema
Acarbose	Higher incidence of gastrointestinal side effects
GLP-1 RA	Higher incidence of gastrointestinal side effects
SGLT2i	Higher risk of urinary tract/genital infections
DDP-4i	Higher risk of upper airways infections
Acetylsalicylic acid	Higher bioavailability. Differences disappear with oral contraceptive pill.
Beta-blockers	Higher plasma levels. Increased renal clearance during pregnancy.
Angiotensin-converting enzyme inhibitors	Higher incidence of cough
Statins	Higher plasma levels
Warfarin	Higher plasma levels

DPP-4i: Dipeptidyl peptidase-4 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; SGLT2i: sodium-glucose co-transporter 2 inhibitors; T2DM: Type 2 diabetes mellitus.

1.8.2 Gender differences in dysglycaemia as a risk factor for coronary artery disease

As noted in the INTERHEART study, diabetes increases the risk of acute myocardial infarction more in men than women (58). Between 1980 and 2000 four large meta-analyses showed that women with diabetes are at a higher risk for fatal CVD compared to men (161-164). Besides, the “female” temporal advantage of CAD presentation seems to be diluted in the presence of

diabetes, especially after menopause (60, 163, 165). It has been debated whether this disadvantageous profile in women with diabetes could be due to an increased risk factor burden and worse control or whether sex-related factors contribute (154, 166, 167). This notion was recently challenged by a large British study in which there was no difference between men and women with newly diagnosed T2DM as regards the risk of myocardial infarction, stroke and cardiovascular death (168). Still, there were important discrepancies in risk factor management in general. Women were prescribed less cardioprotective drugs (including antiplatelet, lipid-lowering and anti-hypertensive agents). In addition, they were more likely to be obese with hypertension and dyslipidaemia (168). This is supposedly more relevant in patients with established CVD, where risk factor control plays a major role.

1.9 New glucose-lowering drugs with cardioprotective effects

In 2008, following the observation that some marketed glucose-lowering agents increased the risk of cardiovascular events and mortality, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) issued a guidance to the pharmaceutical industries, mandating that "concerns about cardiovascular risk should be more thoroughly addressed during drug development" (169, 170). Trials on glucose-lowering agents had to be designed as cardiovascular outcome trials (CVOTs), assessing both cardiovascular efficacy and safety by a primary composite endpoint including three-point major adverse cardiovascular events (3P-MACE), i.e. cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Consequently, trials of glucose-lowering agents belonging to the classes of GLP-1 RA and SGLT2i were conducted as CVOTs (171-178). They showed that these drugs, administered on top of optimized standard therapy, were not only safe, but also superior to placebo in reducing cardiovascular events in patients with T2DM and high cardiovascular risk or established CVD (179-183). Consequently, the European guidelines recommend the use of such agents as first-line glucose lowering therapy in drug-naïve patients with T2DM and established atherosclerotic cardiovascular disease or high cardiovascular risk and recommended them together with metformin if they already were prescribed metformin (56, 184).

1.10 Gaps in knowledge and unmet needs

1.10.1 Screening for dysglycaemia and treatment target attainment in the real world

Since the EUROASPIRE surveys have been reporting a daunting picture as regards management of patients with CAD, it is of interest to observe whether any improvement was achieved after the issue of updated European guidelines, with a special focus on dysglycaemic patients.

1.10.2 Improved screening methods for dysglycaemia

An OGTT requires patients to fast, to drink an unpalatable saccharine solution and is considered time consuming. Therefore, its use has been questioned. Some of these drawbacks can be curbed by obtaining a 1hPG value, thus potentially interrupting the OGTT before two hours. To date, no firmly established thresholds exist for 1hPG values in patients with established CVD.

A test requiring a single blood sample, without the administration of a glucose load, would be even more attractive. Classifying patients with CAD by means of indexes of insulin resistance may offer this opportunity and is biologically sound since insulin resistance may be targeted by lifestyle if needed combined with pharmacological interventions.

1.10.3 Gender differences

A contemporary picture of gender differences in a current, real-world cohort of patients with established CAD and with dysglycaemia, whether previously known or not, is largely missing. Likewise, there is no evidence on the prevalence of undiagnosed dysglycaemia in men and women with established CAD. Moreover, it is debated if management and treatment target attainment differ in men and women according to their glycaemic status. Additionally, whether such findings are generalisable across countries with different healthcare systems and social structures remains to be determined.

1.10.4 Is cardioprotection with new glucose-lowering agents depending on metformin

A controversial point is whether drug-naïve patients with T2DM and an indication to start a GLP-1 RA and/or a SGLT2i for cardioprotection should be prescribed metformin first, or whether the GLP-1 RA/SGLT2i should be prioritized, and metformin added only if additional glycaemic control is needed. The debate is fuelled by the fact that, in CVOT, concomitant metformin use was very frequent, and uncertainty remains regarding whether the cardiovascular benefits of these agents occur in both the presence and absence of metformin (171-178). Therefore, whether these new glucose-lowering drugs require background metformin to exert significant cardiovascular benefits remains unknown (120, 184, 185).

2. AIMS

General objective

To investigate the management of dysglycaemia in patients with cardiovascular disease or at high cardiovascular risk in terms of screening, treatment, gender differences and implementation of new glucose-lowering drugs with cardiovascular benefit.

Specific objectives are to investigate

- The prevalence of dysglycaemia by means of different screening tools in patients with established CAD and without known diabetes (**Study I**) and according to gender (**Study II**).

- New screening methods for dysglycaemia in patients with established CAD and without known dysglycaemia (**Study III** and **IV**).

- The management of dysglycaemic patients with established CAD as regards lifestyle habits, the use of cardioprotective drugs and attainment of treatment targets (**Study I**), and whether there are gender differences in such management (**Study II**).

- Whether the prognosis of patients with established CAD and dysglycaemia differs according to gender (**Study II**).

- If the cardioprotective efficacy of a GLP1-RA in T2DM patients at very high risk or with established CVD is dependent on the use of metformin (**Study V**).

3. MATERIALS AND METHODS

3.1 Study populations

3.1.1 EUROASPIRE (Studies I - IV)

EUROASPIRE IV was a cross-sectional study conducted in 2012 – 2013 in 79 centres across 24 member countries of the ESC.

Patient selection criteria were like those in EUROASPIRE V (see below) apart from that they could be recruited six months to three years prior to the date of the investigation (median time between the index event and the study visit 1.4, interquartile range 1–1.9 years). Of 16,426 patients who were invited to attend a study visit, 7,998 (49%) participated and constitute the study population.

EUROASPIRE V was a cross-sectional study conducted in 2016 – 2017 in 131 centres across 27 member countries of the ESC.

The material included consecutive patients aged 18 to 80 years, who six to 24 months prior to the date of the present investigation had been diagnosed with a first or recurrent (i) elective or emergency coronary artery bypass graft (CABG), (ii) elective or emergency percutaneous coronary intervention (PCI), (iii) acute myocardial infarction (International Classification of Diseases – 10th revision – ICD-10 – I21) and (iv) acute myocardial ischaemia (ICD-10 I20).

Of 16,208 patients who were invited to attend a study visit, 8,261 (51%) accepted and constitute the present study population. The median time between the index event and the study visit was 1.1 years (interquartile range 0.8–1.6). Extensive information was collected by means of interviews and investigations by centrally trained research staff, using standardized methods and uniform equipment. Data were electronically submitted to the data management centre (EURObservational Research Programme (EORP), ESC, Sophia-Antipolis, France).

3.1.2 REWIND (Study V)

The REWIND trial (ClinicalTrials.gov number: NCT01394952) was a multicentre, randomized, double-blind, placebo-controlled trial, conducted at 371 sites in 24 countries (186). Eligible patients were ≥ 50 years old with T2DM, a HbA1c ≤ 9.5% (80 mmol/mol), BMI ≥ 23 kg/m^2 on stable treatment with glucose-lowering drugs since at least three months. The participants had either suffered a previous cardiovascular event or had multiple cardiovascular risk factors. Exclusion criteria were an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2, a history of cancer within five years prior to inclusion, any episode of severe hypoglycaemia in the year prior to inclusion, a life expectancy below one year, a coronary or cerebrovascular event within the previous two months or a planned revascularization.

3.2 Methods

3.2.1 EUROASPIRE IV and V (Studies I – IV)

Measurements

All measurements were standardized and the investigational staff from the participating centres underwent a centralized training session in the use of the investigational equipment and questionnaires.

Height (cm) and *weight* (kg) were recorded in light indoor clothes without shoes (Scales 701 and Measuring stick model 220; SECA Medical Measuring Systems and Scales, Birmingham, U.K.).
Waist circumference was measured with the patient standing, using a metal tape applied horizontally at the midway point on the midaxillary line between the lowest rim of the ribcage and the superior iliac crest.

Blood pressure was measured twice on the right upper arm in the sitting position using an automatic digital sphygmomanometer (Omron M6; OMRON Corporation, Kyoto, Japan). The mean of both measurements was used for the analyses.

Laboratory Investigations were performed on venous blood drawn after ≥ 10 hours fast. The samples were frozen (following centrifugation and as whole blood in EDTA tubes) locally at -70°C and subsequently sent to a central laboratory for final storage and analyses (Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland) accredited by the Finnish Accreditation Service, fulfilling the requirements of the standard SFS-EN International Organization for Standardization/International Electrotechnical Commission 17025:2005.

The following was analysed: total and HDL-C, triglycerides, and HbA1c. LDL-C was calculated by means of Friedewald's formula. Total and HDL-C and triglycerides were analysed on a clinical chemistry analyser (Abbot Architect Analyzer; Abbott Laboratories, Abbott Park, IL) using an enzymatic method for measuring total cholesterol. HbA1c was measured with an immunoturbidimetric International Federation of Clinical Chemistry and Laboratory Medicine aligned method (Abbot Architect Analyzer) in whole blood.

Screening for dysglycaemia by means of an OGTT (75 g glucose in 200 mL water) was performed on all patients without known diabetes. Plasma glucose (PG) was analysed locally in the fasting state (FPG), one hour (1hPG) and two hours after the glucose load (2hPG) with a photometric point-of-care technique (Glucose 201+ (EUROASPIRE IV) or Glucose 201RT (EUROASPIRE V); HemoCue, Ängelholm, Sweden). Since the HemoCue technique is cholesterol-sensitive, glucose values were corrected for cholesterol according to the formula: HemoCue glucose + 0.15 x (total cholesterol - 5). HemoCue automatically converts the venous blood glucose to plasma glucose by using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendation: plasma glucose = 1.11 x whole blood glucose (187, 188).

Serum insulin and C-peptide were measured on frozen samples, obtained during the OGTT, and stored at the central laboratory in Helsinki. Both insulin and C-peptide were measured using chemiluminescent microparticle immunoassay (manufacturer Abbott laboratories, Abbott Park, IL, USA) on a clinical immunochemistry analyser (Architect ci8200, Abbott Laboratories). Sample quality was assessed based on visual evaluation, and internal controls. To ensure standardization of measurements, the laboratory took part in External Quality Assessment Schemes organized by Labquality (Helsinki, Finland). The coefficient of variation (mean±standard deviation - SD) and systematic error (bias) (mean±SD) were 2.2%±0.4 and 1.1%±0.2 for insulin, 4.0%±0.7 and –10.2%±0.5 for C-peptide respectively.

HOMA-IR was calculated according to the formula

$$HOMA - IR = \frac{\text{glucose (mmol/L) x insulin (μU/mL)}}{22.5}$$

HOMA2 based on insulin (*HOMA2-ins*) and on C-peptide (*HOMA2-Cpep*) were obtained by the calculator at https://www.dtu.ox.ac.uk/homacalculator/. The HOMA2 model is an updated

version of the HOMA model which accounts for variations in hepatic and peripheral glucose resistance and the contribution of circulating proinsulin (189). Low HOMA values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity, i.e., insulin resistance.

Definitions

Pharmacological treatment: Information on medication intake was based on the self-reported use at the time of the interview.

Educational level was defined as "low" if the patient reported no further education than completed primary school.

Smoking was defined as self-reported smoking and/or a breath carbon monoxide higher than 10 ppm by means of Smokerlyzer (Bedfont Scientific, Model Micro1) at the time of interview. *Persistent smoking* was defined as smoking at the time of interview among those who smoked the month prior to the index event.

Overweight was defined as Body Mass Index (BMI) 25 - 29.9 kg/m^2 and *obesity* as BMI ≥ 30 kg/m^2.

Central obesity was defined as waist circumference ≥ 88 cm for women and ≥ 102 cm for men.

Physical activity target was defined by the question: "Do you take regular physical activity for at least 30 minutes on average five times a week?''.

Use of four cardioprotective drugs, consisting of antiplatelet drugs, beta-blockers, renin-angiotensin-aldosterone system (RAAS) blockers, and lipid-lowering drugs was assessed at the interview visit.

Treatment target attainment was assessed for blood pressure, LDL-C and HbA1c (for patients with previously known diabetes) according to the 2012 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (190) and the 2013 European Guidelines for Diabetes, Pre-Diabetes and Cardiovascular Disease (191), which were the existing guidelines at the time of the survey.

Glycaemic state was defined according to World Health Organization (**Table 1**) (33).

Previously known diabetes was defined as a self-reported history of diabetes or use of any glucose-lowering medication.

Newly detected dysglycaemia was defined as the presence of IGT or T2DM according to the OGTT performed in patients without previously known diabetes.

Anxiety and depression scores were estimated by means of the Hospital Anxiety and Depression Scale (HADS) questionnaire (192).

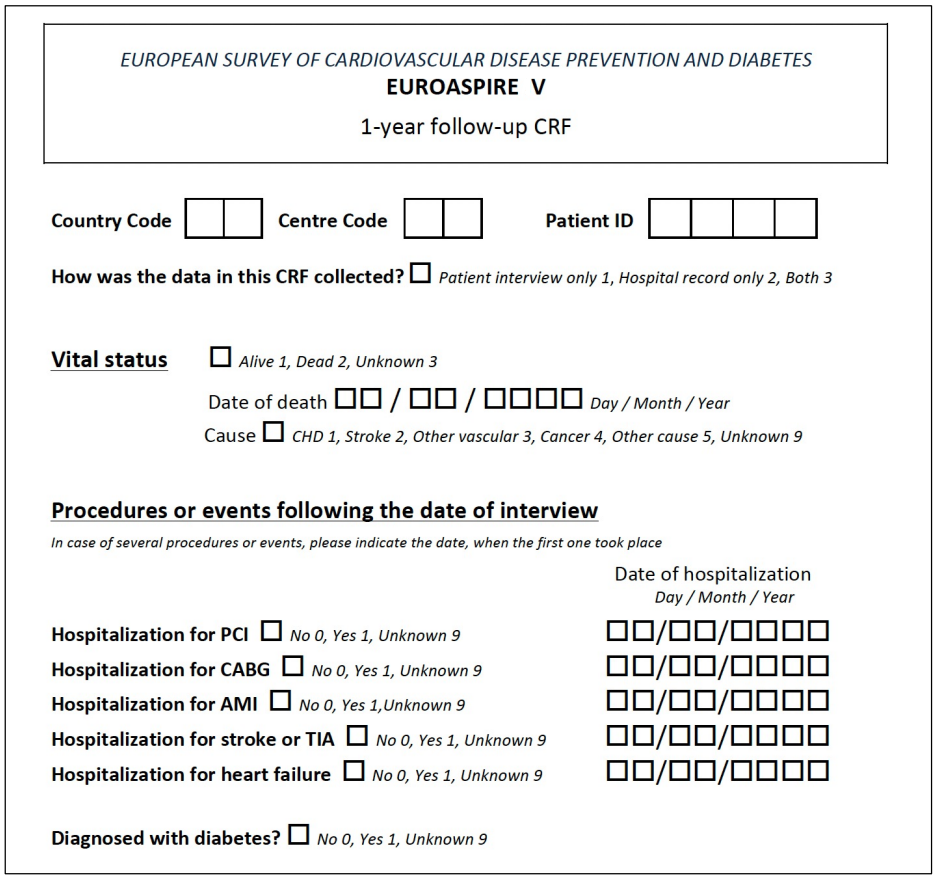
Generic health status was assessed by means of VAS-scale of the EuroQoL 5D questionnaire, varying from 0 (the worst possible health status) to 100 (the best possible health status) (193).

Follow-up

The participants in EUROASPIRE IV and V were followed up by means of a one-page questionnaire after at least one year from index examination, and with information available for at least 90% of the patients from the participating centre as an eligibility criterion (194). Follow-up information was collected from the patients, medical records, registries or databases (mortality registries, municipal records and archives) or by contacting the patients' family or family doctor. The information comprised vital status, date and cause of death (coronary heart

disease, stroke, other vascular, cancer or other causes) and the new hospitalizations following the baseline interview (**Figure 7**).

The first of cardiovascular death or hospitalization for non-fatal myocardial infarction, non-fatal stroke and heart failure served as the primary cardiovascular outcome and death from any cause as the secondary outcome. In case of several non-fatal events the first was considered.



EUROPEAN SURVEY OF CARDIOVASCULAR DISEASE PREVENTION AND DIABETES
EUROASPIRE V
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 7. The form for follow-up of EUROASPIRE V patients.

3.2.2 REWIND (Study V)

The participants were randomly assigned to 1.5 mg of weekly subcutaneous dulaglutide or to a corresponding volume of placebo (186). They underwent scheduled visits after two weeks, three and six months and subsequently every three months for drug dispensing and every six months for a more detailed assessment (178, 186). The investigators were encouraged to promote a healthy lifestyle and defined targets for each cardiovascular risk factor. Apart from another GLP-1 RA or pramlintide they could add any glucose-lowering medication according to local guidelines.

Outcomes
The primary endpoint was the first of 3P-MACE, i.e. a composite of non-fatal myocardial infarction, non-fatal stroke and death from cardiovascular or unknown causes. Three key secondary outcomes were analysed: 1) a composite of clinical microvascular outcome, including retinopathy due to diabetes (defined as need for photocoagulation, anti-vascular endothelial growth factor therapy or vitrectomy) or renal disease (defined as development of a urinary albumin-to-creatinine ratio > 33.9 mg/mmol in those with a lower baseline

concentration, a sustained 30% or greater decline in eGFR based on two consecutive eGFR assessments or need for chronic renal replacement therapy); 2) all-cause death; and 3) heart failure requiring either hospital admission or an urgent visit requiring therapy.

3.3 Statistical Analyses

3.3.1 EUROASPIRE (Studies I – IV)

Electronically collected data from EUROASPIRE IV and V were submitted online to the data management centre (EORP, ESC, Sophia-Antipolis, France). Data analyses were performed at the Department of Public Health and Primary Care, Ghent University, Belgium by means of SAS statistical software release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).
Distributions of baseline characteristics including patients' demographics, risk factor profiles and use of medications in different groups were summarized according to means, standard deviations and proportions.

Study I: To account for the clustering of patients within centres, distributions of characteristics across groups were compared according to linear mixed model analysis for continuous outcomes and mixed logistic model analysis for binary outcomes. Models included age and sex as covariates. Goodness-of-fit statistics for all models demonstrated acceptable fit to the data. A level of alpha < 0.05 was a priori chosen to indicate statistical significance.

Study II: The association between gender and time to the occurrence of the endpoint was evaluated using Cox survival modelling, adjusting for age. The assumption of proportionality of hazards in women and men overtime was checked by fitting a gender-by-time interaction term in the model.

Study III: The optimal threshold for 1hPG was obtained by the maximum Youden's J statistic on receiver operator characteristics (ROC) curves testing the diagnostic performance in diagnosing T2DM, i.e. a 2hPG value of 11.1 mmol/L (200 mg/dL). The optimal threshold was compared with a 1hPG of 12 mmol/L, which the optimal threshold found in the discovery cohort (195).

Study IV: The optimal threshold for FPG, HbA1c, fasting insulin, fasting C-peptide, HOMA-IR, HOMA2-ins and HOMA2-Cpep were tested for both T2DM (2hPG value $\geq$ 11 mmol/L) and dysglycaemia (2hPG value $\geq$ 7.8 mmol/L). The associations between 2hPG and the other screening parameters, as well as between HOMA indexes and clinical features, were analysed by Spearman correlation coefficients.

3.3.2 REWIND (Study V)

The characteristics of participants according to reported baseline metformin were summarized; categorical variables were reported as counts and percentages with the corresponding odds ratios (ORs, i.e. the odds of being on metformin in the presence vs. the absence of the variable); continuous variables were reported as mean and standard deviation with the corresponding ORs (i.e. the odds of being on metformin for every unit increase in the value of the continuous variable). Logistic regression was used to assess the univariable relationship between the baseline characteristics of interest and baseline metformin use. A multivariable logistic regression model was constructed considering all univariable predictors of baseline metformin with a p-value < 0.05 using backward elimination method with alpha-level of 0.05.

The estimated effect of dulaglutide on the study outcomes in participants with and without baseline metformin use was evaluated according to the intention-to-treat principle and included all outcomes occurring on or after randomization in the analysis. Kaplan-Meier estimates were used to generate cumulative incidence risks and Cox proportional hazards models were used to estimate the HR and 95% CI in each of subgroups of baseline metformin use. The Cox models were adjusted for the baseline characteristics identified in the multivariable logistic regression model. The interaction between dulaglutide and metformin use at baseline was assessed by including the subgroup and interaction term in the Cox model.
The effect of dulaglutide on the primary outcome was also evaluated by means of an analysis of three subgroups in relation to glucose lowering therapy at baseline: drug naïve patients (neither on metformin nor on any other glucose drugs); patients on any glucose lowering drug except metformin; and patients on metformin with or without any other glucose lowering drug.

To investigate whether the use of metformin during follow up influenced the effect of dulaglutide on the four major outcomes (MACE, all-cause death, microvascular and heart failure) the hazard of dulaglutide was re-estimated after adjusting for baseline metformin use and metformin use as a time-varying covariate (i.e. at the last visit before either the outcome or censorship).

3.4 Ethical considerations

3.4.1 EUROASPIRE (Studies I – IV)

The EUROASPIRE surveys include countries in the European region according to the World Health Organization. National Coordinators were responsible for obtaining Local Ethics Committees approvals in each of the included countries (24 in EUROASPIRE IV and 27 in EUROASPIRE V). All patients received a patient information brochure explaining the study outline and its purpose, the interview schedule, what happens after the study, and details on results and confidentiality. Written, informed consent was subsequently obtained from each participant and stored in the patient file. The research assistants signed the Case Record Form confirming that informed consent was obtained and stored as instructed. All information on patients was anonymised before electronic transfer to the central storage at the ESC. Patients were managed according to standard care.

All procedures were conducted in compliance with the Declaration of Helsinki. Patients were managed according to current evidence-based treatments, uninfluenced by the participation in the study. All information on patients was anonymized before transfer to the central storage at the European Society of Cardiology.

3.4.2 REWIND (Study V)

Ethics review boards responsible for each participating institution approved the REWIND protocol. All participants provided written informed consent. The trial was carefully monitored by an independent data monitoring committee, who reviewed unblinded data every six months.

4. RESULTS

4.1 Baseline characteristics

4.1.1 Study I: the EUROASPIRE V cohort

In total, 16,208 medical records were reviewed, and 8,261 patients attended the interview (participation rate: 51%) in the study cohort based on EAV. **Figure 8** depicts a flowchart of patient classification according to glycaemic status.

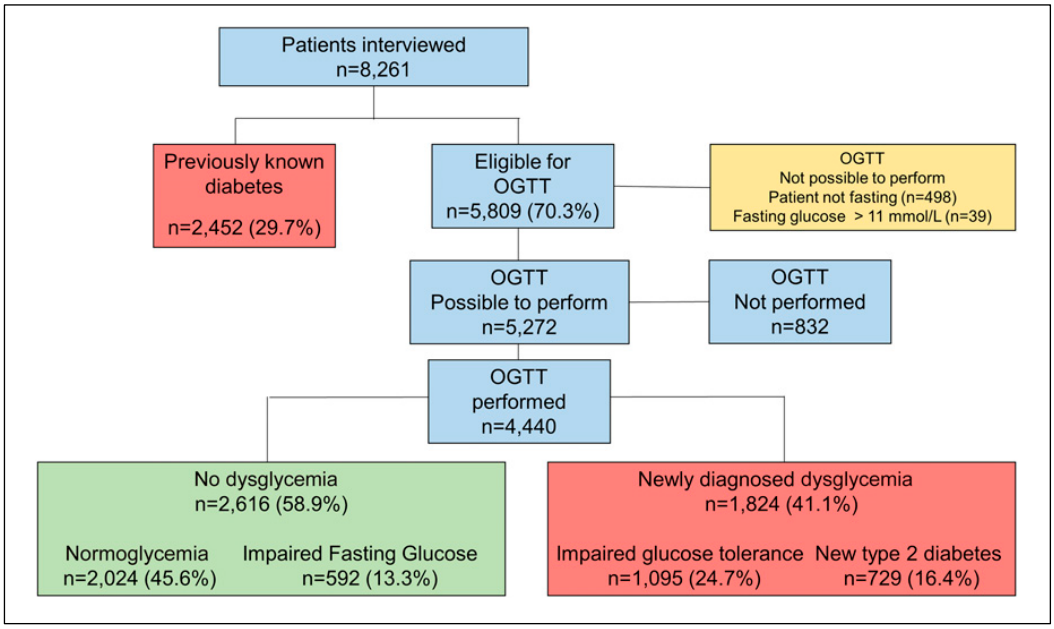


Figure 8. Flowchart of the patients by glucose category. Proportions in the last row refer to the total of patients who underwent an OGTT.

OGTT: oral glucose tolerance test.

Pertinent patient characteristics by glycaemic status at the time of interview are presented in **Table 3**. Overall, the mean (SD) age at interview was 63.6 (9.6) years and 26% were women. Overweight or obesity was most common in patients with known diabetes (89%). Persistent smoking was present in approximately half of the patients, somewhat less frequent in patients with known diabetes. Approximately two-thirds of the patients did not practice physical activity for the recommended amount of at least 30 min 5 times/week, a proportion that was higher among those with known diabetes (72%).

Table 3. Pertinent clinical and lifestyle characteristics by glucose category at the time of the interview.
Data are % (n) or mean (standard deviation). Numbers in brackets = number of patients/total number of observations. If only one number is given the number of observations corresponds to the total population within the group.

	No dysglycaemia * N=2,616	**OGTT eligible, not performed N=832**	**Newly diagnosed IGT N=1,095**	**Newly diagnosed diabetes N=729**	**Previously known diabetes N=2,452**
Age	61.8 (10.0)	62.9 (10.2)	64.4 (9.5)	64.6 (9.4)	64.9 (9.0)
Women	23.4 (613)	23.4 (195)	28.7 (314)	25.0 (182)	29.0 (712)
Glycaemic variables					
FPG (mmol/L)	5.6 (0.69)	5.9 (1.10)	5.9 (0.62)	7.2 (1.07)	8.7 (3.01)
HbA1c (%-mmol/mol), mean♦	5.5 (0.46), 37	5.7 (0.68), 38	5.6 (0.49), 38	5.9 (0.57), 41	7.2 (1.68), 55
Lifestyle					
Persistent smoking †	54.9 (497/996)	55.2 (180)	51.9 (165/318)	48.9 (113/231)	55.6 (336/604)
Overweight or obesity	76.9 (2004/2607)	77.5 (638)	82.7 (904/1,093)	83.9 (610/727)	88.5 (2098/2,370)
Obese with no advice to follow dietary guidelines	37.1 (277/746)	36.3 (94)	42.4 (179/422)	40.3 (122/303)	36.2 (412/1,138)
No regular physical activity ≥ 30 min 5 times/week	60.4 (1430/2368)	63.6 (485)	65.1 (637/979)	67.7 (452/668)	72.2 (1578/2,178)

* Including Impaired Fasting Glucose
♦ Mean HbA1c levels were converted using the NGSP calculator at http://www.ngsp.org/convert1.asp
† Defined as smoking at time of interview among those who smoked in the month prior to the index event
FPG: fasting plasma glucose; HbA1c: glycated haemoglobin A1c.

4.1.2 Study II: the EUROASPIRE IV and V cohorts

Figure 9 depicts a flowchart of patient classification according to gender and glycaemic status. A total of 4,796 (30%) patients had previously known diabetes (women 33% vs. men 29%; p<0.0001), whereof 97% T2DM. An OGTT was performed in 8,655 (76%) of the remaining 11,463 patients. A similar proportion of women and men did not undergo such screening (p=0.26). The final study population of dysglycaemic individuals with CAD comprised 4,796 patients with previously known T2DM and 4,029 with newly detected dysglycaemia.

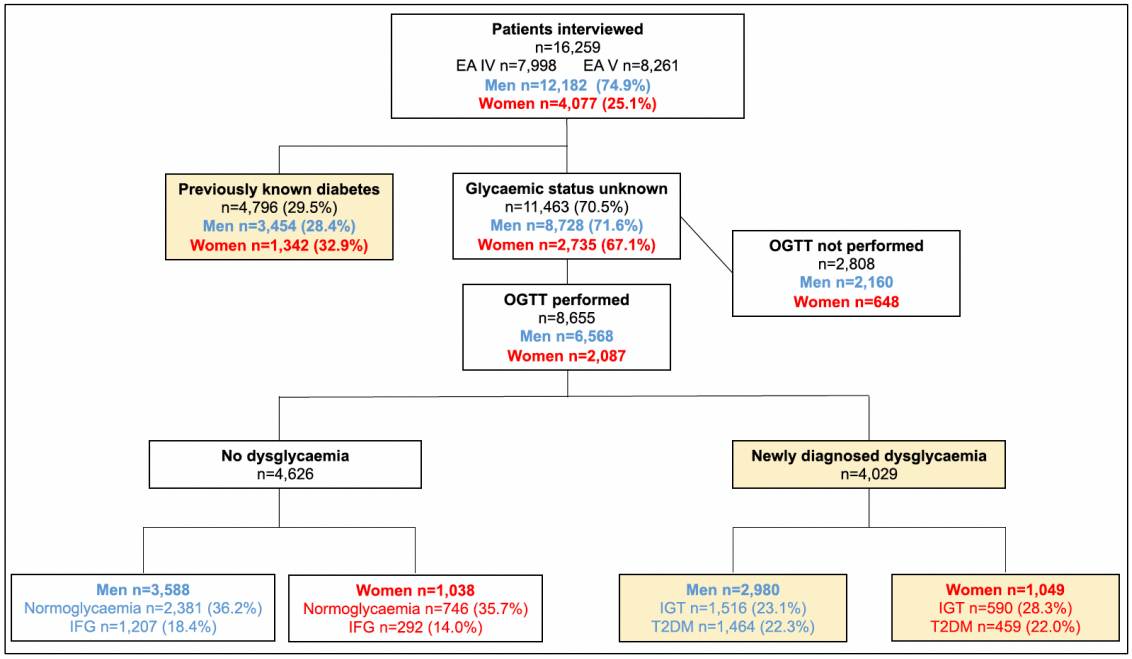


Figure 9. Flowchart of the patients and their glycaemic classification according to the oral glucose tolerance test (OGTT). The dysglycaemic participants are highlighted with yellow background.

EA: EUROASPIRE; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus.

Baseline characteristics of dysglycaemic women and men in EUROASPIRE IV and V at the time of the interview are shown in **Table 4**, separately for those with known diabetes and newly detected dysglycaemia.

Women were older than men, had a lower educational level, and had a higher frequency of hypertension, dyslipidaemia and obesity in both glycaemic categories. Renal function, expressed as eGFR, was better in women than in men. Total cholesterol and LDL-C levels were significantly higher ($p < 0.0001$) in women than in men, both in patients with previously known T2DM and among those with newly detected dysglycaemia. Serum triglycerides were significantly higher in women than in men in those with previously known T2DM. The glycaemic control as assessed by HbA1c was less strict in women than in men with known T2DM ($p < 0.0001$); 51.0% of women and 57.3% of men had a HbA1c < 7% (53 mmol/mol) ($p < 0.0001$).

Less women than men were current smokers, but the proportion of persistent smokers (patients who were smoking at the time of the recruiting event and still smoking at interview) was similar in both genders across the two glycaemic categories.

Table 4. Baseline characteristics according to gender and glycaemic category in the cohorts from EA IV and V. Entries are % (n/total number) or mean (standard deviation).

	Previously known diabetes			**Newly detected dysglycaemia**		
	Women N=1,342	**Men N=3,454**	**p-value** [a]	**Women N=1,049**	**Men N=2,980**	**p-value** [a]
Age (years)	66.6 (8.7)	64.6 (8.9)	<0.0001	66.8 (8.9)	64.0 (9.6)	<0.0001
Low educational level	24.5 (324/1,323)	16.1 (548/3401)	<0.0001	19.9 (208/1,046)	15.4 (456/2,960)	0.0010
Currently smoking	16.1 (216/1,342)	29.0 (1,002/3,454)	<0.0001	22.1 (232/1,049)	33.1 (987/2,980)	<0.0001
Persistent smoking	53.7 (116/216)	53.0 (531/1,002)	0.88	48.3 (112/232)	44.9 (443/987)	0.38
Physical activity level on target	45.8 (594/1,297)	55.2 (1852/3,358)	<0.0001	51.5 (528/1,026)	57.0 (1,665/2,922)	0.002
Medical history						
Hypertension	87.2 (1158/1,328)	79.5 (2,712/3,410)	<0.0001	80.8 (841/1,041)	73.7 (2,172/2,947)	<0.0001
Dyslipidaemia	78.4 (1011/1,289)	75.0 (2,496/3327)	0.016	75.0 (766/1,021)	68.9 (1,977/2,869)	0.0002
Anthropometrics - Vitals						
BMI (kg/m²)	31.6 (5.9)	30.1 (4.8)	0.0001	29.8 (5.5)	29.0 (4.3)	0.002
Obesity	57.7 (754/1,306)	45.6 (1,550/3,396)	0.0001	43.9 (460/1,048)	36.6 (1,089/2,977)	<0.0001
Central obesity	86.7 (1080/1,246)	63.6 (2,077/3,266)	<0.0001	77.3 (789/1,021)	54.2 (1,577/2,909)	<0.0001
SBP (mmHg)	138.3 (20.3)	137.2 (18.9)	0.18	134.4 (19.5)	134.2 (18.6)	0.99
DBP (mmHg)	79.3 (11.6)	80.1 (11.0)	0.036	79.3 (11.3)	80.3 (11.0)	0.001
Heart rate (bpm)	70.9 (11.2)	68.8 (11.1)	<0.0001	69.1 (11.1)	67.9 (11.4)	0.002
Laboratory central assessment						
LDL-C (mmol/L)	2.5 (1.1)	2.2 (0.9)	<0.0001	2.8 (1.1)	2.5 (0.9)	<0.0001
HDL-C (mmol/L)	1.2 (0.3)	1.0 (0.3)	<0.0001	1.3 (0.3)	1.1 (0.3)	<0.0001
Triglycerides (mmol/L)	2.0 (1.7)	1.9 (1.6)	0.0005	1.6 (0.8)	1.6 (1.1)	0.83
FPG (mmol/L)	n.a.	n.a.	n.a.	6.5 (1.0)	6.6 (1.1)	0.007
2hPG (mmol/L)	n.a.	n.a.	n.a.	9.8 (2.4)	9.7 (2.5)	0.07
HbA1c (%)	7.4 (1.7) - 57	7.1 (1.5) - 54	<0.0001	5.8 (0.5) - 40	5.8 (0.6) - 40	0.014
HbA1c (mmol/mol), mean **	57	54	<0.0001	40	40	0.014
Creatinine (µmol/L)	85.3 (53.7)	97.9 (53.2)	<0.0001	78.0 (28.5)	93.4 (37.5)	<0.0001
eGFR (mL/min/1.73m²)	89.2 (24.5)	76.9 (21.2)	<0.0001	93.9 (20.2)	78.5 (18.1)	<0.0001

[*] Significance level for testing differences between men and women in each diagnostic group

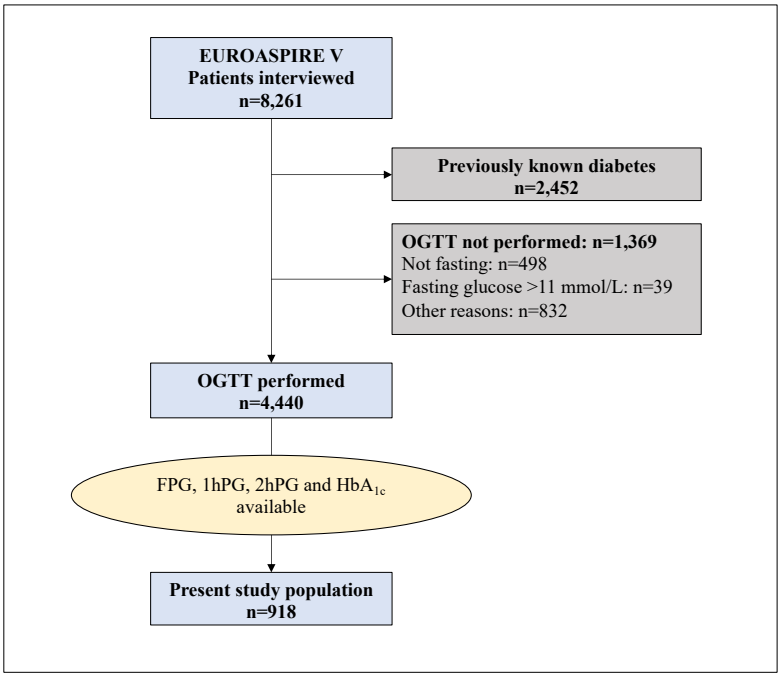
[**] Mean HbA1c levels were converted using the National Glycohemoglobin Standardization Program calculator at http://www.ngsp.org/convert1.asp

2hPG: two-hour postload glucose; BMI: Body Mass Index; DBP: diastolic blood pressure; DEP: diabetes educational programme; eGFR: estimated glomerular filtration rate; EQ-5D: FPG: fasting plasma glucose; HbA1c: glycated haemoglobin; HDL-C: high density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus.

4.1.3 Study III: the EUROASPIRE V cohort

Baseline characteristics of the 918 EUROASPIRE V patients without previously known type 2 diabetes (age: 62.8 ± 10.1 years; women = 24%) in whom HbA1c, FPG, 1hPG and 2hPG were available (**Figure 10**) are shown in **Table 5**.

Figure 10. Patient flow-chart.



1hPG: one-hour plasma glucose; 2hPG: 2-hour plasma glucose; FPG: fasting plasma glucose
HbA1c: glycated haemoglobin; OGTT: oral glucose tolerance test.

Table 5. Pertinent clinical characteristics of the patient population. Entries are % (n/total number) or mean ± standard deviation.

Characteristic	
Age (years)	63 ± 10
Men	76 (693/918)
Body mass index (kg/m^2)	28.6 ± 4.7
Central obesity (waist women >80 cm; men > 102 cm)	52 (439/846)
Hypertension (Blood Pressure ≥ 140/90 mmHg)	33 (302/916)
Blood Pressure Systolic/Diastolic	131 ± 19/79 ± 11
Fasting Plasma Glucose	6.1 ± 1.0
One-hour Plasma Glucose	10.0 ± 2.8
Two-hour Plasma Glucose	7.8 ± 2.5
Glycated hemoglobulin A1c (%) [mmol/mol]	5.6 ± 0.4 [36]
Acetylsalicylic acid /antiplatelets	95 (876/917)
Beta-blockers	81 (739/917)
Angiotensin Converting Enzyme inhibitors	60 (547/917)
Angiotensin-II receptor antagonists	16 (144/917)
Statins	91 (834/917)

4.1.4 Study IV: the EUROASPIRE V cohort

A total of 4,440 patients without known glucose perturbations underwent an OGTT in EUROASPIRE V, from whom 4,036 samples were received and stored at the central laboratory in Helsinki. As detailed in **Figure 11** the samples from 502 patients were considered unreliable, leaving 3,534 samples available for the present investigation. The OGTT revealed that 1,439 (41%) of the 3,534 patients were dysglycaemic (IGT = 24% and T2DM = 16%).

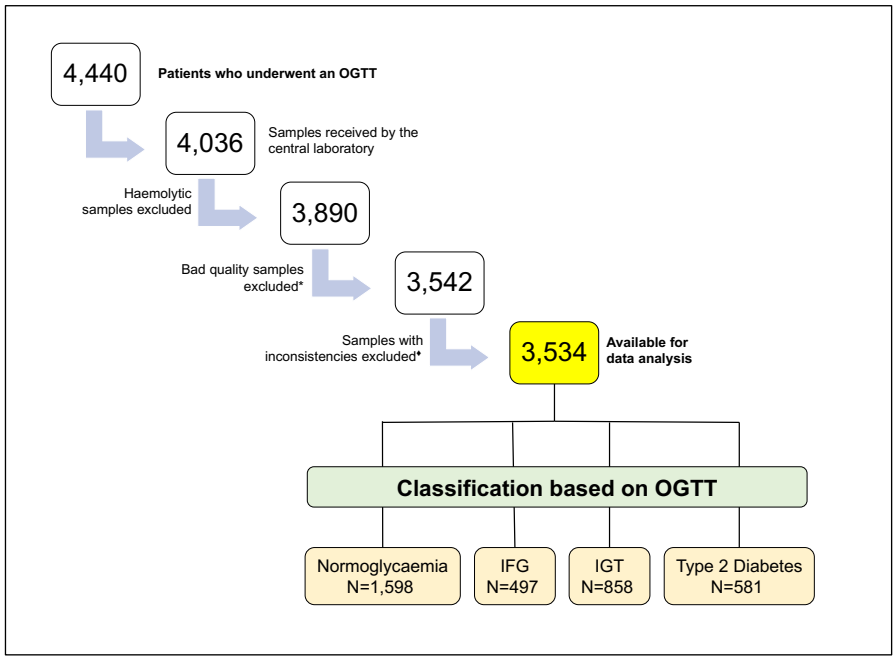


Figure 11. Sample selection. Flowchart describing the sample selection process and reasons for sample exclusion.

*Bad quality including samples with extremely out-of-range insulin and/or C-peptide values, out-of-range calcium values and samples that arrived in poor condition at visual assessment; ♦Inconsistencies including molar ratio of insulin to C-peptide > 1.
IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

Baseline characteristics of the study population, including the complete glycaemic profile (FPG, 2hPG, HbA1c, fasting serum insulin and C-peptide and HOMA indexes) are reported in **Table 6**. The mean age of the patients was 63 years and 25% were women. As regards CV risk factors 54% were centrally obese and 18% current smokers. Their mean blood pressure was 133/80 mmHg and mean LDL-C 2.4 mmol/L.

The mean values of all different screening tests were significantly higher in patients with vs. without newly diagnosed dysglycaemia (all $p < 0.0001$) as reported in **Table 7**.

Table 6. Baseline characteristics of the study population. Data are % (n) or mean (SD) if not stated otherwise.

Variable	All (N=3,534)	Men (N=2,667)	Women (N=867)
FPG (mmol/L)	5.9 (0.9)	6.0 (0.9)	5.9 (0.9)
2hPG (mmol/L)	7.6 (2.5)	7.5 (2.5)	7.8 (2.5)
HbA1c (%) [mmol/mol]	5.6 (0.4) [37]	5.6 (0.4) [37]	5.6 (0.4) [38]
Fasting serum insulin (μU/mL)	11.4 (6.6)	11.4 (6.5)	11.4 (6.9)
Fasting serum C-peptide (nmol/L)	0.7 (0.4)	0.8 (0.4)	0.7 (0.4)
HOMA-IR	3.1 (2.0)	3.1 (1.9)	3.0 (2.0)
HOMA2-ins	1.5 (0.9)	1.5 (0.9)	1.5 (0.9)
HOMA2-Cpep	1.7 (0.9)	1.7 (0.8)	1.7 (0.9)

FPG: fasting plasma glucose; 2hPG: two-hour postload glucose; HbA1c: glycated haemoglobin A1c; HOMA: homeostasis model assessment; HOMA2-ins: homeostasis model assessment 2 based on insulin; HOMA2-Cpep: homeostasis model assessment based on C-peptide.

Table 7. Glycaemic variables in CAD patients without vs. with newly diagnosed dysglycaemia. Dysglycaemia is defined as either impaired glucose tolerance or T2DM according to the oral glucose tolerance test. Cell entries are mean (SD).

Variable	No dysglycaemia N=2,095	Newly diagnosed dysglycaemia N=1,439
FPG (mmol/L)	5.6 (0.7)	6.4 (1.0)
2hPG (mmol/L)	6.1 (1.1)	9.8 (2.3)
HbA1c (%) [mmol/mol]	5.5 (0.3) [37]	5.7 (0.5) [39]
Fasting serum insulin (μU/mL)	10.7 (6.2)	12.4 (7.0)
Fasting serum C-peptide (nmol/L)	0.7 (0.3)	0.8 (0.37)
HOMA-IR	2.7 (1.6)	3.6 (2.2)
HOMA2-ins	1.4 (0.8)	1.7 (0.9)
HOMA2-Cpep	1.6 (0.8)	1.9 (0.9)

FPG: fasting plasma glucose; 2hPG: two-hour postload glucose; HbA1c: glycated haemoglobin A1c; HOMA: homeostasis model assessment; HOMA2-ins: homeostasis model assessment 2 based on insulin; HOMA2-Cpep: homeostasis model assessment based on C-peptide.

4.1.5 Study V: the REWIND trial

In the REWIND trial, a total of 9,901 participants were recruited between August 2011 and August 2014, of whom 4,949 were randomized to dulaglutide and 4,952 to placebo. Patient characteristics are presented in **Table 8**.

At baseline, 8,037 (81%) of the participants were prescribed metformin while 1,864 (19%) were without such therapy. The proportions were similar in the dulaglutide and placebo groups.

At baseline the proportion of female patients was higher in the group without compared to those with metformin (49 vs. 45.7%). In addition, patients on metformin were older (67.8 vs. 65.8 years), slightly less obese (BMI 31.8 vs. 32.4 kg/m^2) and had a history with a higher proportion of previous cardiovascular events (24 vs. 20%), heart failure (13 vs. 8%) and an eGFR < 60 ml/min/1.73 m^2 (35 vs. 19%). Moreover, they had higher use of insulin (30 vs. 22%) and thiazolidinediones (4 vs. 1%) but a lower use of statins (62 vs. 67%) and renin-angiotensin system inhibitors (79% vs. 82%).

Independent determinants of baseline metformin use included age, previous cardiovascular events, heart failure, diabetes duration, eGFR < 60, BMI, diastolic blood pressure, heart rate, LDL-C and use of insulin, thiazolidinediones, renin angiotensin aldosterone system inhibitors and use of statins.

Table 8. Baseline characteristics of patients with and without metformin treatment at baseline. Categorical variables are reported as counts and percentages with the corresponding ORs (i.e. the odds of being on metformin in the presence vs. absence of the variable). Continuous variables are reported as mean and standard deviation with the corresponding ORs (i.e. the odds of being on metformin for every unit increase in the value of the continuous variable).

	Overall	**Metformin**			
Variable	**N=9,901**	**Yes N=8,037**	**No N=1,864**	**OR (95% CI)***	**p-value***
Age (years)	66.2 (6.5)	65.8 (6.3)	67.8 (7.1)	0.95 (0.95,0.96)	<0.0001
Females	4,589 (46.3)	3,675 (45.7)	914 (49.0)	0.88 (0.79,0.97)	0.01
Current tobacco use	1,407 (14.2)	1,157 (14.4)	250 (13.4)	1.09 (0.94,1.26)	0.27
Cardiovascular event	2,035 (20.6)	1,585 (19.7)	450 (24.1)	0.78 (0.69,0.88)	<0.0001
Hypertension	9,224 (93.2)	7,474 (93.0)	1,750 (93.9)	0.87 (0.70,1.07)	0.17
Prior heart failure	853 (8.6)	620 (7.7)	233 (12.5)	0.59 (0.50,0.69)	<0.0001
Diabetes duration (years)	10.5 (7.2)	10.6 (7.0)	10.2 (8.0)	1.0 (1.0,1.0)	0.02
Retinopathy due to diabetes	891 (9.0)	720 (9.0)	171 (9.2)	0.98 (0.82,1.17)	0.82
HbA1c (%), (mmol/mol)	7.3 (1.1); 57	7.4 (1.0); 57	7.3 (1.1); 56	1.05 (1.00,1.11)	0.03
eGFR < 60 (ml/min/1.73m2)	2,199 (22.2)	1,555 (19.3)	644 (34.5)	0.45 (0.41,0.51)	<0.0001
Albuminuria	3,467 (35.0)	2,786 (34.7)	681 (36.5)	0.90 (0.80,1.00)	0.04
Sulphonylurea	4,552 (46.0)	3,723 (46.3)	829 (44.5)	1.08 (0.97,1.19)	0.15
Insulin	2,363 (23.9)	1,800 (22.4)	563 (30.2)	0.67 (0.60,0.75)	<0.0001
DPP4i	564 (5.7)	456 (5.7)	108 (5.8)	0.98 (0.79,1.21)	0.84
Thiazolidinedione	168 (1.7)	97 (1.2)	71 (3.8)	0.31 (0.23,0.42)	<0.0001
Body Mass Index (kg/m^2)	32.3 (5.7)	32.4 (5.7)	31.8 (5.8)	1.02 (1.01,1.03)	<0.0001
Systolic Blood Pressure (mm Hg)	137 (16.8)	137 (16.8)	137 (16.9)	1.00 (1.00,1.01)	0.23
Diastolic Blood Pressure (mm Hg)	78.4 (9.83)	78.7 (9.75)	77.5 (10.1)	1.01 (1.01,1.02)	<0.0001
Heart Rate (beats/min)	71.5 (10.9)	71.7 (10.8)	70.4 (11.1)	1.01 (1.01,1.02)	<0.0001
LDL-C (mmol/L)	2.6 (1.0)	2.5 (1.00)	2.7 (1.00)	0.82 (0.78,0.86)	<0.0001
Triglycerides (mmol/L)	1.6 (1.2,2.2)	1.6 (1.2,2.2)	1.6 (1.2,2.2)	1.01 (0.97,1.06)	0.53
ACEi/ARB	8,068 (81.5)	6,593 (82.0)	1,475 (79.1)	1.20 (1.06,1.37)	0.004
Beta blocker	4,512 (45.6)	3,652 (45.4)	860 (46.1)	0.97 (0.88,1.08)	0.59
Statin	6,547 (66.1)	5,395 (67.1)	1,152 (61.8)	1.26 (1.14,1.40)	<0.0001

ACEi/ARB: ACE inhibitors/angiotensin receptor blockers; BP: blood pressure; CI: Confidence interval; DPP4i: Dipeptidyl Peptidase 4 inhibitors; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; OR: Odds Ratio; MACE: Major Adverse Cardiovascular Events; SD: standard deviation.

4.2 Screening for glucose perturbations

4.2.1 Screening for dysglycaemia in patients with coronary artery disease (Study I)

Among the 8,261 patients in EUROASPIRE V, 2,452 (30%; men 71%; women 29%) had previously known diabetes. Of the remaining patients (n=5,809), 537 were not eligible for an OGTT since they were not fasting (n=498) or had a fasting glucose > 11 mmol/L (n=39) leaving 5,272 eligible for an OGTT, which was performed on 4,440 (84%) while 832 (16%) did not undergo an OGTT by unknown reasons (**Figure 10**).

The proportion of patients with unknown glycaemic state who were identified as dysglycaemic based on screening by means of FPG, 2hPG and HbA1c is shown in **Figure 12**. Of the 729 patients with newly diagnosed T2DM, the proportion identified were: by FPG 59%, by 2hPG 52%, by HbA1c 19%, by FPG + 2hPG 91%, and by HbA1c + FPG: 70%. The proportion with T2DM detected by all three tests was 6%. A total of 238 (30%) patients with T2DM based on the OGTT would not have been detected without this test and the corresponding proportion for IGT patients would have been 70%. In total, OGTT-diagnosed patients with dysglycaemia amounted to 41.1% of the screened population.

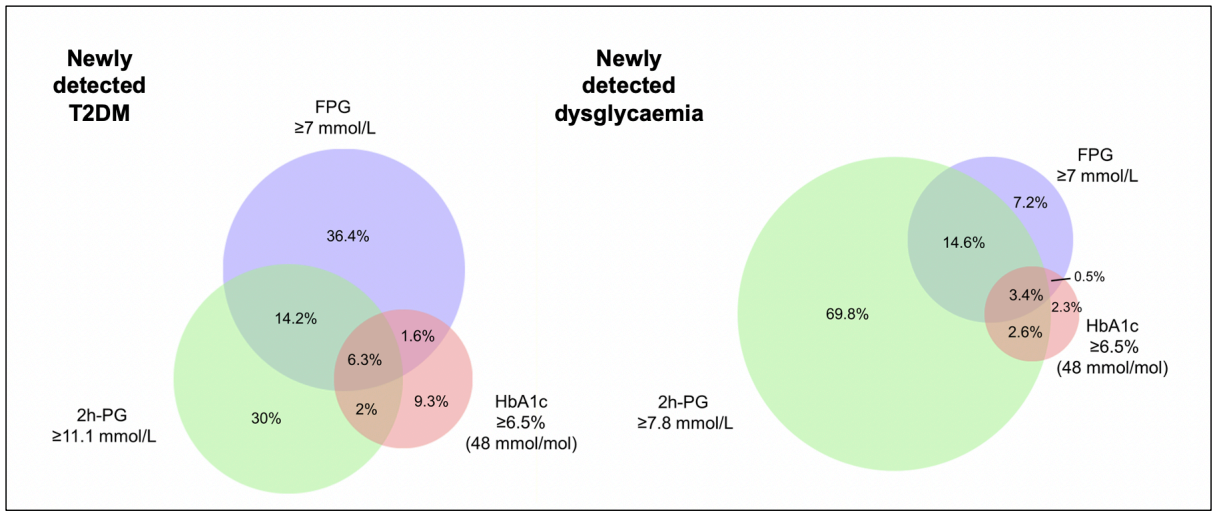


Figure 12. On the left, proportions of patients with newly detected type 2 diabetes who were identified with different screening methods, i.e. with FPG ≥ 7 mmol/L and/or 2hPG ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5% (48 mmol/mol). On the right, proportions of patients with newly detected dysglycaemia who were identified with different screening methods, i.e. with FPG ≥ 7mmol/L and/or 2hPG ≥ 7.8 mmol/L and/or HbA1c ≥ 6.5% (48 mmol/mol).

2hPG: two-hour postload glucose; FPG: fasting plasma glucose; HbA1c: glycated haemoglobin A1c; T2DM: type 2 diabetes mellitus.

The distribution of different glycaemic categories within the present population of patients with established CAD showed that the presence of dysglycaemia almost doubled from the self-reported proportion of 30% to the actual proportion of 59% following guideline recommended screening (**Figure 13**). Indeed, 12% of the subjects were diagnosed with diabetes (men 75%; women 25%) and 19% with IGT (men 71%; women 29%) while 41% were free from dysglycaemia (IFG 9%; normal glucose metabolism 32%; overall proportions of normoglycaemia men 77%; women 23%).

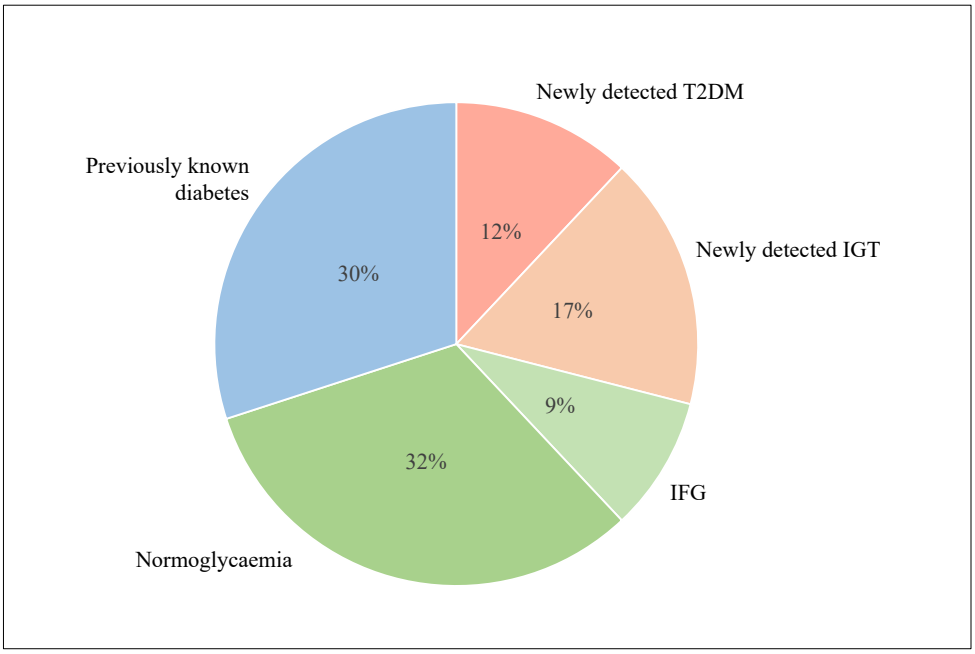


Figure 13. The actual distribution of glucose perturbations in the study population.

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus.

4.2.2 Gender differences in screening for dysglycaemic patients (Study II)

The proportions of women and men with unknown glycaemic state identified as dysglycaemic based on screening by means of FPG, 2hPG and HbA1c are shown in **Figure 14**. The proportion of IGT was significantly higher among women than men (17% vs. 15%; p=0.015) while IFG was less common in women than men (p < 0.0001). Slightly more men had a newly diagnosed T2DM (women 13% vs. men 15%; p=0.020).

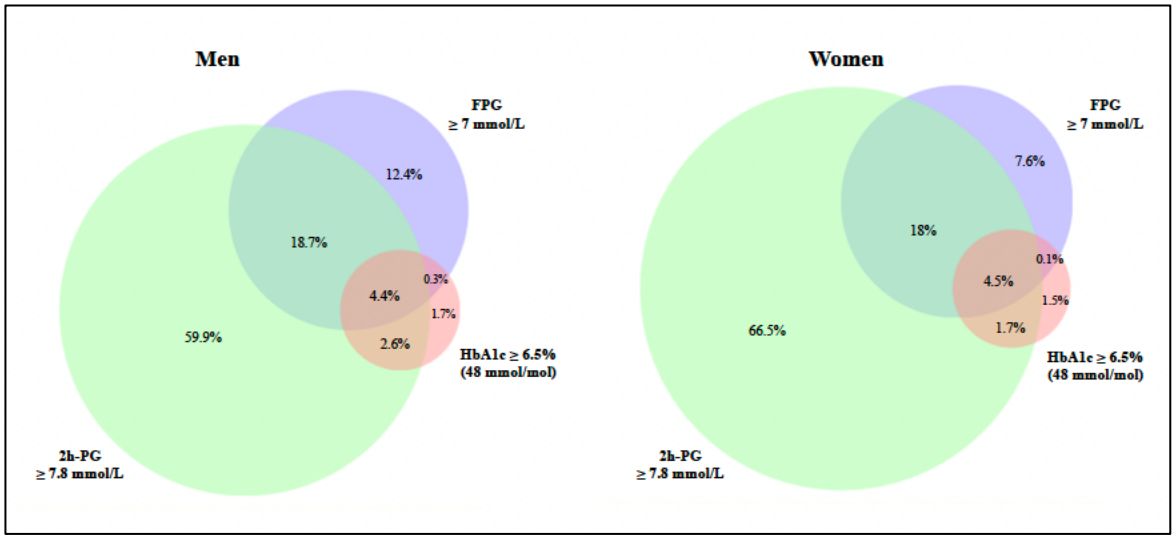


Figure 14. Proportions and their overlap between screening with different methods [FPG ≥ 7 mmol/L, 2hPG mmol/L ≥ 7.8 mmol/L, HbA1c ≥ 6.5% (48 mmol/mol)] and their combinations in men and women with newly detected dysglycaemia.

2hPG: two-hour postload glucose; FPG fasting plasma glucose; HbA1c: glycated haemoglobin A1c.

In the study population with known glycaemic state, a similar proportion of women (22%) and men (24%; p=0.55 after age adjustment) were normoglycaemic. Screening for dysglycaemia based on FPG, 2hPG and HbA1c values, alone or combined, showed that more dysglycaemic women (67%) than men (60%; p < 0.0001) would have remained undetected without the 2hPG value (**Figure 15**). Only 5% of women and 4% of men were identified as dysglycaemic by each of the three tests.

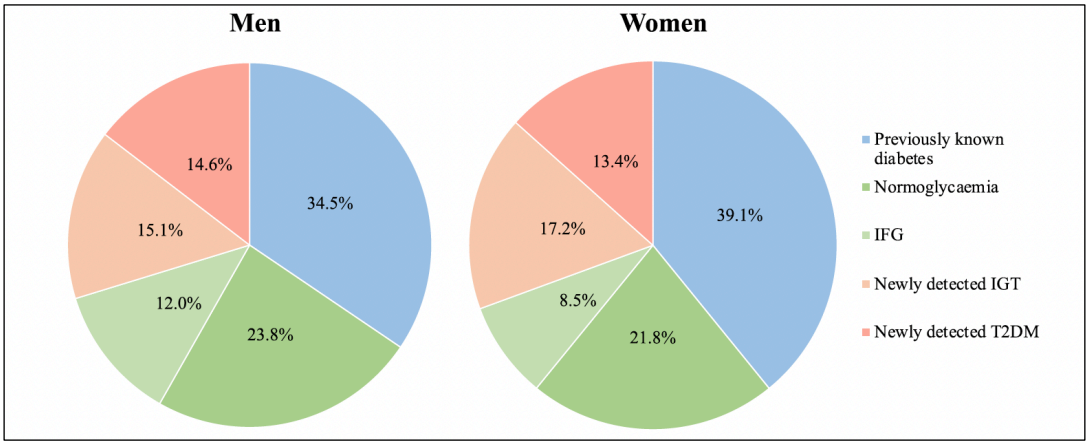


Figure 15. The distribution of glycaemic state divided by gender in the study population.

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus.

4.3 New methods for identifying dysglycaemia in patients with established CAD

4.3.1 Validation of a screening algorithm including 1hPG (Study III)

The receiver operating characteristic (ROC) curve of 1hPG with different thresholds is shown in **Figure 16**. Sensitivity and specificity for 1hPG using the threshold of 12 mmol/L, the one described in a previous report on patients with CAD (195) and validated in this study, gave 76% sensitivity and 84% specificity, with a positive predictive value of 36% and a negative predictive value of 97%. In the present cohort, the optimal balance between sensitivity and specificity according to Youden's J statistic was identified as 11 mmol/L with a sensitivity of 88% and specificity of 74%, while the positive and negative predictive values were 28% and 98%, respectively. The area under the curve (AUC) was 0.89 (95% CI 0.86-0.92).

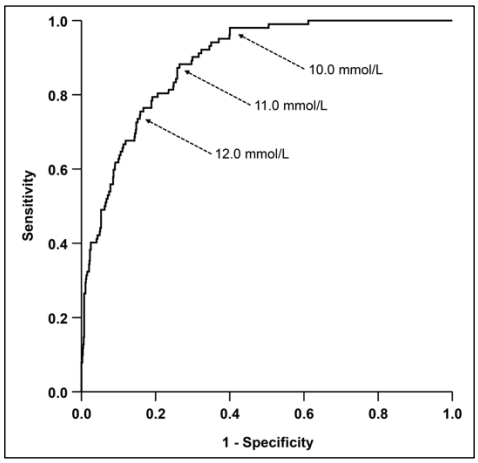


Figure 16. Receiver operating characteristic (ROC) curve testing the diagnostic performance of one-hour plasma glucose values in diagnosing diabetes in our study population. The optimal threshold was obtained by the maximum Youden's J statistic.

A total of 96 patients (10%) fulfilled the diagnostic criteria for T2DM according to a 2hPG ≥ 11.1 mmol/L. Using this definition, in the group of patients with FPG < 6.5 mmol/L and 1hPG < 12, only 5 (1%) were misdiagnosed as not having T2DM (i.e., false negatives). Combining an FPG > 8.0 mmol/L with a 1hPG > 15.0 mmol/L identified 100% of the patients with type 2 diabetes (**Figure 17**).

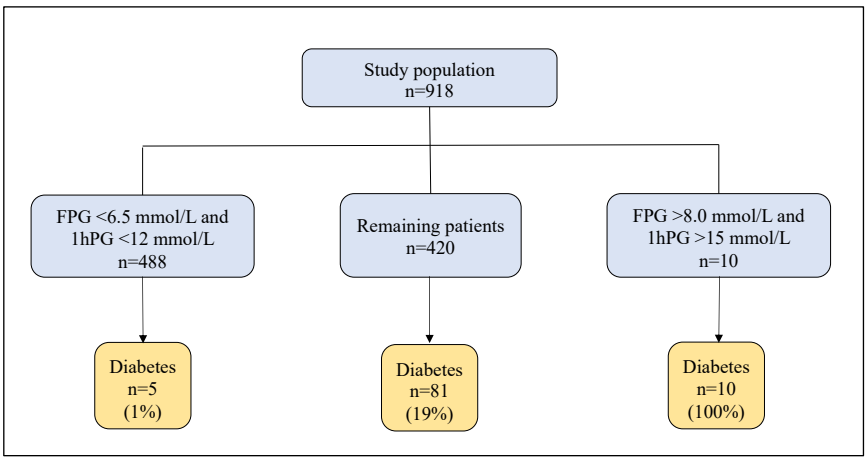


Figure 17. Patients diagnosed with diabetes according to a 2hPG ≥ 11.1 mmol/L (in yellow) in subgroups classified based on FPG and 1hPG.

2hPG: two-hour plasma glucose; FPG: fasting plasma glucose; 1hPG: one-hour plasma glucose.

The proposed screening algorithm for dysglycaemia, based on the previous report (195) and validated in the present study, is presented in **Figure 18**.

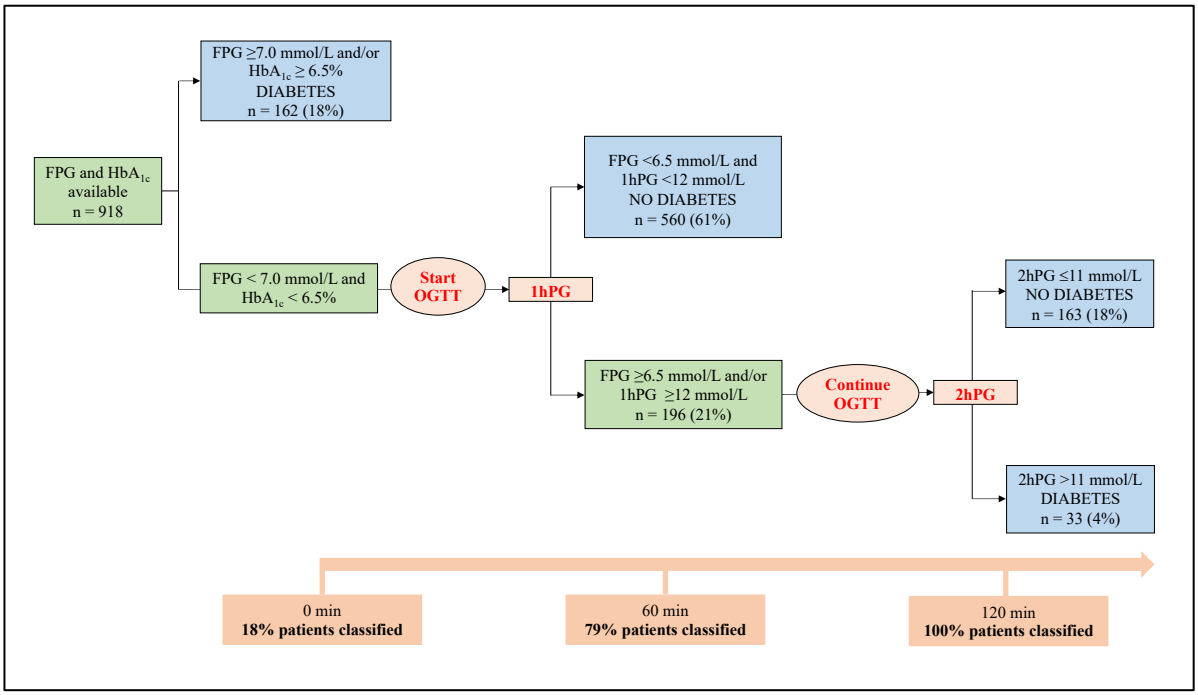


Figure 18. Proposed clinical algorithm with 1hPG for assessing glucometabolic status.

FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; 1hPG = 1-hour plasma glucose; 2hPG = 2-hour plasma glucose.

According to this algorithm 18% of the patients (n=162) were identified as having T2DM already by FPG or HbA1c, leaving 82% (n = 756) to be investigated with an OGTT. The combination of an FPG below 6.5 mmol/L and a 1hPG value < 12 mmol/L excludes type 2 diabetes in 74% of patients undergoing OGTT (n = 560). The remaining 21% (n = 196) needed a 2hPG to be correctly classified. This means that, among the present 723 patients without T2DM, only one out of five patients are in demand of a full two-hour long OGTT for correct classification.

4.3.2. Screening for dysglycaemia by means of measures of insulin resistance (Study V)

The optimal thresholds identified by the ROC analyses for different glycaemic parameters are shown in **Table 9**, for both T2DM (2hPG value ≥ 11 mmol/L) and dysglycaemia (IGT or T2DM, 2hPG value ≥ 7.8 mmol/L). **Table 9** also reports the diagnostic performances of HOMA-IR, HOMA2-ins, HOMA2-Cpep, fasting serum insulin, and fasting serum C-peptide for patients with newly detected T2DM according to a 2hPG value ≥ 11.1 mmol/L and with newly detected dysglycaemia (IGT and T2DM), identified by a 2hPG value ≥ 7.8 mmol/L.

Table 9 depicts the diagnostic performance of some measures of insulin resistance and insulin secretion. As can be seen, the optimal thresholds corresponded to slightly elevated insulin resistance (HOMA-IR) and slightly elevated C-peptide levels, with no major differences between T2DM and dysglycaemia. The diagnostic performance was generally quite low, with for example sensitivity around 68% and specificity around 57% for HOMA-IR in patients with newly diagnosed T2DM. HOMA indexes were slightly, however, not significantly worse than FPG or HbA1c (data not shown) for detecting dysglycaemia. There were no differences in the diagnostic performance of HOMA indexes neither between men and women nor in participants above and below the age of 65 years.

Table 9. Diagnostic performance for T2DM (according to 2hPG value ≥ 11.1 mmol/L) and dysglycaemia (according to 2hPG value ≥ 7.8 mmol/L) of the optimal thresholds of different glycaemic parameters obtained by Youden's J statistic on receiver operator characteristics curves.

	Threshold	Sensitivity (%)	Specificity (%)	AUC
Patients with newly detected type 2 diabetes (N=581)				
HOMA-IR	2.73	68.0	57.2	0.66
HOMA2-ins	1.32	65.0	51.8	0.61
HOMA2-Cpep	1.69	65.6	59.3	0.64
Fasting serum insulin (μU/mL)	7.9	79.2	35.2	0.59
Fasting serum C-peptide (nmol/L)	0.74	61.7	60.4	0.62
Patients with newly detected dysglycaemia (N=1,439)				
HOMA-IR	2.81	54.9	64.1	0.62
HOMA2-ins	1.32	58.2	55.3	0.59
HOMA2-Cpep	1.44	67.6	49.7	0.61
Fasting serum insulin (μU/mL)	7.9	50.3	61.7	0.57
Fasting serum C-peptide (nmol/L)	0.63	65.6	49.8	0.59

HOMA: homeostasis model assessment; HOMA2-ins: homeostasis model assessment 2 based on insulin; HOMA2-Cpep: homeostasis model assessment based on C-peptide; 2hPG: two-hour postload glucose; AUC: area under the curve.

The associations between 2hPG and the other parameters in the total sample were weak (Spearman correlation coefficients: 0.15 for fasting insulin, 0.19 for C-peptide, 0.24 for HOMA-IR, 0.18 for HOMA2-ins and 0.22 for HOMA2-Cpep).

HOMA-IR, HOMA2-ins and C-peptide were strongly correlated with BMI (Spearman correlation coefficient: 0.47 for all three parameters) and waist circumference (Spearman correlation coefficient: 0.43, 0.44 and 0.44 respectively). In contrast FPG, 2hPG and HbA1c did not have any strong correlation with either BMI (Spearman correlation coefficients: 0.14, 0.15 and 0.21 respectively) or waist circumference (Spearman correlation coefficients: 0.16, 0.15 and 0.19 respectively).

4.4 Treatment target attainment

4.4.1 Treatment target attainment in patients with coronary artery disease (Study I)

Anthropometrics and lifestyle

Overweight or obesity was most common in patients with known diabetes (89%) while smoking was less prevalent among them patients (16%) compared to those who were normoglycaemic (21%). Approximately two thirds of the patients did not practice physical activity for at least 150 minutes/week of moderate intensity activity, a proportion that was higher among patients with known diabetes (72%).

Risk factor management

Forty-nine percent of the normoglycaemic patients, 53% of those with newly diagnosed dysglycaemia and 58% of the patients with previously known diabetes were taking a combination of all four cardioprotective drug classes at the time of the interview ($p < 0.0001$ after adjustment for age and gender). The proportion of patients with no dysglycaemia, newly diagnosed dysglycaemia and known diabetes prescribed each different cardioprotective drug is shown in **Figure 19**.

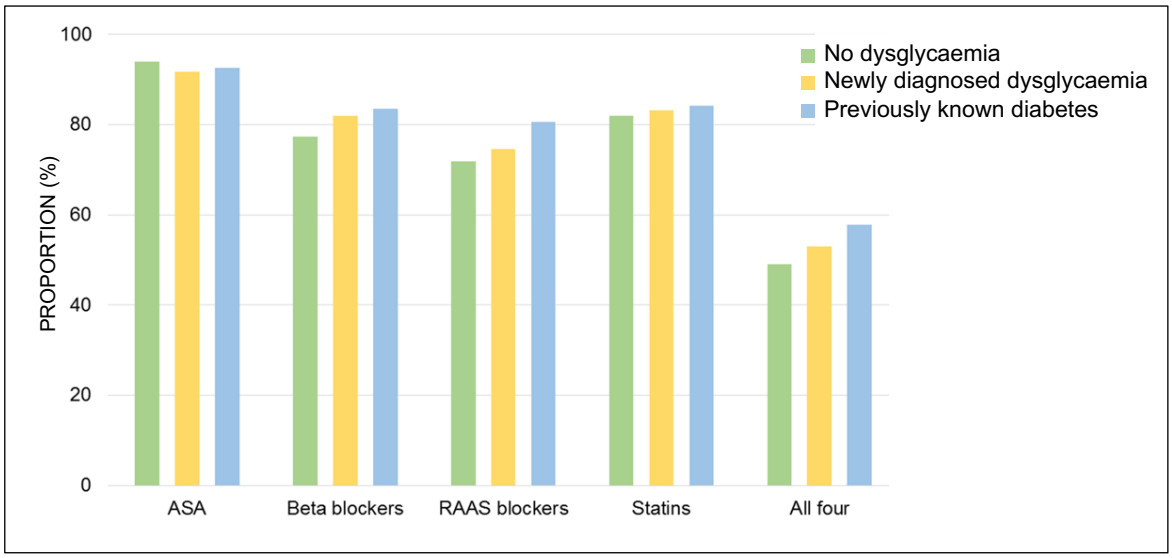


Figure 19. Proportion of patients with no dysglycaemia, newly diagnosed dysglycaemia and previously known diabetes prescribed the different cardioprotective drug class and their combination.

ASA: acetylsalicylic acid; RAAS: renin-angiotensin-aldosterone system.

The proportions of patients in the three glucose categories reaching different blood pressure, (< 130/80, < 140/90, < 150/100 mmHg) and LDL-C (< 1.8, < 2.5, < 3.0, ≥ 3.0 mmol/L) targets are presented in **Figures 20 A** and **B**. **Figure 20 C** presents the glycaemic levels reached in patients with known diabetes (< 6, < 7, < 8, < 9, ≥ 9% corresponding to < 42, < 53, < 64, < 75 and ≥ 75 mmol/mol).

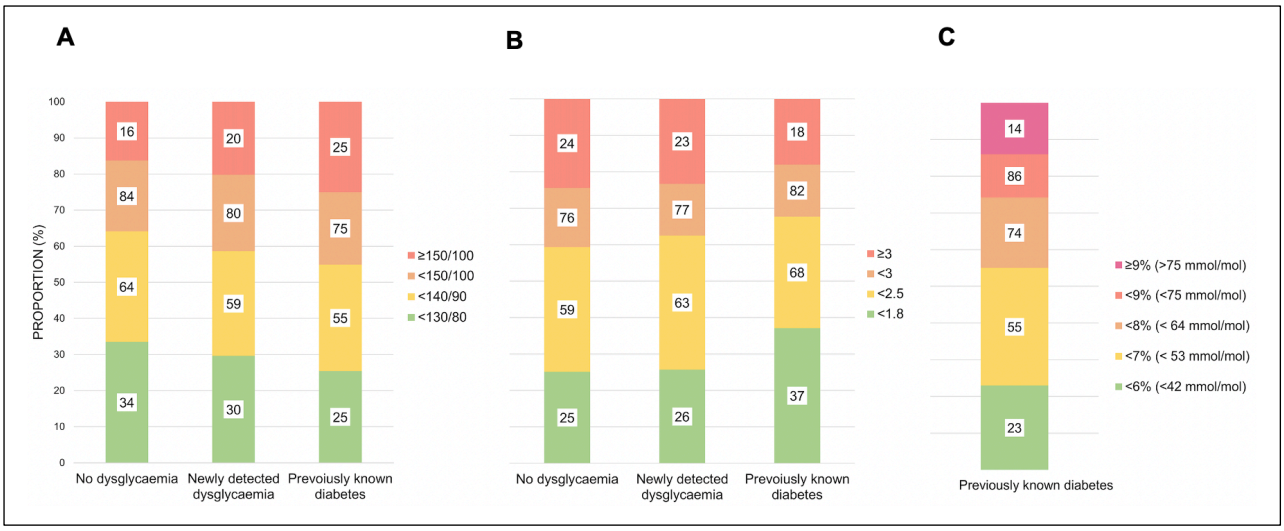


Figure 20. Proportion of patients reaching different **A**: blood pressure and **B**: LDL-C targets in the total cohort, and **C**: HbA1c targets in patients with known diabetes

Fifty seven percent of the patients with established diabetes had been provided with lifestyle and dietary advice. Seventy-five percent of them were on glucose-lowering therapy, whereof metformin was the most common (60%), followed by insulin (30%), sulphonylureas (19%) and incretins (11%: DPP-4 inhibitors 10% and GLP-1 RA 1%) and SGLT2i, glitazones, glinides and alpha-glucose oxidase inhibitors 1% each.

Level of care
In the EUROASPIRE V cohort, 78% reported to be under the care of a cardiologist, 57% of a general practitioner, 11% of a diabetologist/endocrinologist and 4% of a specialist cardiac nurse. Self-monitoring of plasma glucose was practiced by 73% of patients with previously known diabetes (insulin users 89% vs. others 67%). A total of 31% patients with known diabetes had been advised to attend a diabetes school or another diabetes educational program, but only 24% had taken active part in such education.

Diabetes-related complications
The prevalence of different diabetes-related complications among patients with previously known diabetes was retinopathy 19%, renal involvement 10% and neuropathy 19%.

4.4.2 Gender differences in treatment target attainment and outcomes of dysglycaemic patients (Study II)

Lifestyle and quality of life
Less women than men had been advised on and increased their physical activity (**Table 10**). Significantly less women than men attended a cardiac prevention and rehabilitation programme in both glycaemic categories, but there was no gender difference in the attendance at a Diabetes Educational Programme in patients with previously known T2DM. The scores expressing quality of life, i.e., EuroQoL 5D and HeartQoL, were significantly lower in women than men. Women in both glycaemic categories, previously known diabetes and newly detected respectively, were prescribed significantly more antidepressant/antianxiety drugs than men.

Pharmacological treatment
The proportion of patients taking each of four cardioprotective drug classes and their combination did not differ according to gender in the two glycaemic categories, except for RAAS blockers, that were prescribed less frequently to women than men with newly detected dysglycaemia (73% vs. 76%; p=0.046), and lipid-lowering therapy, which was taken less often to women than men with previously known T2DM (84% vs. 88%; p=0.00046) (**Table 10**). The combination of all four cardioprotective drugs was taken by less than 60% of patients, without any difference between genders. Compared with men, women with known T2DM were more frequently prescribed insulin (33% vs. 25%; p<0.0001) while less women than men used metformin (53% vs. 59%; p<0.0001).

Table 10. Gender differences in pharmacological treatment and lifestyle advice. Entries are % (n/total number) or mean (standard deviation).

	Previously known diabetes			Newly detected dysglycaemia		
	Women N=1,342	**Men N=3,454**	**p-value** [a]	**Women N=1,049**	**Men N=2,980**	**p-value** [*]
Pharmacological treatment						
RAAS blockers	80.5 (1,070/1,329)	79.7 (2,723/3,418)	0.55	72.8 (759/1,042)	76.0 (2,251/2,963)	0.046
Beta blockers	85.7 (1,138/1,328)	83.7 (2,860/3,419)	0.084	83.3 (869/1,043)	82.5 (2,444/2,964)	0.54
Antiaggregants	93.7 (1,242/1,325)	93.1 (3,184/3,419)	0.48	91.3 (952/1,043)	92.6 (2,747/2,965)	0.16
Lipid-lowering	83.7 (1,112/1,329)	87.6 (2,991/3,414)	0.00046	83.2 (866/1,041)	85.7 (2,540/2,963)	0.06
Statins	82.5 (1,097/1,329)	86.5 (2,952/3,414)	0.00071	82.1 (855/1,041)	85.0 (2,519/2,963)	0.030
Ezetimibe	3.1 (41/1,329)	3.1 (105/3,419)	1.00	2.2 (23/1,043)	2.5 (75/2,966)	0.64
All four drug classes	58.6 (775/1,323)	58.9 (2009/3,413)	0.87	52.0 (541/1,040)	55.0 (1,628/2,960)	0.10
Diuretics	48.2 (640/1,329)	41.5 (1420/3,418)	<0.0001	37.2 (388/1,042)	29.3 (869/2,964)	<0.0001
Glucose-lowering drugs	92.7 (1244/1,342)	91.6 (3162/3,451)	0.24	n.a.	n.a.	n.a.
Antidepressant/antianxiety drugs	9.6 (128/1,330)	7.1 (224/3,418)	0.004	9.8 (102/1,042)	5.2 (155/2,963)	<0.0001
Advice on lifestyle changes						
Stop smoking	83.7 (169/202)	86.2 (833/966)	0.38	84.9 (191/225)	84.5 (792/937)	1.00
Healthy diet	91.2 (1105/1,212)	89.4 (2,849/3,186)	0.093	83.6 (806/964)	85.8 (2347/2734)	0.10
Weight loss	72.8 (929/1,276)	74.0 (2,463/3,327)	0.41	63.9 (647/1012)	67.4 (1953/2898)	0.049
Increase physical activity	59.7 (762/277)	65.6 (2,176/3,315)	0.00018	58.8 (597/1016)	63.3 (1821/2879)	0.012
Actions taken to change lifestyle						
Stop smoking	79.7 (165/207)	76.0 (728/958)	0.28	85.8 (193/225)	82.0 (769/938)	0.20
Healthy diet	89.9 (1,064/1,183)	89.1 (2,809/3,152)	0.47	90.1 (858/952)	89.0 (2,385/2,679)	0.36
Weight loss	58.8 (741/1,260)	61.3 (2,021/3,299)	0.14	58.0 (583/1006)	60.1 (1,720/2,861)	0.23
Increase physical activity	25.0 (301/1,203)	33.5 (1,065/3,183)	<0.0001	32.3 (307/951)	40.2 (1,100/2,738)	<0.0001
Attended a CPRP	27.0 (355/1,315)	33.7 (1,147/3,404)	<0.0001	32.1 (332/1035)	35.7 (1,052/2,943)	0.034
Attended a DEP	25.8 (314/1,217)	26.0 (809/3,116)	0.94	n.a.	n.a.	n.a.
Quality of Life Assessment						
EQ-5D VAS score	56.1 (26.3)	60.6 (27.5)	<0.0001	59.2 (27.1)	63.4 (27.7)	<0.0001
HeartQoL Global score	1.8 (0.7)	2.1 (0.7)	<0.0001	2.00 (0.7)	2.3 (0.62)	<0.0001
HeartQoL Physical score	1.8 (0.7)	2.17 (0.7)	<0.0001	2.00 (0.7)	2.31 (0.6)	<0.0001
HeartQoL Emotional score	1.7 (0.8)	2.08 (0.7)	<0.0001	1.9 (0.8)	2.18 (0.7)	<0.0001

[*] significance level for testing differences between men and women in each diagnostic group

CPRP: Cardiac Prevention and Rehabilitation Programme; DBP: diastolic blood pressure; DEP: diabetes educational programme; EQ-5D: EuroQol 5D Questionnaire; Heart QoL: Heart Quality of Life; RAAS: renin-angiotensin-aldosterone system; VAS: visual analogue scale.

Target attainment

The proportion of men and women reaching different blood pressure and LDL-C targets is shown in **Figure 21**. Among patients with previously known T2DM more women than men had a blood pressure ≥ 150/100 mmHg (28% vs. 24%; p < 0.0034) and an LDL-C ≥ 3.0 mmol/L (24% vs. 16%; p < 0.0001). Moreover, they achieved an LDL-C level < 1.8 mmol/L in a significantly lower proportion (26%; vs. men 36%; p < 0.0001). A similar pattern was observed in patients with newly diagnosed dysglycaemia with women having a higher proportion of LDL-C ≥ 3.0 mmol/L and a lower proportion of LDL-C < 1.8 mmol/L.

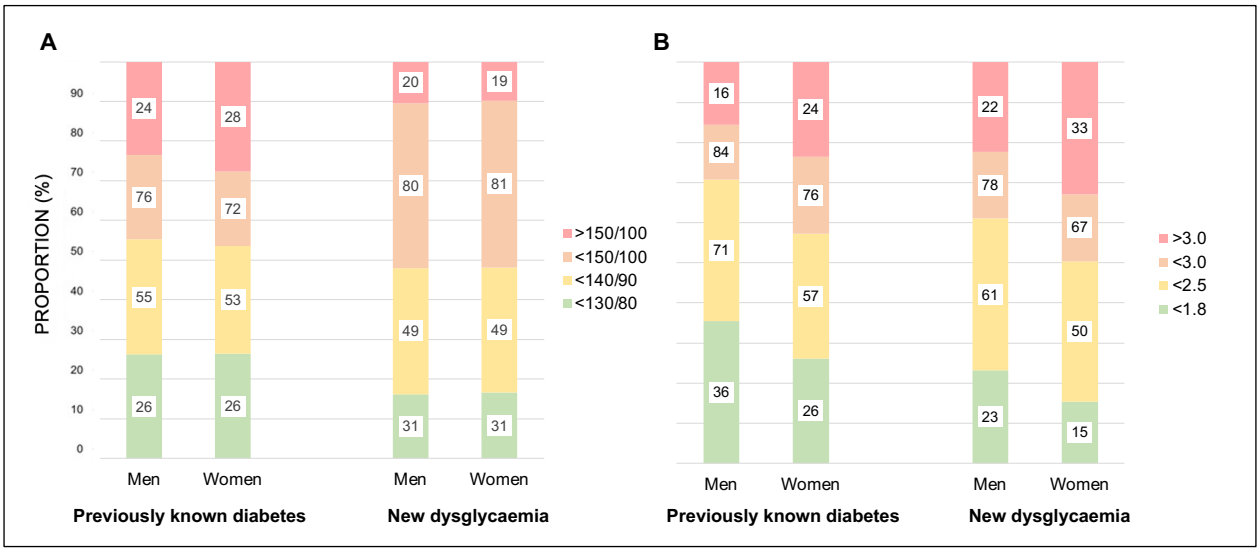


Figure 21. Proportion of patients with previously known diabetes and newly detected dysglycaemia reaching different blood pressure (A) and LDL-C (B) targets in the total cohort.

LDL-C: low-density lipoprotein cholesterol.

Diabetes-related microvascular complications

Microvascular complications were significantly more common in women than men with previously known T2DM: retinopathy (25% vs. 16%; p < 0.0001), renal involvement (5% vs. 3%; p=0.03) and neuropathy (24% vs. 15%; p < 0.0001).

Outcomes

The median follow-up time was 1.7 years during which 23,703 person-years were observed. The number of primary events (the first of cardiovascular death or hospitalisation for non-fatal myocardial infarction, stroke, heart failure or revascularization) were 105 in women and 340 in men with newly detected dysglycaemia. The corresponding numbers in patients with known T2DM were 233 and 500, respectively. A detailed description of the events is given in **Table 11**.

The age-adjusted incidence of the primary endpoint was significantly higher in women than in men with known T2DM (125 vs. 101/1,000 person-years) with a HR (95% CI; p-value) of women vs. men of 1.22 (1.04 – 1.43; p=0.015). There was no significant gender difference in the age-adjusted incidence of the endpoint in patients with newly detected dysglycaemia (women vs. men: incidence 65.9 vs. 75.4/1,000 person-years), with a HR of 0.86 (95% CI 0.69 – 1.08; p=0.19).

Table 11. Number of primary events in participants with newly detected dysglycaemia and with previously known diabetes by gender in EUROASPIRE IV and V.

Type of event	Previously known diabetes		Newly detected dysglycaemia	
	Men N=3,188	Women N=1,222	Men N=2,812	Women N=980
Primary composite	500	233	340	105
Fatal CVD	50	20	30	7
PCI	212	81	169	44
CABG	34	15	14	4
Acute MI	85	40	59	14
Stroke	70	31	45	11
Heart failure	150	90	86	37

CABG: coronary artery bypass grafting; CVD: cardiovascular disease; MI: myocardial infarction; PCI: percutaneous coronary intervention.

4.5 Cardioprotection with a GLP1-RA by baseline metformin (Study V)

During a median follow-up of 5.4 years (interquartile range 5.1–5.9), the primary outcome occurred in 976 (12%) participants with baseline metformin and 281 (15%) without metformin. As depicted in **Table 12**, dulaglutide reduced the risk of the primary endpoint (MACE) with an HR of 0.88 (95% CI 0.79 – 0.99) in the entire REWIND cohort. The impact was similar in participants with and without baseline metformin (p-value for interaction = 0.26). Likewise, the effect on microvascular endpoints was similar irrespective of baseline metformin (p-value for interaction = 0.12), as well as for all-cause death (interaction p = 0.81) and heart failure (interaction p = 0.85).
Additional analyses confirmed the absence of any interaction between baseline metformin use and the effect of dulaglutide on the individual MACE components and between sub-groups defined by type of glucose lowering therapy and dulaglutide (p-value for interaction = 0.53). Moreover, post-randomization use of metformin did not influence the effect of dulaglutide on the study outcomes.

Individuals who were taking metformin at baseline differed from those not on metformin in several ways (**Table 8**): they were younger, less likely to be women and have a previous cardiovascular event, with better renal function. The effect of dulaglutide in the presence and absence of metformin was therefore assessed after accounting for the independent determinants of metformin use as listed above. The absence of any significant interaction (all interaction p-values > 0.1) provides no support for any differential effect of dulaglutide according to baseline metformin use (**Figure 22**). There was no significant difference in the effect of dulaglutide on the primary outcome in patients with or without metformin at baseline: adjusted HR 0.92 (95% CI 0.81–1.05) vs. 0.78 (95% CI 0.61–0.99) respectively; p-value for interaction was 0.18.

The risk for the microvascular endpoint, all-cause death and heart failure was similar in patients treated with dulaglutide irrespective of use of baseline metformin both before and after adjusting for the independent determinants of metformin use (all p for interaction > 0.1).

Table 12. Number, proportions and annual incidence of events for each outcome in the total cohort and in the dulaglutide and placebo groups respectively, in patients with and without metformin at baseline.

	Dulaglutide			Placebo			HR (95% CI)	p-value*
	Total N	N (%)	%/year	Total N	N (%)	%/year		
MACE	4,949	594 (12.0)	2.35	4952	663 (13.4)	2.66	0.88 (0.79-0.99)	0.26
Metformin	4,022	470 (11.7)	2.28	4015	506 (12.6)	2.49	0.91 (0.81-1.04)	
No Metformin	927	124 (13.4)	2.67	937	157 (16.8)	3.40	0.78 (0.62-0.99)	
Microvascular	4,949	910 (18.4)	3.76	4952	1,019 (20.6)	4.31	0.87 (0.80-0.95)	0.12
Metformin	4,022	734 (18.3)	3.72	4015	847 (21.1)	4.40	0.84 (0.76-0.93)	
No Metformin	927	176 (19.0)	3.97	937	172 (18.4)	3.90	1.01 (0.82-1.25)	
All-Cause mortality	4,949	536 (10.8)	2.06	4952	592 (12.0)	2.29	0.90 (0.80-1.01)	0.81
Metformin	4,022	413 (10.3)	1.95	4,015	452 (11.3)	2.15	0.90 (0.79-1.03)	
No Metformin	927	123 (13.3)	2.57	937	140 (14.9)	2.93	0.87 (0.69-1.11)	
Heart Failure	4,949	213 (4.3)	0.83	4952	226 (4.6)	0.89	0.93 (0.77-1.12)	0.85
Metformin	4,022	162 (4.0)	0.77	4015	170 (4.2)	0.82	0.94 (0.76-1.17)	
No Metformin	927	51 (5.5)	1.08	937	56 (6.0)	1.20	0.90 (0.62-1.32)	

*Unadjusted p-value for interaction from Cox proportional hazards regression models.

CI: Confidence interval; HR: Hazard Ratio; MACE: Major Adverse Cardiovascular Events.

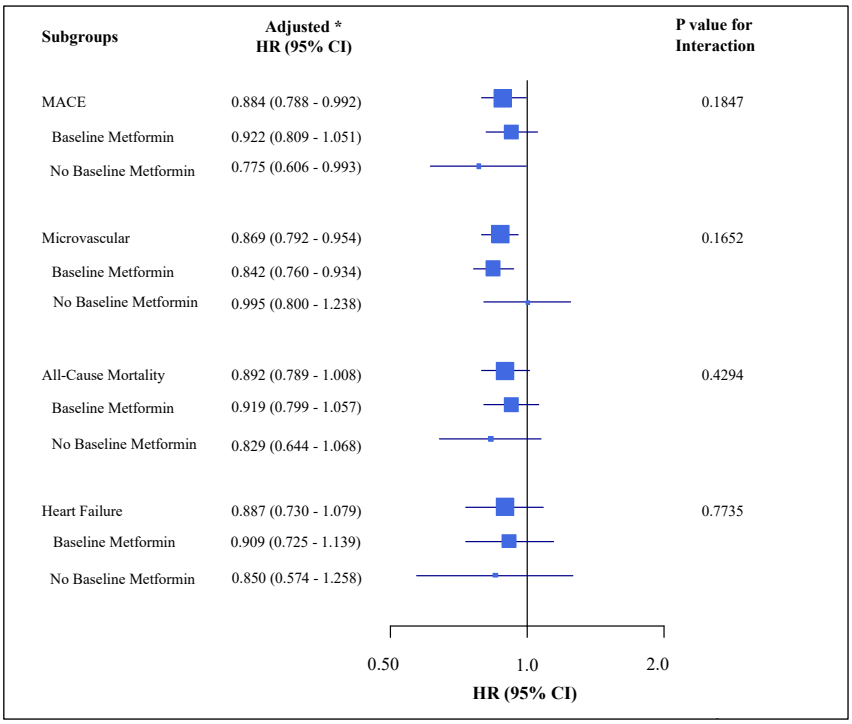


Figure 22. Cardiovascular outcomes, microvascular outcome, all-cause death and heart failure in participants by the use of metformin at baseline, following adjustment for the independent determinants of metformin use. The size of each box is proportional to the number of events.

*Adjusted for: age, previous cardiovascular events and heart failure, diabetes duration, eGFR < 60 ml/min/1.73m^2, insulin use, thiazolidinedione use, body mass index, diastolic blood pressure, heart rate, low-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, use of statins.

HR: Hazard Ratio; MACE: Major Adverse Cardiovascular Events.

Kaplan-Meier curves for the primary outcome in people with and without baseline metformin are shown in **Figure 23A** and **B** respectively.

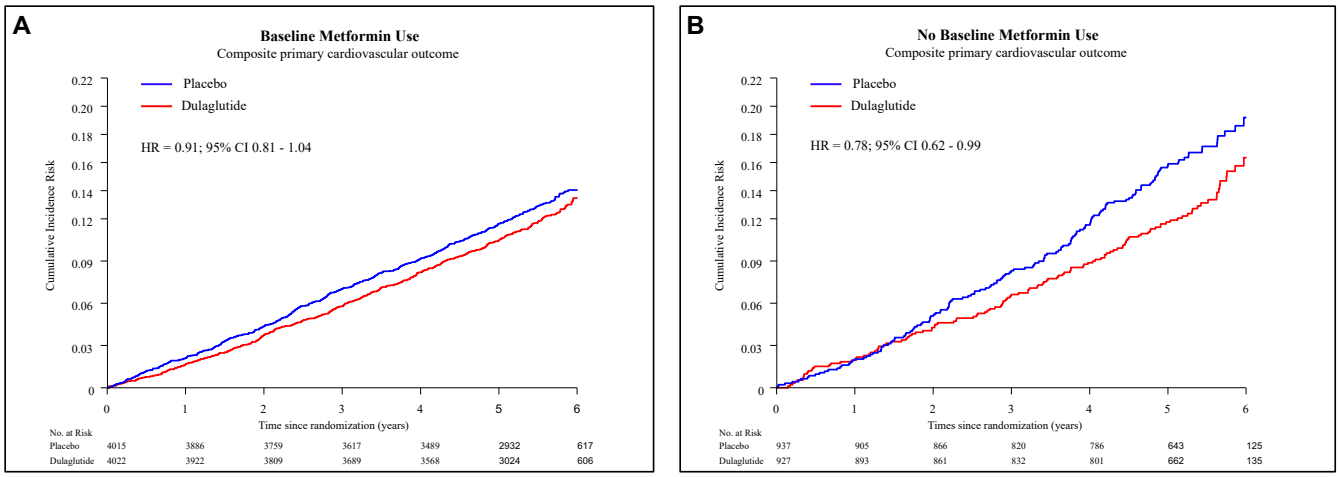


Figure 23. Kaplan-Meier curves showing the cumulative incidence of the primary outcome in participants with baseline metformin (panel A) and without baseline metformin use (panel B).

HR: Hazard Ratio.

5. Discussion

5.1 Screening for dysglycaemia in patients with established CAD

Guidelines advocating screening for glucose perturbations in patients with CVD have been released by the ESC and partner societies since 2007 (56, 191, 196, 197). Considering this, the finding in **Study I** that screening for dysglycaemia is still poorly performed in such patients must be considered a great disappointment. When accurately tested, approximately 40% of all patients without known diabetes were dysglycaemic, i.e. proportions similar to those originally identified by the GAMI study (117) and confirmed in the Euro and China Heart Surveys (118, 119). In a recent meta-analysis by Laichuthai et al, the pooled prevalence of newly discovered abnormal glucose tolerance (including IFG, IGT and HbA1c-based diagnosis) was 48% (95% CI 40.2 – 56.6) in subjects after an acute myocardial infarction (198).

The EUROASPIRE surveys, conducted to determine guideline adherence in clinical practice, offer a possibility to follow the development of screening for dysglycaemia in patients with CVD over time. The time trends are unfortunately discouraging. In EUROASPIRE IV, performed 2012 – 2013, the proportion of patients with diabetes who were detected by screening was 29% (199). EUROASPIRE V, conducted 2016 – 2017, was no exception as regards screening for dysglycaemia, highlighting the persisting need for improvement (200).

The second pivotal finding of **Study I** is that 30% of patients with newly diagnosed T2DM and 40% with newly diagnosed IGT would have remained undetected without an OGTT, summing up to a proportion for undetected dysglycaemia of about 70%. The identification of IGT should not be overlooked considering its dismal prognostic implication as regards progress to diabetes and incident cardiovascular events and the existing possibility of targeted interventions. The latest International Diabetes Federation Atlas, issued in 2021, refers to IGT as a standalone entity, acknowledging the evidence on preventive measures (30). In the Da Qing Study, the effects of dietary modification, exercise, or both was compared with no intervention in high-risk Chinese adults with IGT (201), resulting in reduced incidence of diabetes, retinopathy and significant reductions in cardiovascular (41%) and all-cause (29%) death at the extended follow-up after 23 years (91). The Finnish Diabetes Prevention Study, the Diabetes Prevention Program, two Indian Diabetes Prevention Programme studies and two Japanese studies all reported on a reduced risk of incident diabetes in adults with IGT who underwent lifestyle modifications (89, 202-206). As regards pharmacological interventions, several trials have established that thiazolidinediones prevent diabetes onset in people with IGT through improvement of insulin sensitivity (46). A meta-analysis of randomized trials of metformin in individuals with pre-diabetes (defined as "high-risk HbA1c", IFG and/or IGT) showed that metformin decreased the onset of diabetes compared with standard diet and exercise (207). Currently, the ADA recommends metformin therapy for prevention of T2DM in adults with prediabetes, "especially those aged 25–59 years with BMI ≥ 35 kg/m^2, higher FPG (e.g., ≥110 mg/dL), and higher HbA1c (e.g. ≥ 6.0%), and in women with prior gestational diabetes mellitus" (34).

To date, there are no trials that specifically assessed the effect of lifestyle vs. pharmacological interventions on cardiovascular outcomes in IGT patients with or without CVD, as underlined by Madsen et al other studies (207). However, the fact that IGT is an independent, prognostically unfavorable condition is supported by multiple investigations. The long-term follow-up of the GAMI study showed that the cardiovascular prognosis in post-myocardial infarction patients with newly detected IGT is as unfavourable as among those with newly detected T2DM (133). Abnormal 2hPG (either in the IGT or in the T2DM range) was a predictor of incident cardiovascular events in a Japanese cohort of 275 patients with previous

acute MI, either with established or previously unknown dysglycaemia (134). Similar findings have been reported in the Silent Diabetes Study, comparing HbA1c with OGTT results in 1,015 patients without previously diagnosed diabetes who underwent coronary angiography: 2hPG values related to CAD extent and subsequent mortality (137). Chattopadhyay et al. showed that a 2hPG value was an independent predictor of mortality and recurrent non-fatal myocardial infarction in patients with acute CAD without previously known diabetes even after adjusting for variables constituting the Global Registry of Acute Coronary Events (GRACE) score (135). In a cohort of 768 post-myocardial infarction patients from Yorkshire without known glucose abnormalities, both newly diagnosed IGT and T2DM independently predicted the incidence of cardiovascular death, non-fatal myocardial infarction, severe heart failure and non-haemorrhagic stroke (136). A 2hPG ≥ 7.8 mmol/L was an independent predictor of all-cause mortality, nonfatal myocardial and or nonfatal stroke in 758 Chinese patients with established CAD admitted for elective angiography due to angina whereas HbA1c carried no predictive value (138). In EUROASPIRE IV, 2hPG was superior to FPG and HbA1c in providing prognostic information (139). These studies were included in a recent meta-analysis which demonstrated an association between prediabetes and all-cause mortality as well as recurrent MACE, cardiovascular death and hospitalization for heart failure in patients who had suffered an acute myocardial infarction (198). This association was present whether prediabetes was defined by 2hPG or based on HbA1c or FPG. A direct comparison of the prognostic ability of the three methods was, however, not performed since patient-level data were not available. Moreover, the results from EUROASPIRE IV, analysing almost 4,000 patients, were not included by unknown reasons (139). The authors recommend using HbA1c during the hospitalization, as it is not influenced by acute conditions, but underline that an OGTT should follow because of its prognostic implication (198).

In **Study I**, a 2hPG identified more patients with dysglycaemia than FPG and/or HbA1c in patients with established CAD, supporting the use of OGTT as the ideal screening method, in particular since successful interventions are available for those identified as dysglycaemic.

Whether screening with an OGTT is superior to screening with HbA1c in terms of prognostic capability in patients with CAD is a subject of controversy (123, 124). The low concordance between these screening methods, in **Study I** as well as in other reports, suggests that they mirror different pathophysiological processes of dysglycaemia (208, 209).
HbA1c testing has some advantages compared to an OGTT: it does not require fasting or timed samples, and it is not affected by recent changes in diet or physical activity (125, 210). A concern is that common conditions such as anaemia, erythropoietin therapy, hemodialysis, haemoglobinopathies, uremia, pregnancy, recent blood loss or transfusion, glucose-6-phosphate dehydrogenase deficiency, and human immunodeficiency virus infection might influence HbA1c measurement (40). Moreover, the chronic use of aspirin causes haemoglobin acetylation, possibly interfering with liquid chromatography and electrophoresis assays (211, 212). Even if this effect is deemed minimal, it may be of importance in people with CAD, being prescribed aspirin for secondary prevention.

The prognostic value of HbA1c has been studied in unselected populations across the cardiovascular risk spectrum. An increasing HbA1c was continuously and significantly associated with CVD and all-cause mortality irrespective of the presence of known diabetes and previous CVD in the Norfolk population study (126). In the Atherosclerosis Risk in Communities (ARIC) study, HbA1c was a stronger predictor of incident diabetes than FPG, and more strongly associated with the risk of CVD and all-cause death (127). Even other studies reported on an association between HbA1c and cardiovascular outcomes in people without known diabetes (128, 129). Data from the UK Biobank, including 357,833 participants without baseline CVD or known diabetes, confirmed the association between increasing HbA1c and

cardiovascular outcomes. HbA1c did, however, not improve CVD risk prediction in any meaningful way when added to traditional risk factors (213).
A few studies have investigated whether HbA1c might be of prognostic value in coronary patients without known diabetes, but most of them do not report a direct comparison with OGTT-based screening. HbA1c improved risk stratification for future cardiovascular events in a Chinese study enrolling 549 patients with acute coronary syndromes undergoing percutaneous revascularization (130). Moreover, HbA1c was associated with mortality in an observational study including 4,176 patients without known diabetes admitted with ST-segment-elevation myocardial infarction (131).

In a Swedish study including 841 patients with a recent acute myocardial infarction and no known history of diabetes, HbA1c in the prediabetes range (≥ 5.7% – 39 mmol/mol) was superior to all other screening tools, including a 2hPG, in predicting the composite of a first of myocardial infarction, heart failure, ischaemic stroke or mortality (132). These results are in conflict with the aforementioned reports by Shahim et al and Chen et al (138, 139). The validity of the study by Karayiannides et al (132) is, however, limited by the fact that patients with newly detected T2DM by the OGTT were immediately instructed on lifestyle modifications and were referred for further management. The implication is that these patients, compared with those with prediabetes according to the HbA1c criterion, were more likely to be promptly subjected to an efficient secondary prevention and weakening the association with outcomes (132). These discrepant findings highlight that further studies are needed to specifically assess the relative prognostic power of these different screening tools (209). If HbA1c had been the sole screening tool in **Study I**, only 19% of patients with unknown T2DM and 9% with unknown dysglycaemia would have been detected. These proportion must be considered unsatisfactory for the purpose of offering these patients appropriate care.

In summary, presently available data support the use of OGTT as the preferred screening test for dysglycaemia in the high-risk population of patients with CAD and unknown glycaemic status. Performing an OGTT might not be sustainable and practical for some healthcare systems, and HbA1c should continue to be the preferred test when assessing glycaemic control. Nonetheless, performing an OGTT might allow to put in practice preventive measures, avoiding subsequent deterioration of the dysglycaemic state and hopefully even cardiovascular events. The latter possibility needs further testing in clinical trials, and there is also a demand of further head-to-head comparisons between the predictive value of 2hPG and HbA1c and possibly phenotyping patients who might benefit from one test or the other.

5.2 Gender differences in screening

Screening CAD patients with unknown glycaemic status revealed that more dysglycaemic women than men would have remained undetected without the use of an OGTT because significantly more women than men had an IGT, while IFG and known T2DM was more frequent in men (**Study II**).

The present findings are in line with previous reports from general populations (214-216). As outlined in the introduction, the pathophysiology behind IFG and IGT differs. Insulin sensitivity in the skeletal muscle and late-phase insulin secretion is more compromised in IGT, while there is a greater contribution of increased hepatic glucose production and compromised early insulin secretion in IFG (37). It has been suggested that the most important factor causing increased post-load plasma glucose levels is impaired peripheral insulin sensitivity, rather than a defect in insulin secretion (217). Females in general accumulate visceral fat and increase in BMI to a greater extent than males after menopause, contributing to increased insulin resistance

(218, 219). This is consistent with our finding that the proportions of obesity, central obesity and a higher BMI were more frequent in women.

In conclusion, screening with an OGTT seems to be particularly important in women with CAD, aiming at detecting IGT and setting up preventive measures and structured follow-up, given their already very high cardiovascular risk.

5.3 Validation of a screening algorithm including 1hPG

Among the reasons for the inertia to screen for glucose perturbations by means of a standard two-hour OGTT in patients with CVD is that it is considered time-consuming (123). One way to overcome this obstacle would be to shorten the OGTT by looking at the diagnostic features of postload glucose values obtained earlier than two hours.

Population-based investigations have proposed values of 1hPG during an OGTT that correctly identify individuals at high risk of progression to T2DM (48-50). Moreover, several other reports in the general population indicate that elevated 1hPG is more strongly correlated with features of the metabolic syndrome and high cardiovascular risk than FPG, HbA1c and 2hPG (220-226). As regards the association with CVD, 1hPG values above 8.6 mmol/L were associated with a higher risk of myocardial infarction and fatal ischemic heart disease in a cohort from the Malmö Preventive Project (227). Cao et al. investigated 1hPG in 266 individuals with CAD and normal glucose levels, who underwent coronary angiography. People with a 1hPG > 8.6 mmol/L had a higher incidence of multivessel disease and risk of hospital re-admission within one year (228). In 109 patients with an acute coronary syndrome and normal FPG and HbA1c, those with both 1hPG ≥ 8.6 mmol/L and a 2hPG ≥ 7.8 mmol/L had a more severe myocardial injury and a longer hospitalization (229).

To date, there are no thresholds for the detection of diabetes by means of 1hPG values in patients with CVD. In a previous report from our group based on the EUROASPIRE IV cohort, a new screening algorithm, based on a 1hPG threshold of 12 mmol/L, was proposed for patients with CAD decreasing the need for a two-hour OGTT by 71% (195). This algorithm was, however, in need of further validation before clinical application. Therefore, the opportunity for such validation in EUROASPIRE V was caught. Compared with the yield of a two-hour OGTT, the suggested threshold had a sensitivity of 76% and a specificity of 84%, with a positive and negative predictive value of 36% and 97% respectively. Only 18% of the patient cohort were correctly identified as having diabetes by HbA1c and FPG, and the 1hPG contributed by diagnosing an additional 61%. In practical terms, the good negative predictive value translated into a possibility of correctly identifying 79% of patients with diabetes according to the standard 2hPG definition (**Study III**).

In a recent meta-analysis, Ahuja et al (53) suggest an 1hPG ≥ 11.6 mmol/L as the optimal value for detection of T2DM by means of a 1hPG, with reference to a 2hPG ≥ 11.1 mmol/L as the gold standard. This level is indeed quite close to the one validated in **Study III**. Of notice, in our cohort, the optimal balance between sensitivity and specificity according to Youden's J statistic was identified at 11 mmol/L (AUC 0.89), suggesting that the most reliable value for screening lies between 11 and 12 mmol/L. This is in full accordance with the value of 11.6 mmol/L found in the meta-analysis, confirming that it is applicable to patients with established CVD.

In conclusion, **Study III** confirms that screening for T2DM in coronary patients by means of an algorithm combining FPG and 1hPG limits the demand of a two-hour OGTT in approximately three out of four patients.

5.4 Screening for dysglycaemia by means of insulin resistance

Using indexes of insulin resistance to screen for dysglycaemia in CAD patients, determined with a single blood sample and not requiring an OGTT, could potentially overcome several of the problems highlighted with this test. Moreover, insulin resistance can be targeted with lifestyle measures and, potentially, with pharmacological therapy. In light of the IRIS trial (93, 94) the ADA included a recommendation to consider pioglitazone to lower the risk of myocardial infarction and stroke in people with a history of stroke and evidence of insulin resistance and prediabetes in the 2023 Standards of Care in Diabetes (121).

HOMA indexes, fasting insulin and fasting C-peptide did, however, not provide a useful diagnostic capacity for dysglycaemia and diabetes as diagnosed by 2hPG criteria (**Study IV)**. A likely reason is that HOMA indexes mainly mirror hepatic insulin resistance, which primarily characterizes IFG, but not IGT (230, 231). In other words, characterization of insulin resistance by HOMA indexes might discriminate IFG but does not align with abnormal 2hPG levels, as the latter mostly reflects deficient second-phase insulin release and muscle insulin resistance (37). In **Study IV**, HOMA indexes were not investigated in people with IFG and a combined glucose intolerance (i.e., IFG and IGT), as the specific goal was to find an alternative to OGTT when aiming at identifying dysglycaemia (i.e., IGT and T2DM).

The use of HOMA indexes as screening and prognostic tools has been investigated in previous studies in diverse cohorts, different settings, and with conflicting results. In a cohort of Taiwanese participants without previous CVD the HOMA-IR index correlated significantly with several cardiovascular risk factors and with the Framingham risk score (232). In the Verona Diabetes Complications study, including patients with T2DM, HOMA-IR was an independent predictor of both prevalent and incident CVD (106). Moreover, HOMA-IR was associated with incident fatal and nonfatal myocardial infarction and stroke, transient ischemic attack, and revascularization procedures in the unselected population of another Italian study (233). One Japanese study exploring insulin resistance in subjects with CAD normal glucose tolerance, previously screened with an OGTT, found that fasting hyperinsulinemia and HOMA-IR were associated with subsequent cardiovascular events (234). A Swedish study found an association between HOMA-IR and CVD in sedentary men (235). In a meta-analysis by Gast and colleagues, including only patients without diabetes an increase of one standard deviation in HOMA was associated with an increased relative risk of CVD (236). In contrast a HOMA insulin sensitivity index was not associated with all-cause mortality and only modestly with CVD events in the Australian Diabetes, Obesity and Lifestyle Study, (237). Likewise, HOMA-IR did not predict incident CVD in 2,898 people without diabetes or CVD in the Framingham Offspring study (238). The divergent results may of course relate to differences in patient populations and study designs.

It must be concluded that robust evidence on this matter is still lacking, mainly due to small study with short follow-up and relatively few events. Further studies on well-defined and adequately sized populations are warranted to explore whether HOMA indexes, in one form or another, may be used as sensitive screening tools carrying prognostic information in patients with established CVD.

5.5 Multifactorial management

Contemporary international guidelines strongly underline that patient with T2DM should be offered a multifactorial management (56, 122). Nevertheless, the burden of cardiovascular events and deaths in patients with T2DM remains significantly higher than in the general population (239). A key reason is that the recommended multifactorial management is not sufficiently implemented in clinical practice, as depicted by the EUROASPIRE surveys, focusing on secondary cardiovascular prevention over the last twenty years (240). Treatment target attainment related to life-style risk factors and pharmacological management in patients with CAD and dysglycaemia in the most recent EUROASPIRE V survey (2016 – 2017) was poor (**Study I**). The proportion of overweight or obesity was approximately 80% regardless of glycaemic status, reaching almost 90% in patients with known diabetes. Moreover, half of patients with obesity did not attempt to lose weight, and a significant proportion of them had not received any advice on weight loss by diet or physical activity. Most of the patients did not perform or plan to engage in physical activity. Approximately half of the patients were persistent smokers, meaning that they were smokers before the index acute coronary event. LDL-C and blood pressure levels reached by patients included was equally discouraging, especially considering that, according to the most recent guidelines, targets are even stricter, i.e., 1.4 mmol/L for LDL-C and 130/80 mmHg for blood pressure (56). Among patients with known diabetes, only a small minority were taking cardioprotective glucose-lowering drugs. This is somehow more understandable considering that cardiovascular benefit of SGLT2i and GLP-1 RA was first established in 2015.

A multifactorial, target-driven approach reduces cardiovascular morbidity and mortality in people with DM, as first indicated by the observational Euro Heart Survey, subsequently proven by the randomized STENO 2 trial and confirmed in the Swedish Diabetes Registry (141, 241-243). Patients with diabetes at target for HbA1c, LDL-C and blood pressure had a 62% lower risk of subsequent CVD events over 11 years of follow-up in a pooled project including three prospective cohort studies (244). In patients with diabetes and CAD enrolled in the Bypass Angioplasty Investigation Revascularization 2 Diabetes (BARI 2D) trial, the number of risk factors at target was inversely related to cardiovascular events and survival (245). In the Trial Evaluating Cardiovascular Outcomes with sitagliptin (TECOS), including patients with diabetes and CVD, the presence of five secondary prevention measures (aspirin use, lipid control, blood control, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use and non-smoking status) was associated with a 40% lower risk of subsequent cardiovascular events compared with presence of two or fewer measures (246).

Our results are similar to those reported in the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) trial, including patients with a previous coronary event (247). The achievement of recommended targets was low, despite STABILITY being a randomised controlled trial with a presumably even more selected population. Comprehensive data from the US Diabetes Collaborative Registry reported on treatment target attainment in 74,393 American patients with diabetes, of whom almost 70% with known atherosclerotic cardiovascular disease (248). Compared with results of **Study I**, a higher proportion reached treatment targets for HbA1c (78% vs. 55% < 7% - 53 mmol/mol), LDL-C (42% vs 37% < 1.8 mmol/L) and blood pressure (70% vs. 55% < 140/90 mmHg). However, only one in five patients reached all three recommended targets simultaneously (248). Similarly, in a multicentre survey including 4,056 Chinese adults with diabetes, only 11% were at goals for LDL-C, blood pressure and FPG (249). When including obesity status in the treatment targets, the picture is even more discouraging, and in accordance with the present results. In the US National Health and Nutrition Examination Survey (NHANES) only 7% of patients with T2DM and known CVD were at target for HbA1c, blood pressure, LDL-C, and

non-smoking status simultaneously. When a BMI < 30 kg/m^2 was included, only 3% were optimally controlled (250).

Finally, comparing centres participating both in **Study I** and EUROASPIRE IV (146) proportions of obese and overweight subjects was unchanged, and the low level of physical activity increased. In addition, the proportion with an LDL-C <1.8 mmol/L was similar (48%), and even if slightly more patients had a HbA1c < 7% - 53 mmol/mol (57% vs. 54%) and a blood pressure <140/85 mmHg (27% vs. 37%) target attainment in these respects was only marginally improved. Time trends in patient management is therefore clearly disappointing. This is consistent with American data comparing NHANES 2013-2016 with NHANES 1999 – 2010, where no substantial improvement was found for isolated risk factors, and with a composite target control of HbA1c, LDL-C, and blood pressure control even less satisfactory (250, 251).

The reasons for the poor implementation of guideline recommended management are reasonably varied. A prerequisite for success is of course a distribution of guideline-based knowledge to those in charge of the patient group in focus. Professional societies are, with all rights, keen on updating existing guidelines and issuing new ones, while investments in distributing knowledge on their contents seem to be lower on their agenda (252). Moreover, since different professional organisations are issuing their own guidelines, the number becomes overwhelming with sometimes diverging information. The complexity and size may also become burdensome. As an example, the most recent standards of medical care in diabetes issued by the American Diabetes Association amounts to 17 chapters on 298 pages (253). Even the abridged version for primary care is a dense, 28-pages document (254). Considering that many of the actual group of patients are cared for in primary care and considering that those working there are burdened by many other guidelines, it is easy to understand that this educational task is substantial and complex (255). For the future, it would probably be helpful with shared production of guidelines according to a standardized methodology, with a simplified content and adapted to local standards (252).

The prescription of secondary prevention drugs is not sufficient since the dose and the adherence significantly influences prognosis. For instance, in a description of dyslipidaemia management in EUROASPIRE V, 88% of the whole population was on lipid-lowering treatment, which can be considered satisfactory; however, only 59% of them were on high-intensity regimens (256). To ascertain that patients are taking the drugs in the recommended dose and that the necessary uptitration is being performed requires frequent and structured visits.

Another concern is the involvement of several healthcare professionals, and that the organisation of healthcare systems might not be appropriately structured. Patients in EUROASPIRE V were, as described, followed by a diversity of health care professionals, and only 24% had taken part in any type of diabetes school. This entails a risk for a somewhat fragmented care, where different healthcare professionals trust the others to take the full responsibility for a comprehensive management (12). Those who initiate the diagnostic and therapeutic process in patients with CAD and diabetes, known and newly detected, must ascertain that treatment targets and how they should be reached is transferred to those in charge for the continued patient care, often primary care physicians, and likewise that patients are informed on the contents of a holistic, target-driven management.

To motivate patients to adhere to a healthy lifestyle necessitates adequate communicative skills and time during the outpatient visits to explain the implications. This presents various challenges. First, sufficient knowledge in behavioural sciences to assure efficacious communication is confined to minimal parts of educational programs, that mainly focus on

strict medical aspects. In patients who suffered a coronary event, in whom the presence of anxiety symptoms is substantial, lack of motivation and receptivity can be difficult to overcome (257). Second, physicians usually have to squeeze physical examinations, administrative work, and conversation with patients in a very limited time, making it virtually impossible to assess all issues during a single encounter (255).

One may raise the question if it is possible to reach targets as outlined in guidelines or if they are wishful dreams rather than realistic goals in daily care. One might argue that national regulatory aspects and different healthcare structures limit guideline applicability. This does not seem to be true. An example from EUROASPIRE V shows the heterogeneity of blood pressure control in different centres within the same country (**Figure 24**). A similar picture has been presented by the SWEDEHEART registry (258) It informs that it is the ambition among those locally in charge of patient care that is probably of greatest importance for the therapeutic outcome.

Several of the obstacles to the achievement of a satisfactory management may be overcome by establishing a transprofessional team lead by the physician in charge and composed of nurses, physiotherapists, psychologists and dietitians (259). Structured programs with clear treatment goals including different healthcare providers have been successful (260). In the Randomized Evaluation of Secondary Prevention by Outpatient Nurse Specialists 2 trial, comprehensive lifestyle programmes (including weight reduction, physical activity, and smoking cessation) on top of usual care were more effective than usual care only on meeting the targets (261). A nurse-led, multidisciplinary hospital programme significantly improved diet and physical activity levels in the EUROACTION trial (262). Another solution is to discuss guideline content on a local level with all involved stakeholders, analysing cost-effectiveness, policies and possible regulatory hinders (252).

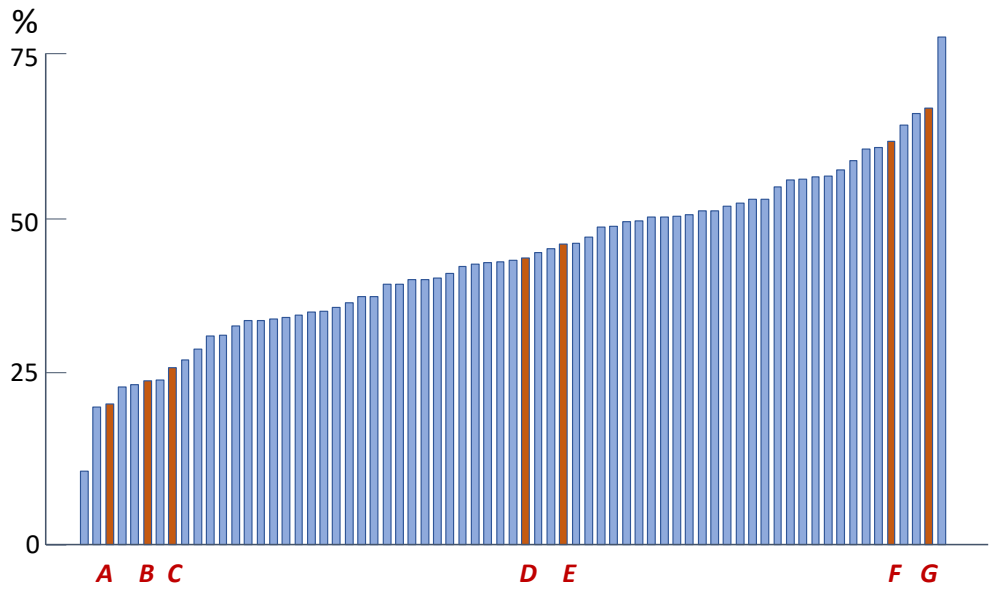


Figure 24. Age- and gender- adjusted prevalence of blood pressure >140/90 mmHg by centre with >30 patients in EUROASPIRE V. A, B, C, D, E, F and G are centres within the same country. The average prevalence is 40%.

Source Rydén, Ferrannini and the EUROASPIRE team – data on file.

In conclusion, there is a compelling need to improve the management of patients with dysglycaemia and CAD. Just to update guidelines without investing in treatment implementation, scheduled follow-up and multidisciplinary care is obviously insufficient.

5.2 Gender differences in multifactorial management, treatment target achievement and prognosis

Risk factor control was generally worse in women than in men in EUROASPIRE IV and EUROASPIRE V (**Study II**). This is in accordance with several previous reports. A German population study reported that women with T2DM and CVD were more likely to have blood pressure, LDL-C and HbA1c above target compared with men (263), and similar findings were reported from 8000 Croatian patients with T2DM (264). The SWEDEHEART registry has consistently indicated that less women than men reach the blood pressure and LDL-C targets one year after an acute myocardial infarction (265). A study on CAD patients (32% T2DM) conducted in 11 countries reported that all lifestyle and pharmacological targets were achieved by a significantly lower proportion of women than men (266). In contrast, such differences were not reported in NHANES 2013 – 2016, where the only difference in the relatively small subgroup of patients with established CVD was that women were less likely to take lipid-lowering medications than men (250). In the US Diabetes Collaborative Registry, women were less well managed as regards all risk factors compared with men (248). HbA1c in women with previously known T2DM was higher than in men, despite glucose-lowering drugs being prescribed in similar proportions, as reported in a large American study including 10,876 men and 19,278 women patients and in a cross-sectional analysis of almost 4,000 individuals, where one-third had established CAD (267, 268).

Regarding lifestyle-related factors women smoke less than men. The physical activity target was reached by fewer women, and they attended cardiac prevention and rehabilitation programs in lower proportions than men. Obesity was significantly more prevalent among women than men, despite being advised on and having pursued weight loss in similarly low proportions (**Study II**). A possible explanation is that the two genders have different preferences, compliance and response to lifestyle management (269).

Quality of life indicators are all to the disadvantage of women, consistently with the fact that they are more often prescribed antidepressants and antianxiety drugs than men (270).

Women with known T2DM in EUROASPIRE IV and V had a significantly poorer prognosis than men (**Study II)**. This is in accordance with recent nationwide studies (168, 271). Moreover, they had significantly more microvascular complications, most likely reflecting their less-than-optimal glycaemic control (272, 273). There was no difference in the association with outcome between men and women with newly diagnosed dysglycaemia in **Study II**, possibly indicating that there should be no difference between the two genders if they are equally treated. In a cross-sectional report of 3,540 subjects with varying glucose tolerance status, the relative risk of all-cause death, coronary events and stroke was not higher in women vs. men with prediabetes (diagnosed according to either HbA1c or OGTT) (274). Notwithstanding the important sex differences and underlying mechanisms, it is undeniable that the worse prognosis in women is, at least in great part, attributable to poorer risk factor control, which escalates to a greater extent as their glycaemic status worsens (275).

A reasonable conclusion is that special efforts should be put into managing cardiometabolic risk in women by securing access to available preventive measures.

5.6 Cardioprotection with a GLP-1 RA by baseline metformin

The effect of dulaglutide on cardiovascular and microvascular outcomes was similar in participants irrespective of metformin treatment at baseline. This statement gains support by the absence of an interaction between randomization to dulaglutide and metformin therapy at baseline for the trial outcomes, after adjusting for confounders. Two consistency analyses further strengthen this finding: the first stratifies the main analysis by baseline glucose-lowering therapy (drug naïve, those who received any glucose-lowering therapy except metformin, and those taking metformin), and the second considering post-randomization changes in metformin use (**Study V**).

This post-hoc analysis was performed to clarify one of the major guideline controversies at the time, i.e. whether cardioprotective glucose-lowering drugs belonging to the classes of SGLT2i and GLP-1 RA should be prescribed first-line glucose lowering therapy in people with T2DM at high cardiovascular risk independently from the presence of metformin, or whether metformin should be prioritized (56, 276). Metformin has been considered as the cornerstone of T2DM therapeutic armamentarium, and it may have independent cardiovascular benefits (23, 277-279).

The best evidence on the matter would be supported by a CVOT assessing the effect of metformin vs. placebo on MACE in people with T2DM, but no such trial is available. In a 21-year median follow-up of participants with IGT in the DPP trial and DPP Outcomes Study, metformin was not associated with a reduced risk of MACE vs. placebo (280). A meta-analysis of 35 randomized clinical trials comparing metformin to placebo and other glucose-lowering medications showed that metformin significantly reduced MACE, peripheral artery disease, and cardiovascular death vs. placebo, but not when compared to the other drugs (281).

No clear heterogeneity in the cardiovascular efficacy of the GLP-1 RA liraglutide in relation to the background use of metformin was found in a post-hoc analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (282). Similarly, albiglutide had similar beneficial effect in prespecified subgroups with and without metformin in participants of the Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and established CVD (Harmony Outcomes) (177). However, the latter report was descriptive without any new modelling or adjustments for covariates. A post-hoc analysis of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial found that the effect estimates remained robust after adjusting for unbalanced use of other glucose-lowering drugs between the exenatide and the placebo groups (283).

The 2023 ADA clinical practice recommendations now state that “people with T2DM with or at high risk for atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease should be treated with a cardioprotective SGLT2i and/or GLP-1 RA as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the regimen of care irrespective of the need for additional glucose lowering, and irrespective of metformin use” (122). Therefore, guideline recommendations have been updated towards the direction supported by the findings in **Study V**.

5.7 Limitations

EUROASPIRE surveys

In **Studies I to IV**, formal geographical comparisons were not performed because of the relatively low numbers in each country. Nevertheless, there did not seem to be any major discrepancy in management regarding different European areas, as within-country differences

were as apparent as those in between-countries. This supports the concept that treatment implementation is widely needed.

The relatively low participation rate, 51%, should be considered as a limitation, because it generates a selection bias. A contributing factor might have been different local restrictions as regards contacting patients according to diverse application of the General Data Protection Regulation rules. Besides, those unwilling to participate are usually sicker, with poorer risk factor control, and live in worse socio-economic conditions. In addition, centres that choose to participate in the surveys may be more motivated as regards detection and management of cardiovascular risk. Taking these two possibilities into account, the overall pattern of screening and management of the investigated patient population if anything may be overestimated, which would leave a more complete picture of the present adherence to guideline recommendations as even worse.

A potential limitation is that screening for dysglycaemia was only performed once, while current guidelines recommend at least two positive results to confirm the diagnosis of T2DM (33). However, the outcome of a single OGTT performed four to five days after an acute coronary event classified dysglycaemic patients in way that strongly correlated with subsequent tests three and 12 months later (284). Moreover, a single screening test identified patients with a less favourable prognosis in previous studies (133, 139).

In **Study II**, the proportion of women (approximately 25%) was low, although the absolute number was large (4,077 of whom 2,391 were dysglycaemic). However, this is a representative gender distribution of CAD patients considering the given age restriction. Since it is virtually impossible to randomise patients genderwise, longitudinal studies on large populations like ours may be considered as providing a reasonably good level of evidence. Finally, gender was defined as a binary variable (women/men), but gender diversity might include a broader spectrum of identities which were not systematically investigated in our study.

In **Study III**, the algorithm based on FPG and 1hPG did not cover patients with IGT. There were several reasons not to include IGT. Since the primary aim was to validate an existing algorithm, the same selection criteria as in the discovery cohort were applied. Second, 1hPG is not an official diagnostic criterion for glucose disturbances besides gestational diabetes mellitus, and the validation should start from T2DM which is a well-recognised, high-risk entity. Third, the pathophysiological mechanisms behind IGT might not be well represented by 1hPG.

REWIND

The results should be considered indicative rather than proof of evidence, since REWIND was not specifically designed to assess differences between randomisation groups in relation to baseline therapy. Still, the results are seemingly robust considering the possibility to account for a great number of potential confounders. Another concern is that the study population is a selected trial cohort, that may not be fully representative of a wider population of patients with T2DM and high cardiovascular risk or established CVD. However, an analysis comparing the key characteristics of participants of GLP-1 RAs CVOTs to a reference American population who matched the enrolment criteria found that the REWIND population was most representative (285). Lastly, the relatively small proportion of participants without metformin at baseline could have decreased the power of this analysis.

5.8 Future perspectives

This thesis leaves some questions open, paving the way for future research.

- The hope is that a higher proportion of patients without known dysglycaemia is identified and offered optimal care. The EUROASPIRE VI survey will enrol patients in 2023 and 2024, thus referring to standards of care recommended by the most recent guidelines on diabetes and cardiovascular disease (56, 122).
- Information is needed on the prognostic capability of the 1hPG, before it can be recommended as a possibility to shorten the OGTT in a high proportion of patients. The 1hPG value assessment during a standard two-hour OGTT will be included in EUROASPIRE VI and patients will be followed up to five years, offering an opportunity to investigate this association.
- The implementation of guideline-directed management of patients with diabetes and cardiovascular disease is still a major necessity, and how this is conducted in countries outside Europe and the US is still largely unknown. The INTERASPIRE survey, enrolling patients from six different WHO regions, will provide a picture of management of CAD patients in relation to different international and national guidelines, and possibly highlight the variation in preventive cardiology practice across countries (286).
- Implementation of guideline-directed management may be improved by means of technical support, including artificial intelligence integrated with medical records. Self-monitoring by means of technological devices may also enhance achievement of treatment targets and patients' compliance.
- The awareness on gender gaps in multiple fields has substantially increased in the last five years, hopefully leading to better care of women. Gender discrepancies in screening and management of coronary patients with dysglycaemia will be further explored in EUROASPIRE VI.
- New cardiovascular outcome trials on GLP-1 RA and SGLT2i have included patients without diabetes, broadening the indications for these drugs (e.g., obesity and heart failure). How this great popularity in clinical research has translated into real-world care across different countries with diverse healthcare policies is largely unexplored, and a comprehensive overview will be provided by EUROASPIRE VI results.

6. Conclusions

There is a compelling need to improve both screening and management of risk factors in patients with dysglycaemia and coronary artery disease.

A standard oral glucose tolerance test should be preferred for screening, being able to detect more patients with diabetes compared with the other screening tools and as the only to diagnose impaired glucose tolerance. This condition confers a clearcut prognostic disadvantage and can be targeted by lifestyle, and possibly pharmacological, measures that not only prevent further cardiovascular events, but also hamper the progress towards diabetes.

The one-hour postload glucose value is a validated screening tool that should be incorporated in international guidelines, considering large available evidence and because it limits the demand of a two-hour oral glucose tolerance test. Efforts should be put in further evaluation of its prognostic role, especially as regards future cardiovascular events.

Considerably more resources need to be invested in implementing guideline recommendations as regards lifestyle and pharmacological interventions.

Screening for dysglycaemia in coronary artery disease is of special significance in women, who more often have impaired glucose tolerance. Women also carry a higher burden of cardiovascular risk factors and their glycaemic control is generally poorer than in men whether they have known diabetes, because of less efficient control, which is ultimately leads to a more dismal prognosis.

The cardioprotective effect of dulaglutide does not seem to be dependent on background metformin therapy. Therefore, glucagon-like peptide-1 receptor agonists should be prioritised as first-line treatment in patients with type 2 diabetes and high cardiovascular risk.

7. Acknowledgements

To my main supervisor *Linda Mellbin* for endless patience and support. I realise how hard it is to have to deal with a hot-tempered, impatient Italian and I could not be happier to have received your endless professional support and valuable insights in our work. Besides, I cannot put into words all the personal support I received from you, but you know what I am talking about. Thank you from the bottom of my heart!

To my supervisor *Lars Rydén* because you are the reason why I moved to Sweden and dedicated myself to research. Every single hour I spent discussing with you has been enriching and a lot of fun. You are brilliant and passionate about what we do as a research group and as people. You know every detail about what I have been going through during these years and I could have never made it without you. Thank you with infinite gratitude!

To my supervisor *Anna Norhammar* for always finding time and energy for me, for encouraging my growth and for always having that fundamental "extra-kick" point of view scientifically. I am honoured to look up to you!

To my supervisor *Viveca Gyberg* for your previous work on EUROASPIRE, which has been inspiring this thesis, and for your very good "fresh eye" on this thesis!

To my mentor professor *Francesco Cosentino*, for your kindness and support, for all late-afternoon chats ("Italian time" at Norrbacka) and for bringing up the name of us Italians!
To professors *John Pernow*, *Frieder Braunschweig*, *Cecilia Linde*, *Lars Lund* for always having a nice word for me.

This thesis has been supported by grants from *Hjärt-Lungfonden* and the *Erling-Perssons Stiftelse*.
Thank you to all patients who were willing to participate in these studies.
To the EUROASPIRE steering committee: thank you professor *Dirk De Bacquer* for all your help with the statistical work, for patiently answering all my questions and for always being available. Thank you professors *Guy De Backer*, *David Wood*, and *Kornelia Kotseva* for welcoming me in the project. To professor *Hertzel G. Gerstein*: thank you for supporting me in the work on REWIND and sharing your infinite knowledge in such instructing way.
This thesis would basically not exist without all of you.

To the whole "korridoren" at Norrbacka! You guys have not only supported my work and listened to my whining, but also made it FUN! Thank you *Raquel Binisi* for all administrative and "spiritual" support. Thank you *Britt-Marie Höglund, Helena Sundling* and *Liza Cheadle* for all your organizational help, *Victoria Boström-Nilsson*, *Stina Smetana*, *Kerstin Höglund*, *Eva Ólafsdóttir*, *Eva Wallgren*, *Camilla Hage*, *Ann Hultman-Cadring*, *Isabel Tronstad, Emma Jonsson*, *Barbro Kjellström, Ashwin Venkateshvaran, Matthias Lidin*, *Magnus Mossfeldt, David Ersgård* because you have been caring and close to me in the darkest days and are related to the happiest memories.
To my fellow PhD students and postdocs: thank you so much! *Elena Fortin*, for being the smartest and the coolest to hang out with; *Elina Rautio*, for being close and cheering me up during travels and afterworks; *Federica Guidetti*, for your strength and your jokes; *Isabelle Johansson*, *Anne Wang*, *Peter Moritz Becher*, *Davide Stolfo*, *Benedikt Schrage*, *Felix Lindberg*, *Mikael Erhardsson*, *Ava Azari*, and all research fellows here for the fun times.

To *Anne Braunschweig* for welcoming me at Löwenströmska and putting up with "my mood swings and my humor (humör och humor)". You are a real role model.
To all my colleagues at the Internal Medicine Unit, Södertälje hospital: you made me feel safe and part of the group from day one, I am learning and growing besides expectations, you are engaged and hard-working and we always "klarar oss" even when the burden feels hard to overcome. It is awesome to work with you. Thank you!

To my safety net: *Alessandro Volpicella*, you really are the wisest, most positive person and endless source of fun, silly videos and trash music we both love. *Sonia Youhanna*, you are the strongest woman I know and the craziest, most dramatic table games player. *Paolo Gatti*, you are the most generous, likeable (check!) and supportive person. *Gianluigi Savarese*, where should I start when thanking you? Endless working opportunities? Role model for all young researchers? I feel I must thank you the most for always being there for me in all ways. You guys have seen and endured it all and you are my family.
To all my other friends here, especially *Dora Pavone* and *Giulia Galieti* (you gals have superpowers!); and in Italy, thank you for all "distance aperitivi", for running up and down Europe just to meet a few hours.

To my wonderful parents *Daniela* and *Ele* for your support to pursue my career without forgetting what really matters. You are not "ordinary people" by any means, and I feel so lucky to be loved by you. Thank you.
To the most important thing for me and biggest gift I ever received: my siblings *Claudia*, *Silvia*, *Anna*, *Elena* and *Andrea*. You give meaning, value and beauty to my life. Thank you.

To *Matteo*: thank you for everything. I love you and cannot wait for the rest of our lives together.

8. References

1. Papyrus Ebers. Bull Med Libr Assoc. 1912;2(1):12.
2. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23(4):373-8.
3. Ryden L, Lindsten J. The history of the Nobel prize for the discovery of insulin. Diabetes Res Clin Pract. 2021;175:108819.
4. Langerhans P. Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse: Inaugural-Dissertaton. Berlin. 1869.
5. Lancereaux E. Notes et reflexions a propos de deux cas de diabete sucre avec alteration du pancreas. Bull Acad Med Paris. 1877; 6: 1215-1240.
6. Porta M. One hundred years ago: the dawning of the insulin era. Acta Diabetol. 2021;58(1):1-4.
7. Paulesco N. Action de l'extract pancréatique injecté dans le sang, chez un animal diabétique. Compte Rendus des Séances de la Société de Biologie Roumaine. 1921; 85: 555-557.
8. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014;383(9922):1068-83.
9. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-85.
10. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011;91(2):733-94.
11. Nauck MA, Wefers J, Meier JJ. Treatment of type 2 diabetes: challenges, hopes, and anticipated successes. Lancet Diabetes Endocrinol. 2021;9(8):525-44.
12. Ferrannini G, Norhammar A, Gyberg V, Mellbin L, Ryden L. Is Coronary Artery Disease Inevitable in Type 2 Diabetes? From a Glucocentric to a Holistic View on Patient Management. Diabetes Care. 2020;43(9):2001-9.
13. Biorck G, Blomqvist G, Sievers J. Studies on myocardial infarction in Malmo 1935 to 1954. I. Morbidity and mortality in a hospital material. Acta Med Scand. 1957;159(4):253-74.
14. Ryden L. Early achievements in cardiovascular care as reflected in the Journal of Internal Medicine. J Intern Med. 2013;274(6):529-40.
15. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241(19):2035-8.
16. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol. 1972;30(6):595-602.
17. Epstein FH. Hyperglycemia. A risk factor in coronary heart disease. Circulation. 1967;36(4):609-19.
18. The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of pheniformin therapy. Diabetes. 1975;24 Suppl 1:65-184.
19. Blackburn H, Jacobs DR, Jr. The University Group Diabetes Program 1961-1978: pioneering randomized controlled trial. Int J Epidemiol. 2017;46(5):1354-64.
20. UK prospective study of therapies of maturity-onset diabetes. I. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia. 1983;24(6):404-11.
21. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes Care. 1999;22(6):960-4.

22. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.
23. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65.
24. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):703-13.
25. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):713-20.
26. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):720-6.
27. Diabetes C, Complications Trial Research G, Nathan DM, Genuth S, Lachin J, Cleary P, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
28. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643-53.
29. Schnell O, Ryden L, Standl E, Ceriello A, Group CES. Updates on cardiovascular outcome trials in diabetes. Cardiovasc Diabetol. 2017;16(1):128.
30. International Diabetes Federation. IDF Diabetes Atlas 2021 - 10th edition. Available at www.diabetesatlas.org. Accessed on Nov 22, 2022. [
31. American Diabetes Association Professional Practice C. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17-S38.
32. Nathan DM, Bennett PH, Crandall JP, Edelstein SL, Goldberg RB, Kahn SE, et al. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? Diabetologia. 2019;62(8):1319-28.
33. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation 2020. Available from: https://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/. Accessed on Nov 22, 2022.
.
34. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Supplement_1):S19-S40.
35. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ. 1994;308(6940):1323-8.
36. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med. 2002;19(9):708-23.
37. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care. 2006;29(5):1130-9.

38. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20(7):1183-97.
39. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1(Suppl 1):S62-9.
40. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS. Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. Diabetes Care. 2010;33(10):2184-9.
41. World Health Organization. Use of Glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. 2019 [Available from: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf (June 14 2019). Accessed on Nov 22, 2022. [
42. Collaboration NCDRF. Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331,288 participants. Lancet Diabetes Endocrinol. 2015;3(8):624-37.
43. Hage C, Lundman P, Ryden L, Mellbin L. Fasting glucose, HbA1c, or oral glucose tolerance testing for the detection of glucose abnormalities in patients with acute coronary syndromes. Eur J Prev Cardiol. 2013;20(4):549-54.
44. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV--a survey from the European Society of Cardiology. Eur Heart J. 2015;36(19):1171-7.
45. Diabetes Prevention Program Research G. HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. Diabetes Care. 2015;38(1):51-8.
46. Cefalu WT, Buse JB, Tuomilehto J, Fleming GA, Ferrannini E, Gerstein HC, et al. Update and Next Steps for Real-World Translation of Interventions for Type 2 Diabetes Prevention: Reflections From a Diabetes Care Editors' Expert Forum. Diabetes Care. 2016;39(7):1186-201.
47. Bergman M, Manco M, Sesti G, Dankner R, Pareek M, Jagannathan R, et al. Petition to replace current OGTT criteria for diagnosing prediabetes with the 1-hour post-load plasma glucose >/= 155 mg/dl (8.6 mmol/L). Diabetes Res Clin Pract. 2018;146:18-33.
48. Bianchi C, Miccoli R, Trombetta M, Giorgino F, Frontoni S, Faloia E, et al. Elevated 1-hour postload plasma glucose levels identify subjects with normal glucose tolerance but impaired beta-cell function, insulin resistance, and worse cardiovascular risk profile: the GENFIEV study. J Clin Endocrinol Metab. 2013;98(5):2100-5.
49. Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Groop L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. Diabetes Care. 2009;32(2):281-6.
50. Alyass A, Almgren P, Akerlund M, Dushoff J, Isomaa B, Nilsson P, et al. Modelling of OGTT curve identifies 1 h plasma glucose level as a strong predictor of incident type 2 diabetes: results from two prospective cohorts. Diabetologia. 2015;58(1):87-97.
51. Zhou W, Gu Y, Li H, Luo M. Assessing 1-h plasma glucose and shape of the glucose curve during oral glucose tolerance test. Eur J Endocrinol. 2006;155(1):191-7.
52. Paddock E, Looker HC, Piaggi P, Knowler WC, Krakoff J, Chang DC. One-Hour Plasma Glucose Compared With Two-Hour Plasma Glucose in Relation to Diabetic Retinopathy in American Indians. Diabetes Care. 2018;41(6):1212-7.
53. Ahuja V, Aronen P, Pramodkumar TA, Looker H, Chetrit A, Bloigu AH, et al. Accuracy of 1-Hour Plasma Glucose During the Oral Glucose Tolerance Test in Diagnosis of Type 2 Diabetes in Adults: A Meta-analysis. Diabetes Care. 2021;44(4):1062-9.

54. World Health Organization. Global Health Estimates: Leading causes of DALYs. Disease Burden, 2000-2019. 2020. Available from https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys. Accessed on Nov 23, 2022. [
55. World Health Organization. The top 10 causes of death. 2020. Available at https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed on Nov 23, 2022. .
56. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323.
57. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41(2):105-14.
58. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
59. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364(9):829-41.
60. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
61. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290(7):898-904.
62. Farkouh ME. Primary prevention of atherosclerotic cardiovascular disease: bringing clinicians and patients to the starting line. J Am Coll Cardiol. 2014;64(10):969-70.
63. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018;6(5):361-9.
64. Safai N, Ali A, Rossing P, Ridderstrale M. Stratification of type 2 diabetes based on routine clinical markers. Diabetes Res Clin Pract. 2018;141:275-83.
65. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes. 1995;44(4):369-74.
66. Ferrannini E, Manca ML, Ferrannini G, Andreotti F, Andreini D, Latini R, et al. Differential Proteomics of Cardiovascular Risk and Coronary Artery Disease in Humans. Front Cardiovasc Med. 2021;8:790289.
67. WHO. Global status report on noncommunicable diseases 2014.
68. Emerging Risk Factors C, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
69. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105-13.
70. Rodriguez-Araujo G, Nakagami H. Pathophysiology of cardiovascular disease in diabetes mellitus. Cardiovasc Endocrinol Metab. 2018;7(1):4-9.
71. Keating ST, Plutzky J, El-Osta A. Epigenetic Changes in Diabetes and Cardiovascular Risk. Circ Res. 2016;118(11):1706-22.
72. Ramana KV, Friedrich B, Srivastava S, Bhatnagar A, Srivastava SK. Activation of nuclear factor-kappaB by hyperglycemia in vascular smooth muscle cells is regulated by aldose reductase. Diabetes. 2004;53(11):2910-20.

73. Reichert S, Triebert U, Santos AN, Hofmann B, Schaller HG, Schlitt A, et al. Soluble form of receptor for advanced glycation end products and incidence of new cardiovascular events among patients with cardiovascular disease. Atherosclerosis. 2017;266:234-9.
74. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-72.
75. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.
76. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-39.
77. Investigators OT, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319-28.
78. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol. 1995;26(1):57-65.
79. Ritsinger V, Malmberg K, Martensson A, Ryden L, Wedel H, Norhammar A. Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. Lancet Diabetes Endocrinol. 2014;2(8):627-33.
80. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005;26(7):650-61.
81. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003;46(1):3-19.
82. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607.
83. Young LH, Viscoli CM, Curtis JP, Inzucchi SE, Schwartz GG, Lovejoy AM, et al. Cardiac Outcomes After Ischemic Stroke or Transient Ischemic Attack: Effects of Pioglitazone in Patients With Insulin Resistance Without Diabetes Mellitus. Circulation. 2017;135(20):1882-93.
84. Ryden L, Mellbin L. New Hope For People With Dysglycemia and Cardiovascular Disease Manifestations: Reduction of Acute Coronary Events With Pioglitazone. Circulation. 135. United States2017. p. 1894-6.
85. Pfeifle B, Ditschuneit H. Effect of insulin on growth of cultured human arterial smooth muscle cells. Diabetologia. 1981;20(2):155-8.
86. Aziz A, Wheatcroft S. Insulin resistance in Type 2 diabetes and obesity: implications for endothelial function. Expert Rev Cardiovasc Ther. 2011;9(4):403-7.
87. Sung HH, Park CE, Gi MY, Cha JA, Moon AE, Kang JK, et al. The association of the visceral adiposity index with insulin resistance and beta-cell function in Korean adults with and without type 2 diabetes mellitus. Endocr J. 2020;67(6):613-21.
88. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116(1):39-48.
89. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.

90. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343-50.
91. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014;2(6):474-80.
92. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279-89.
93. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016;374(14):1321-31.
94. Spence JD, Viscoli CM, Inzucchi SE, Dearborn-Tomazos J, Ford GA, Gorman M, et al. Pioglitazone Therapy in Patients With Stroke and Prediabetes: A Post Hoc Analysis of the IRIS Randomized Clinical Trial. JAMA Neurol. 2019;76(5):526-35.
95. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979;237(3):E214-23.
96. Lorenzo C, Haffner SM, Stancakova A, Laakso M. Relation of direct and surrogate measures of insulin resistance to cardiovascular risk factors in nondiabetic finnish offspring of type 2 diabetic individuals. J Clin Endocrinol Metab. 2010;95(11):5082-90.
97. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
98. Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol. 1993;137(9):959-65.
99. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med. 1999;16(5):442-3.
100. Hosker JP, Matthews DR, Rudenski AS, Burnett MA, Darling P, Bown EG, et al. Continuous infusion of glucose with model assessment: measurement of insulin resistance and beta-cell function in man. Diabetologia. 1985;28(7):401-11.
101. Buchanan TA, Watanabe RM, Xiang AH. Limitations in surrogate measures of insulin resistance. J Clin Endocrinol Metab. 95. United States2010. p. 4874-6.
102. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care. 2003;26(12):3320-5.
103. Lee KK, Fortmann SP, Fair JM, Iribarren C, Rubin GD, Varady A, et al. Insulin resistance independently predicts the progression of coronary artery calcification. Am Heart J. 2009;157(5):939-45.
104. Caccamo G, Bonura F, Vitale G, Novo G, Evola S, Evola G, et al. Insulin resistance and acute coronary syndrome. Atherosclerosis. 2010;211(2):672-5.
105. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care. 2002;25(7):1177-84.
106. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care. 2002;25(7):1135-41.

107. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013;30(7):803-17.
108. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 2017;8(3):475-87.
109. Marx N. C-peptide as a mediator of lesion development in early diabetes--a novel hypothesis. Trends Cardiovasc Med. 2008;18(2):67-71.
110. Hirai FE, Moss SE, Klein BE, Klein R. Relationship of glycemic control, exogenous insulin, and C-peptide levels to ischemic heart disease mortality over a 16-year period in people with older-onset diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Diabetes Care. 2008;31(3):493-7.
111. Bo S, Gentile L, Castiglione A, Prandi V, Canil S, Ghigo E, et al. C-peptide and the risk for incident complications and mortality in type 2 diabetic patients: a retrospective cohort study after a 14-year follow-up. Eur J Endocrinol. 2012;167(2):173-80.
112. Kim ST, Kim BJ, Lim DM, Song IG, Jung JH, Lee KW, et al. Basal C-peptide Level as a Surrogate Marker of Subclinical Atherosclerosis in Type 2 Diabetic Patients. Diabetes Metab J. 2011;35(1):41-9.
113. Cabrera de Leon A, Oliva Garcia JG, Marcelino Rodriguez I, Almeida Gonzalez D, Aleman Sanchez JJ, Brito Diaz B, et al. C-peptide as a risk factor of coronary artery disease in the general population. Diab Vasc Dis Res. 2015;12(3):199-207.
114. Marx N, Silbernagel G, Brandenburg V, Burgmaier M, Kleber ME, Grammer TB, et al. C-peptide levels are associated with mortality and cardiovascular mortality in patients undergoing angiography: the LURIC study. Diabetes Care. 2013;36(3):708-14.
115. Andrade RLM, Callo G, Horta BL. [C-peptide and cardiovascular mortality: systematic review and meta-analysisPeptido C y mortalidad cardiovascular: revision sistematica y metanalisis]. Rev Panam Salud Publica. 2019;43:e23.
116. Harnishsingh B, Rama B. Is C-peptide a predictor of severity of coronary artery disease in metabolic syndrome? An observational study. Indian Heart J. 2018;70 Suppl 3(Suppl 3):S105-S9.
117. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet. 2002;359(9324):2140-4.
118. Bartnik M, Rydén L, Ferrari R, Malmberg K, Pyörälä K, Simoons M, et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. Eur Heart J. 2004;25(21):1880-90.
119. Hu DY, Pan CY, Yu JM. The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey. Eur Heart J. 2006;27(21):2573-9.
120. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487-93.
121. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Supplement_1):S41-S8.
122. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Supplement_1):S158-S90.
123. Sattar N, Preiss D. Screening for diabetes in patients with cardiovascular disease: HbA1c trumps oral glucose tolerance testing. Lancet Diabetes Endocrinol. 2016;4(7):560-2.

124. Rydén L, Gyberg V, Schnell O, Tuomilehto J. Oral glucose tolerance testing and cardiovascular disease. Lancet Diabetes Endocrinol. 2016;4(9):732-3.
125. Buse JB. Screening for diabetes and prediabetes with proposed A1C-based diagnostic criteria: comment on Olson et al. Diabetes Care. 2010;33(12):e174; author reply e5.
126. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med. 2004;141(6):413-20.
127. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800-11.
128. Hernandez D, Espejo-Gil A, Bernal-Lopez MR, Mancera-Romero J, Baca-Osorio AJ, Tinahones FJ, et al. Association of HbA1c and cardiovascular and renal disease in an adult Mediterranean population. BMC Nephrol. 2013;14:151.
129. Sinning C, Makarova N, Volzke H, Schnabel RB, Ojeda F, Dorr M, et al. Association of glycated hemoglobin A(1c) levels with cardiovascular outcomes in the general population: results from the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium. Cardiovasc Diabetol. 2021;20(1):223.
130. Liu XJ, Wan ZF, Zhao N, Zhang YP, Mi L, Wang XH, et al. Adjustment of the GRACE score by HemoglobinA1c enables a more accurate prediction of long-term major adverse cardiac events in acute coronary syndrome without diabetes undergoing percutaneous coronary intervention. Cardiovasc Diabetol. 2015;14:110.
131. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, et al. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation. 2011;124(6):704-11.
132. Karayiannides S, Djupsjo C, Kuhl J, Hofman-Bang C, Norhammar A, Holzmann MJ, et al. Long-term prognosis in patients with acute myocardial infarction and newly detected glucose abnormalities: predictive value of oral glucose tolerance test and HbA1c. Cardiovasc Diabetol. 2021;20(1):122.
133. Ritsinger V, Tanoglidi E, Malmberg K, Näsman P, Rydén L, Tenerz Å, et al. Sustained prognostic implications of newly detected glucose abnormalities in patients with acute myocardial infarction: long-term follow-up of the Glucose Tolerance in Patients with Acute Myocardial Infarction cohort. Diab Vasc Dis Res. 2015;12(1):23-32.
134. Tamita K, Katayama M, Takagi T, Yamamuro A, Kaji S, Yoshikawa J, et al. Newly diagnosed glucose intolerance and prognosis after acute myocardial infarction: comparison of post-challenge versus fasting glucose concentrations. Heart. 2012;98(11):848-54.
135. Chattopadhyay S, George A, John J, Sathyapalan T. Adjustment of the GRACE score by 2-hour post-load glucose improves prediction of long-term major adverse cardiac events in acute coronary syndrome in patients without known diabetes. Eur Heart J. 2018;39(29):2740-5.
136. George A, Bhatia RT, Buchanan GL, Whiteside A, Moisey RS, Beer SF, et al. Impaired Glucose Tolerance or Newly Diagnosed Diabetes Mellitus Diagnosed during Admission Adversely Affects Prognosis after Myocardial Infarction: An Observational Study. PLoS One. 2015;10(11):e0142045.
137. Schnell O, Doerr R, Lodwig V, Weissmann J, Lohmann T. A 3-year follow-up of the Silent Diabetes Study. Diabetologia. 2014;57(12):2596-8.
138. Chen WL, Sheu WH, Li YH, Wang JS, Lee WJ, Liang KW, et al. Newly diagnosed diabetes based on an oral glucose tolerance test predicts cardiovascular outcomes in patients with coronary artery disease: An observational study. Medicine (Baltimore). 2022;101(28):e29557.

139. Shahim B, De Bacquer D, De Backer G, Gyberg V, Kotseva K, Mellbin L, et al. 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;40(9):1233-40.
140. Anselmino M, Malmberg K, Ohrvik J, Ryden L. Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. Eur J Cardiovasc Prev Rehabil. 2008;15(2):216-23.
141. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91.
142. Rawshani A, Rawshani A, Franzen S, Sattar N, Eliasson B, Svensson AM, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379(7):633-44.
143. Gyberg V, De Bacquer D, De Backer G, Jennings C, Kotseva K, Mellbin L, et al. Patients with coronary artery disease and diabetes need improved management: a report from the EUROASPIRE IV survey: a registry from the EuroObservational Research Programme of the European Society of Cardiology. Cardiovasc Diabetol. 2015;14:133.
144. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. Circulation. 2008;117(23):3031-8.
145. Euroaspire I, Group II, European Action on Secondary Prevention by Intervention to Reduce E. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. Lancet. 2001;357(9261):995-1001.
146. Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016;23(6):636-48.
147. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019;26(8):824-35.
148. Schiebinger L, Klinge I, Sánchez de Madariaga I, Paik H, Schraudner M, Stefanick M. Gendered innovations in science, health, medicine, engineering and environment. 2011–2015. Available at http://genderedinnovations.stanford.edu/ Accessed January 23, 2023.
149. https://cihr-irsc.gc.ca/e/48642.html. Accessed january 23, 2023.
150. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.
151. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016;133(9):916-47.
152. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med. 1999;341(4):226-32.
153. Yusuf S, Pearson M, Sterry H, Parish S, Ramsdale D, Rossi P, et al. The entry ECG in the early diagnosis and prognostic stratification of patients with suspected acute myocardial infarction. Eur Heart J. 1984;5(9):690-6.
154. Norhammar A, Schenck-Gustafsson K. Type 2 diabetes and cardiovascular disease in women. Diabetologia. 2013;56(1):1-9.

155. Campesi I, Seghieri G, Franconi F. Type 2 diabetic women are not small type 2 diabetic men: Sex-and-gender differences in antidiabetic drugs. Curr Opin Pharmacol. 2021;60:40-5.
156. Tamargo J, Rosano G, Walther T, Duarte J, Niessner A, Kaski JC, et al. Gender differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother. 2017;3(3):163-82.
157. Lee TTL, Hui JMH, Lee YHA, Satti DI, Shum YKL, Kiu PTH, et al. Sulfonylurea Is Associated With Higher Risks of Ventricular Arrhythmia or Sudden Cardiac Death Compared With Metformin: A Population-Based Cohort Study. J Am Heart Assoc. 2022;11(18):e026289.
158. Joung KI, Jung GW, Park HH, Lee H, Park SH, Shin JY. Gender differences in adverse event reports associated with antidiabetic drugs. Sci Rep. 2020;10(1):17545.
159. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes. 2010;3(2):135-42.
160. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur Heart J. 2006;27(8):994-1005.
161. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet. 2014;383(9933):1973-80.
162. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014;57(8):1542-51.
163. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. Bmj. 2006;332(7533):73-8.
164. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. Lancet Diabetes Endocrinol. 2018;6(7):538-46.
165. Dotevall A, Rosengren A, Bartnik M, Malmberg K, Ohrvik J, Simoons M, et al. Sex-related aspects on abnormal glucose regulation in patients with coronary artery disease. Eur Heart J. 2007;28(3):310-5.
166. Peters SA, Huxley RR, Sattar N, Woodward M. Sex Differences in the Excess Risk of Cardiovascular Diseases Associated with Type 2 Diabetes: Potential Explanations and Clinical Implications. Curr Cardiovasc Risk Rep. 9. United States2015. p. 36.
167. Donahue RP, Rejman K, Rafalson LB, Dmochowski J, Stranges S, Trevisan M. Sex differences in endothelial function markers before conversion to pre-diabetes: does the clock start ticking earlier among women? The Western New York Study. Diabetes Care. 2007;30(2):354-9.
168. Wright AK, Kontopantelis E, Emsley R, Buchan I, Mamas MA, Sattar N, et al. Cardiovascular Risk and Risk Factor Management in Type 2 Diabetes Mellitus. Circulation. 2019;139(24):2742-53.
169. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457-71.
170. Hennekens CH, Hebert PR, Schneider WR, O'Brien P, Demets D, Borer JS. Academic perspectives on the United States Food and Drug Administration's guidance for industry on diabetes mellitus. Contemp Clin Trials. 2010;31(5):411-3.
171. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.

172. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-57.
173. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.
174. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-22.
175. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-44.
176. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019;381(9):841-51.
177. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519-29.
178. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-30.
179. Rydén L, Ferrannini G, Mellbin L. Is cardioprotection with GLP-1 receptor agonists a class effect? Eur J Prev Cardiol. 2021;28(1):18-21.
180. Ferrannini G, Savarese G, Rydén L. Sodium glucose transporter inhibition in heart failure From an unexpected side effect to a novel treatment possibility. Diabetes Res Clin Pract. 2021:108796.
181. Giugliano D, Longo M, Signoriello S, Maiorino MI, Solerte B, Chiodini P, et al. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. Cardiovasc Diabetol. 2022;21(1):42.
182. Ferrari F, Scheffel RS, Martins VM, Santos RD, Stein R. Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes Mellitus and Cardiovascular Disease: The Past, Present, and Future. Am J Cardiovasc Drugs. 2022;22(4):363-83.
183. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021;6(2):148-58.
184. Standl E, Schnell O. Treatment Paradigm Shifting Implications of Recent Cardiovascular Outcome Trials: Core Insights on the Brink of the 2020ies. Diabetes Res Clin Pract. 2020:108054.
185. Inzucchi SE, Fitchett D, Jurišić-Eržen D, Woo V, Hantel S, Janista C, et al. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? Diabetes Obes Metab. 2020;22(4):631-9.
186. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. Diabetes Obes Metab. 2018;20(1):42-9.
187. Segerhag E, Gyberg V, Ioannides K, Jennings C, Ryden L, Stagmo M, et al. Accuracy of a Simplified Glucose Measurement Device--The HemoCue Glucose 201RT. Diabetes Technol Ther. 2015;17(10):755-8.

188. 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 Dysglycemia in Patients with Coronary Artery Disease. Diabetes Technol Ther. 2018;20(9):596-602.
189. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21(12):2191-2.
190. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701.
191. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035-87.
192. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
193. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
194. De Bacquer D, De Smedt D, Kotseva K, Jennings C, Wood D, Ryden L, et al. Incidence of cardiovascular events in patients with stabilized coronary heart disease: the EUROASPIRE IV follow-up study. Eur J Epidemiol. 2019;34(3):247-58.
195. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Tuomilehto J, et al. Time-saving screening for diabetes in patients with coronary artery disease: a report from EUROASPIRE IV. BMJ Open. 2016;6(12):e013835.
196. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28(1):88-136.
197. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81.
198. Laichuthai N, Abdul-Ghani M, Kosiborod M, Parksook WW, Kerr SJ, DeFronzo RA. Newly Discovered Abnormal Glucose Tolerance in Patients With Acute Myocardial Infarction and Cardiovascular Outcomes: A Meta-analysis. Diabetes Care. 2020;43(8):1958-66.
199. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV--a survey from the European Society of Cardiology. Eur Heart J. 2015;36(19):1171-7.
200. Ferrannini G, De Bacquer D, De Backer G, Kotseva K, Mellbin L, Wood D, et al. Screening for Glucose Perturbations and Risk Factor Management in Dysglycemic Patients With Coronary Artery Disease-A Persistent Challenge in Need of Substantial Improvement: A Report From ESC EORP EUROASPIRE V. Diabetes Care. 2020;43(4):726-33.
201. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20(4):537-44.

202. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, et al. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care. 2003;26(12):3230-6.
203. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97.
204. Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC, et al. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetologia. 2009;52(6):1019-26.
205. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005;67(2):152-62.
206. Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, et al. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 2011;171(15):1352-60.
207. Madsen KS, Chi Y, Metzendorf MI, Richter B, Hemmingsen B. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database Syst Rev. 2019;12(12):CD008558.
208. Chatzianagnostou K, Vigna L, Di Piazza S, Tirelli AS, Napolitano F, Tomaino L, et al. Low concordance between HbA1c and OGTT to diagnose prediabetes and diabetes in overweight or obesity. Clin Endocrinol (Oxf). 2019;91(3):411-6.
209. Evans WJ. Diagnostic criteria for the diagnosis of type 2 diabetes: Discordance of multiple measures. Clin Endocrinol (Oxf). 2019;91(6):716-7.
210. Malkani S, Mordes JP. Implications of using hemoglobin A1C for diagnosing diabetes mellitus. Am J Med. 2011;124(5):395-401.
211. Bridges KR, Schmidt GJ, Jensen M, Cerami A, Bunn HF. The acetylation of hemoglobin by aspirin. In vitro and in vivo. J Clin Invest. 1975;56(1):201-7.
212. Weykamp CW, Penders TJ, Muskiet FA, van der Slik W. Influence of hemoglobin variants and derivatives on glycohemoglobin determinations, as investigated by 102 laboratories using 16 methods. Clin Chem. 1993;39(8):1717-23.
213. Welsh C, Welsh P, Celis-Morales CA, Mark PB, Mackay D, Ghouri N, et al. Glycated Hemoglobin, Prediabetes, and the Links to Cardiovascular Disease: Data From UK Biobank. Diabetes Care. 2020;43(2):440-5.
214. Group DS. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care. 2003;26(1):61-9.
215. Glumer C, Jorgensen T, Borch-Johnsen K, Inter s. Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. Diabetes Care. 2003;26(8):2335-40.
216. Qiao Q, Hu G, Tuomilehto J, Nakagami T, Balkau B, Borch-Johnsen K, et al. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care. 2003;26(6):1770-80.
217. Succurro E, Marini MA, Riccio A, Fiorentino TV, Perticone M, Sciacqua A, et al. Sex-differences in insulin sensitivity and insulin secretion in subjects with impaired fasting glucose and impaired glucose tolerance. Diabetes Res Clin Pract. 2022;194:110185.
218. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016;37(3):278-316.

219. Logue J, Walker JJ, Colhoun HM, Leese GP, Lindsay RS, McKnight JA, et al. Do men develop type 2 diabetes at lower body mass indices than women? Diabetologia. 2011;54(12):3003-6.
220. Peddinti G, Bergman M, Tuomi T, Groop L. 1-Hour Post-OGTT Glucose Improves the Early Prediction of Type 2 Diabetes by Clinical and Metabolic Markers. J Clin Endocrinol Metab. 2019;104(4):1131-40.
221. Fiorentino TV, Andreozzi F, Mannino GC, Pedace E, Perticone M, Sciacqua A, et al. One-Hour Postload Hyperglycemia Confers Higher Risk of Hepatic Steatosis to HbA1c-Defined Prediabetic Subjects. J Clin Endocrinol Metab. 2016;101(11):4030-8.
222. Jagannathan R, Sevick MA, Fink D, Dankner R, Chetrit A, Roth J, et al. The 1-hour post-load glucose level is more effective than HbA1c for screening dysglycemia. Acta Diabetol. 2016;53(4):543-50.
223. Park SK, Ryoo JH, Oh CM, Choi JM, Jung JY. 1-Hour and 2-Hour Postload Glucose Level on Oral Glucose Tolerance Test and the Risk of Incident Metabolic Syndrome. J Clin Endocrinol Metab. 2019;104(2):539-49.
224. Lizarzaburu-Robles JC, Torres-Aparcana L, Mansilla R, Valera J, Vargas G, Vento F, et al. A Cross-Sectional Study of the Association between the 1-Hour Oral Glucose Tolerance Test and the Metabolic Syndrome in a High-Risk Sample with Impaired Fasting Glucose. Endocr Pract. 2020;26(5):529-34.
225. Succurro E, Marini MA, Arturi F, Grembiale A, Lugara M, Andreozzi F, et al. Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. Atherosclerosis. 2009;207(1):245-9.
226. Sciacqua A, Maio R, Miceli S, Pascale A, Carullo G, Grillo N, et al. Association between one-hour post-load plasma glucose levels and vascular stiffness in essential hypertension. PLoS One. 2012;7(9):e44470.
227. Pareek M, Bhatt DL, Nielsen ML, Jagannathan R, Eriksson KF, Nilsson PM, et al. Enhanced Predictive Capability of a 1-Hour Oral Glucose Tolerance Test: A Prospective Population-Based Cohort Study. Diabetes Care. 2018;41(1):171-7.
228. Cao L, Wang P, Luan H, Chen H, Luo C, Zhu D, et al. Elevated 1-h postload plasma glucose levels identify coronary heart disease patients with greater severity of coronary artery lesions and higher risk of 1-year re-admission. Diab Vasc Dis Res. 2020;17(1):1479164119896978.
229. Zywicki V, Capozza P, Caravelli P, Del Prato S, De Caterina R. Glucose tolerance and markers of myocardial injury after an acute coronary syndrome: predictive role of the 1-h plus 2-h plasma glucose at the oral glucose tolerance test. Cardiovasc Diabetol. 2022;21(1):152.
230. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, Temelkova-Kurktschiev T, et al. Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: the risk factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study. Diabetes Care. 2003;26(3):868-74.
231. Tripathy D, Carlsson M, Almgren P, Isomaa B, Taskinen MR, Tuomi T, et al. Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. Diabetes. 2000;49(6):975-80.
232. Lu MC, Fang WC, Li WC, Yeh WC, Shieh YH, Chen JY. The Association between Insulin Resistance and Cardiovascular Disease Risk: A Community-Based Cross-Sectional Study among Taiwanese People Aged over 50 Years. Int J Environ Res Public Health. 2020;17(19).
233. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. Diabetes Care. 2007;30(2):318-24.

234. Yanase M, Takatsu F, Tagawa T, Kato T, Arai K, Koyasu M, et al. Insulin resistance and fasting hyperinsulinemia are risk factors for new cardiovascular events in patients with prior coronary artery disease and normal glucose tolerance. Circ J. 2004;68(1):47-52.
235. Hellgren MI, Daka B, Jansson PA, Lindblad U, Larsson CA. Insulin resistance predicts early cardiovascular morbidity in men without diabetes mellitus, with effect modification by physical activity. Eur J Prev Cardiol. 2015;22(7):940-9.
236. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One. 2012;7(12):e52036.
237. Barr EL, Cameron AJ, Balkau B, Zimmet PZ, Welborn TA, Tonkin AM, et al. HOMA insulin sensitivity index and the risk of all-cause mortality and cardiovascular disease events in the general population: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) study. Diabetologia. 2010;53(1):79-88.
238. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Sr., Wilson PW. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes. 2005;54(11):3252-7.
239. Rawshani A, Rawshani A, Franzen S, Eliasson B, Svensson AM, Miftaraj M, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med. 2017;376(15):1407-18.
240. EUROASPIRE. A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. EUROASPIRE Study Group. European Action on Secondary Prevention through Intervention to Reduce Events. Eur Heart J. 1997;18(10):1569-82.
241. Anselmino M, Malmberg K, Ohrvik J, Ryden L, Euro Heart Survey I. Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. Eur J Cardiovasc Prev Rehabil. 2008;15(2):216-23.
242. Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379(7):633-44.
243. Oellgaard J, Gaede P, Rossing P, Rorth R, Kober L, Parving HH, et al. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study. Diabetologia. 2018;61(8):1724-33.
244. Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, et al. Cardiovascular Risk Factor Targets and Cardiovascular Disease Event Risk in Diabetes: A Pooling Project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. Diabetes Care. 2016;39(5):668-76.
245. Bittner V, Bertolet M, Barraza Felix R, Farkouh ME, Goldberg S, Ramanathan KB, et al. Comprehensive Cardiovascular Risk Factor Control Improves Survival: The BARI 2D Trial. J Am Coll Cardiol. 2015;66(7):765-73.
246. Pagidipati NJ, Navar AM, Pieper KS, Green JB, Bethel MA, Armstrong PW, et al. Secondary Prevention of Cardiovascular Disease in Patients With Type 2 Diabetes Mellitus: International Insights From the TECOS Trial (Trial Evaluating Cardiovascular Outcomes With Sitagliptin). Circulation. 2017;136(13):1193-203.
247. Vedin O, Hagstrom E, Stewart R, Brown R, Krug-Gourley S, Davies R, et al. Secondary prevention and risk factor target achievement in a global, high-risk population with established coronary heart disease: baseline results from the STABILITY study. Eur J Prev Cardiol. 2013;20(4):678-85.

248. Fan W, Song Y, Inzucchi SE, Sperling L, Cannon CP, Arnold SV, et al. Composite cardiovascular risk factor target achievement and its predictors in US adults with diabetes: The Diabetes Collaborative Registry. Diabetes Obes Metab. 2019;21(5):1121-7.
249. Zuo HJ, Wang WH, Deng LQ, Su JL. Control of cardiovascular disease risk factors among patients with type II diabetes in a primary-care setting in Beijing. J Am Soc Hypertens. 2018;12(2):128-34.
250. Andary R, Fan W, Wong ND. Control of Cardiovascular Risk Factors Among US Adults With Type 2 Diabetes With and Without Cardiovascular Disease. Am J Cardiol. 2019;124(4):522-7.
251. Wong ND, Patao C, Wong K, Malik S, Franklin SS, Iloeje U. Trends in control of cardiovascular risk factors among US adults with type 2 diabetes from 1999 to 2010: comparison by prevalent cardiovascular disease status. Diab Vasc Dis Res. 2013;10(6):505-13.
252. Marx N, Ryden L, Brosius F, Ceriello A, Cheung M, Cosentino F, et al. Proceedings of the Guideline Workshop 2019 - Strategies for the optimization of guideline processes in diabetes, cardiovascular diseases and kidney diseases. Diabetes Res Clin Pract. 2020;162:108092.
253. American Diabetes Association. Standards of Care in Diabetes - 2023. https://diabetesjournals.org/care/issue/46/Supplement_1. Accessed 16 January 2023.
254. American Diabetes Association. Standards of Care in Diabetes—2023 Abridged for Primary Care Providers. https://diabetesjournals.org/clinical/article/doi/10.2337/cd23-as01/148029/Standards-of-Care-in-Diabetes-2023-Abridged-for. Accessed 16 January 2023.
255. Johansson M, Guyatt G, Montori V. Guidelines should consider clinicians' time needed to treat. BMJ. 2023;380:e072953.
256. De Backer G, Jankowski P, Kotseva K, Mirrakhimov E, Reiner Z, Ryden L, et al. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. Atherosclerosis. 2019;285:135-46.
257. Pogosova N, Kotseva K, De Bacquer D, von Kanel R, De Smedt D, Bruthans J, et al. Psychosocial risk factors in relation to other cardiovascular risk factors in coronary heart disease: Results from the EUROASPIRE IV survey. A registry from the European Society of Cardiology. Eur J Prev Cardiol. 2017;24(13):1371-80.
258. SWEDEHEART Annual Report 2021. https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh. Accessed on 06 February, 2023.
259. Michelsen HO, Henriksson P, Wallert J, Back M, Sjolin I, Schlyter M, et al. Organizational and patient-level predictors for attaining key risk factor targets in cardiac rehabilitation after myocardial infarction: The Perfect-CR study. Int J Cardiol. 2023;371:40-8.
260. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. Ann Intern Med. 2005;143(9):659-72.
261. Minneboo M, Lachman S, Snaterse M, Jorstad HT, Ter Riet G, Boekholdt SM, et al. Community-Based Lifestyle Intervention in Patients With Coronary Artery Disease: The RESPONSE-2 Trial. J Am Coll Cardiol. 2017;70(3):318-27.
262. Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, et al. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. Lancet. 2008;371(9629):1999-2012.
263. Gouni-Berthold I, Berthold HK, Mantzoros CS, Böhm M, Krone W. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. Diabetes Care. 2008;31(7):1389-91.

264. Sekerija M, Poljicanin T, Erjavec K, Liberati-Cizmek AM, Prašek M, Metelko Z. Gender differences in the control of cardiovascular risk factors in patients with type 2 diabetes -a cross-sectional study. Intern Med. 2012;51(2):161-6.
265. Hambraeus K, Tydén P, Lindahl B. Time trends and gender differences in prevention guideline adherence and outcome after myocardial infarction: Data from the SWEDEHEART registry. Eur J Prev Cardiol. 2016;23(4):340-8.
266. Zhao M, Vaartjes I, Graham I, Grobbee D, Spiering W, Klipstein-Grobusch K, et al. Sex differences in risk factor management of coronary heart disease across three regions. Heart. 2017;103(20):1587-94.
267. Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. Sex differences in the risk of stroke and HbA(1c) among diabetic patients. Diabetologia. 2014;57(5):918-26.
268. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. Diabetes Care. 2005;28(3):514-20.
269. Norhammar A. Diabetes and cardiovascular mortality: the impact of sex. Lancet Diabetes Endocrinol. 2018;6(7):517-9.
270. Sardinha A, Araújo CG, Soares-Filho GL, Nardi AE. Anxiety, panic disorder and coronary artery disease: issues concerning physical exercise and cognitive behavioral therapy. Expert Rev Cardiovasc Ther. 2011;9(2):165-75.
271. Malmborg M, Schmiegelow MDS, Nørgaard CH, Munch A, Gerds T, Schou M, et al. Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared with men? Eur Heart J. 2020;41(13):1346-53.
272. Sara JD, Taher R, Kolluri N, Vella A, Lerman LO, Lerman A. Coronary microvascular dysfunction is associated with poor glycemic control amongst female diabetics with chest pain and non-obstructive coronary artery disease. Cardiovasc Diabetol. 2019;18(1):22.
273. Brzezinski RY, Etz-Hadar I, Grupper A, Ehrenwald M, Shapira I, Zeltser D, et al. Sex difference in the risk for exercise-induced albuminuria correlates with hemoglobin A1C and abnormal exercise ECG test findings. Cardiovasc Diabetol. 2017;16(1):79.
274. Succurro E, Fiorentino TV, Miceli S, Perticone M, Sciacqua A, Andreozzi F, et al. Relative Risk of Cardiovascular Disease Is Higher in Women With Type 2 Diabetes, but Not in Those With Prediabetes, as Compared With Men. Diabetes Care. 2020;43(12):3070-8.
275. Juutilainen A, Kortelainen S, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care. 2004;27(12):2898-904.
276. Standl E, Schnell O. Treatment paradigm shifting implications of recent cardiovascular outcome trials: Core insights on the brink of the 2020ies. Diabetes Res Clin Pract. 2020;161:108054.
277. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.
278. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med. 2016;164(11):740-51.
279. Scheen AJ, Paquot N. Metformin revisited: a critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. Diabetes Metab. 2013;39(3):179-90.
280. Goldberg RB, Orchard TJ, Crandall JP, Boyko EJ, Budoff M, Dabelea D, et al. Effects of Long-term Metformin and Lifestyle Interventions on Cardiovascular Events in the Diabetes Prevention Program and Its Outcome Study. Circulation. 2022;145(22):1632-41.
281. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2011;13(3):221-8.

282. Crowley MJ, McGuire DK, Alexopoulos AS, Jensen TJ, Rasmussen S, Saevereid HA, et al. Effects of Liraglutide on Cardiovascular Outcomes in Type 2 Diabetes Patients With and Without Baseline Metformin Use: Post Hoc Analyses of the LEADER Trial. Diabetes Care. 2020.
283. Bethel MA, Stevens SR, Buse JB, Choi J, Gustavson SM, Iqbal N, et al. Exploring the Possible Impact of Unbalanced Open-Label Drop-In of Glucose-Lowering Medications on EXSCEL Outcomes. Circulation. 2020;141(17):1360-70.
284. Wallander M, Malmberg K, Norhammar A, Ryden L, Tenerz A. Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study. Diabetes Care. 2008;31(1):36-8.
285. Boye KS, Riddle MC, Gerstein HC, Mody R, Garcia-Perez LE, Karanikas CA, et al. Generalizability of glucagon-like peptide-1 receptor agonist cardiovascular outcome trials to the overall type 2 diabetes population in the United States. Diabetes Obes Metab. 2019;21(6):1299-304.
286. McEvoy JW, Jennings C, Kotseva K, De Backer G, De Bacquer D, Erlund I, et al. INTERASPIRE: an International Survey of Coronary Patients; Their Cardiometabolic, Renal and Biomarker Status; and the Quality of Preventive Care Delivered in All WHO Regions : In Partnership with the World Heart Federation, European Society of Cardiology, Asia Pacific Society of Cardiology, InterAmerican Society of Cardiology, and PanAfrican Society of Cardiology. Curr Cardiol Rep. 2021;23(10):136.