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

Causes and mechanisms of an adverse outcome in patients with glucose abnormalities and cardiovascular disease – epidemiological and biochemical analyses

by

Viveca Ritsinger

Karolinska Institutet

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To my family

”Den mätta dagen, den är aldrig störst.
Den bästa dagen är en dag av törst.
Nog finns det mål och mening i vår färd -
men det är vägen, som är mödan värd.
Det bästa målet är en nattlång rast,
där elden tänds och brödet bryts i hast.
På ställen, där man sover blott en gång,
blir sömnen trygg och drömmen full av sång.
Bryt upp, bryt upp! Den nya dagen gryr.
Oändligt är vårt stora äventyr.”

I rörelse. Karin Boye 1927

CONTENTS

Abstract

Background: Diabetes and previously undetected glucose abnormalities are common in patients with acute myocardial infarction (AMI). It is well established that patients with diabetes have a higher mortality rate after coronary events than patients without diabetes but the complication pattern in a contemporary perspective, the impact of glucose control and whether unknown glucose abnormalities affect the long-term prognosis is less well studied. Data on the prognostic implications of adipokines in patients with prevalent coronary heart disease are contradictory and long-term outcome studies are lacking.

Aims: To identify high-risk individuals and study long-term prognosis by

1. Investigating the lasting effect of intensified, insulin-based glucose control on mortality after AMI in patients with diabetes.
2. Analysing mortality and morbidity patterns after AMI in patients with newly discovered glucose abnormalities.
3. Investigating complication patterns after a first percutaneous coronary intervention.
4. Analysing the significance of adiponectin and leptin as biomarkers of cardiovascular complications.

Glucose control and mortality after AMI: 306 patients with AMI and diabetes were randomised to intensified insulin-based glycaemic control while 314 served as controls in the DIGAMI-study. During a mean follow-up of 7.3 years 90% of the study population died. The median survival was 2.3 years longer in patients receiving intensified insulin-based glycaemic control after AMI (7.0 years) compared to patients in the control group (4.7 years).

Impact of undetected glucose abnormalities on long-term outcome after AMI: Patients (n=167) with AMI and healthy controls (n=184) without previously known diabetes (included in the GAMI study) were investigated with an oral glucose tolerance test (OGTT) at the time of hospital discharge (patients) or at inclusion (controls). Cardiovascular events (cardiovascular mortality, AMI, heart failure and stroke) during 10 years of follow-up were more frequent in patients with abnormal glucose tolerance than in patients with normal glucose tolerance and in controls. Abnormal glucose tolerance at the OGTT was independently associated with future cardiovascular events after an AMI (HR 2.30; 95% CI 1.24-4.25, p=0.008) in contrast to HbA1c (p=0.81) and fasting blood glucose (p=0.52).

Long-term outcome after coronary artery disease and revascularisation: High event rates of mortality, heart failure, myocardial infarction and stroke were demonstrated after a first percutaneous coronary intervention in patients with diabetes followed up to five years after inclusion in the Swedish Coronary Angiography Angioplasty Registry (SCAAR) between 2006-2010 (n=58891, 19% with diabetes). Diabetes was an independent predictor for mortality and cardiovascular events. Insulin-treated patients were at a particularly high risk.

Adiponectin and leptin as biomarkers for identifying high risk patients: In 180 patients with AMI and without diabetes (the GAMI cohort) elevated levels of adiponectin at discharge independently predicted mortality (HR 1.79; 95% CI 1.07-3.00, p=0.027) but not cardiovascular events the coming decade. High levels of leptin at day 2 were associated with cardiovascular events during the first seven years but did not predict mortality.

Conclusion: Diabetes and previously undetected glucose abnormalities are common in patients with coronary events and their presence has a negative influence on the prognosis. Despite improved longevity patients with diabetes are still at increased risk for mortality and cardiovascular complications. An OGTT, but not HbA1c, identifies patients with previously undetected glucose abnormalities at increased cardiovascular risk the next coming 10 years. These findings support that an OGTT should be considered as an important screening tool after AMI. High levels of adiponectin and leptin identifies patients with compromised outcome after AMI. Future studies are warranted to confirm their role as suitable biomarkers. Finally a close follow-up of patients with glucose abnormalities is advocated where multifactorial treatment is important to improve long-term survival after AMI. The present studies do also underline that new treatment strategies are highly warranted.

SAMMANFATTNING

Bakgrund: Diabetes och tidigare oupptäckt glukosstörning är vanligt hos patienter med akut hjärtinfarkt. Patienter med diabetes har högre dödlighet efter kranskärlshändelser men hur komplikationerna ser ut i ett modernt perspektiv efter en sådan händelse är mindre känt. Vidare är det oklart om glukoskontroll och okända glukosstörningar påverkar den långsiktiga prognosen. Uppgifter om adipokiners prognostiska roll hos patienter med akut hjärtinfarkt är motsägelsefulla och långtidsstudier saknas.

Mål: Att identifiera högriskindivider och studera den långsiktiga prognosen genom att

1. Utvärdera den varaktiga effekten av intensifierad insulinbaserad blodsockerkontroll efter akut hjärtinfarkt hos patienter med känd diabetes
2. Undersöka komplikationsmönster efter hjärtinfarkt hos patienter med nyupptäckta glukosstörningar
3. Studera komplikationsmönster efter ett första kateterburet kranskärlsingrepp
4. Analysera betydelsen av biomarkörerna adiponektin och leptin för kardiovaskulära komplikationer efter en akut hjärtinfarkt

Glukoskontroll och dödlighet efter akut hjärtinfarkt: I DIGAMI-studien randomiserades 306 patienter med akut hjärtinfarkt och diabetes till intensifierad insulinbaserad glukoskontroll och 314 till konventionell behandling. Under en genomsnittlig uppföljningsperiod på 7.3 år avled 90% av studiepopulationen. Medianöverlevnaden ökade med 2.3 år hos patienter som erhöll intensifierad insulinbaserad glukoskontroll jämfört med patienterna i kontrollgruppen.

Långsiktiga effekter av oupptäckta glukosstörningar vid akut hjärtinfarkt: I GAMI-studien undersöktes patienter (n=167) med akut hjärtinfarkt och friska kontroller (n=184) utan tidigare känd diabetes med glukosbelastning (OGTT) vid utskrivning (patienter) eller vid inklusion (kontroller). Under den 10 år långa uppföljningen var kardiovaskulära händelser (kardiovaskulär dödlighet, hjärtinfarkt, hjärtsvikt och stroke) vanligare hos patienter med nyupptäckt glukosstörning jämfört med patienter med normal glukostolerans och vanligare än i kontrollgruppen. Glukosstörning upptäckt med OGTT var en oberoende riskfaktor för framtida kardiovaskulära händelser efter akut hjärtinfarkt (HR 2.30, 95% CI 1.24-4.25, p=0.008) till skillnad från HbA1c (p=0.81) och fasteblodsocker (p=0.52).

Långsiktig prognos efter kranskärlssjukdom och revaskularisering: En hög komplikationsfrekvens (dödlighet, hjärtsvikt, hjärtinfarkt och stroke) under fem års uppföljning sågs hos patienter med diabetes som genomgick ett första kateterburet kranskärlsingrepp och inkluderades i Svenska Koronarangiografi och Angioplastik Registret (SCAAR) mellan 2006-2010 (n=58891, 19% med diabetes). Diabetes var en oberoende riskfaktor för dödlighet och kardiovaskulära händelser där särskilt hög risk sågs hos insulinbehandlade patienter.

Adiponektin och leptin som biomarkörer för att identifiera högriskpatienter: Förhöjda nivåer av adiponektin 4-5 dagar efter en hjärtinfarkt var en oberoende markör för dödlighet det följande decenniet (HR 1.79; 95% CI 1.07-3.00, p=0.027) men inte för kardiovaskulära händelser hos patienter utan tidigare känd diabetes (n=180; GAMI kohorten). Höga nivåer av leptin dag två var relaterat till kardiovaskulära händelser under de följande sju åren men var inte relaterat till dödlighet.

Slutsats: Diabetes och tidigare oupptäckt glukosstörning är vanligt hos patienter med kranskärlssjukdom och påverkar prognosen negativt. Trots förbättrad livslängd har patienter med diabetes fortfarande en ökad risk för förtida dödlighet samt nya kardiovaskulära händelser. OGTT, men inte HbA1c, identifierar individer med tidigare oupptäckt glukosstörning och med samtidig ökad risk för kardiovaskulära händelser det kommande decenniet efter en hjärtinfarkt. OGTT bör därför övervägas utgöra ett screeningverktyg efter akut hjärtinfarkt. Höga nivåer av adiponektin och leptin identifierar patienter med sämre prognos efter akut hjärtinfarkt. Sammantaget bör patienter med glukosstörningar bli föremål för en noggrann uppföljning där multifaktoriell behandling och nya behandlingsstrategier är viktigt för att förbättra den långsiktiga överlevnaden och minska sjukligheten efter hjärtinfarkt.

List of Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AGT	Abnormal glucose tolerance
AMI	Acute myocardial infarction
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
DCCT	The Diabetes Control and Complications Trial
DIGAMI	Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction
EMPA-REG OUTCOME	(Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
FFA	Free fatty acids
GAMI	Glucose Tolerance in Patients with Acute Myocardial Infarction
HOMA-IR	Homeostasis model assessment of insulin resistance
IFG	Impaired fasting glucose
IGI	Insulinogenic index
IGT	Impaired glucose tolerance
IKKβ	IkappaB kinase-beta
IL-6	Interleukin-6
JNK	Jun N-terminal kinase
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
NFkB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen activator inhibitor-1
PCI	Percutaneous coronary intervention
ROS	Reactive oxygen species
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
TNF-α	Tumor necrosis factor-alpha
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation

List of Original Papers

This thesis is based on the following studies, which will be referred to by their Roman numerals.

I. Ritsinger V, Malmberg K, Mårtensson A, Rydén L, Wedel H, Norhammar A.
Intensified insulin-based glycaemic control after myocardial infarction improves long-term survival. Twenty-year follow-up of the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study.
Lancet Diabetes Endocrinol 2014;2(8):627-33.

II. Ritsinger V, Tanoglidi E, Malmberg K, Näsman P, Rydén L, Tenerz Å, Norhammar A.
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.

III. Ritsinger V, Saleh N, Lagerqvist B, Norhammar A.
High event rate after a first percutaneous coronary intervention (PCI) in patients with diabetes. Results from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).
Circ Cardiovasc Interv 2015;8(6):e002328.

IV. Ritsinger V, Brismar K, Malmberg K, Mellbin L, Näsman P, Rydén L, Söderberg S, Tenerz Å, Norhammar A.
Elevated levels of adipokines predict outcome after acute myocardial infarction – a long-term follow up of the GAMI cohort.
Diab Vasc Dis Res 2017; In press.

Introduction

Diabetes from an historical perspective

Diabetes has been known for thousands of years and a disease resembling diabetes was first described by the Egyptians 3000-1500 years before Christ. Aretaeus of Cappadocia referred to the disease as diabetes, a composite of the Greek words *dia* (across) and *bainein* (to straddle) meaning "the passage of large quantities of urine". *Mellitus* (honey) was added by Thomas Willis as the glucose-rich urine tasted like honey. In 1776, the glucose concentration in urine was shown to be increased in patients with diabetes.[1] However, until the beginning of the 19th century, the diagnosis of diabetes was mainly based on the taste of urine and as a result the diagnosis was fairly uncommon. In 1869, Paul Langerhans reported two cellular systems in the pancreas and several years later one of them was named the "islets of Langerhans" by Gustave-Édouard Laguesse. Twenty years later, in 1889, Joseph von Mering and Oskar Minkowski demonstrated that dogs in which the pancreas had been removed developed diabetes.[2] At the end of the 19th century tools for measuring glucose in urine became available to the public. Accordingly, there was a rise in the diagnosis of diabetes but still without any possible treatment. In 1921, a dramatic change took place in the lives of patients with diabetes, as insulin was discovered by Frederick Banting and Charles Best and the first patient was treated in 1922 (Figure 1).[3] Since then, the pathophysiology of diabetes has been further examined also enabling the development of other classes of glucose-lowering medication. In 1965, the first classification of diabetes was published by the WHO (classification by age). Since then, the WHO has continued to publish and detail the diagnostic criteria for diabetes in 1980,[4] 1985 (1980 and 1985 classification by insulin dependence was used),[5] 1999 (classification by aetiology starts),[6] 2006[7] and 2011.[8]

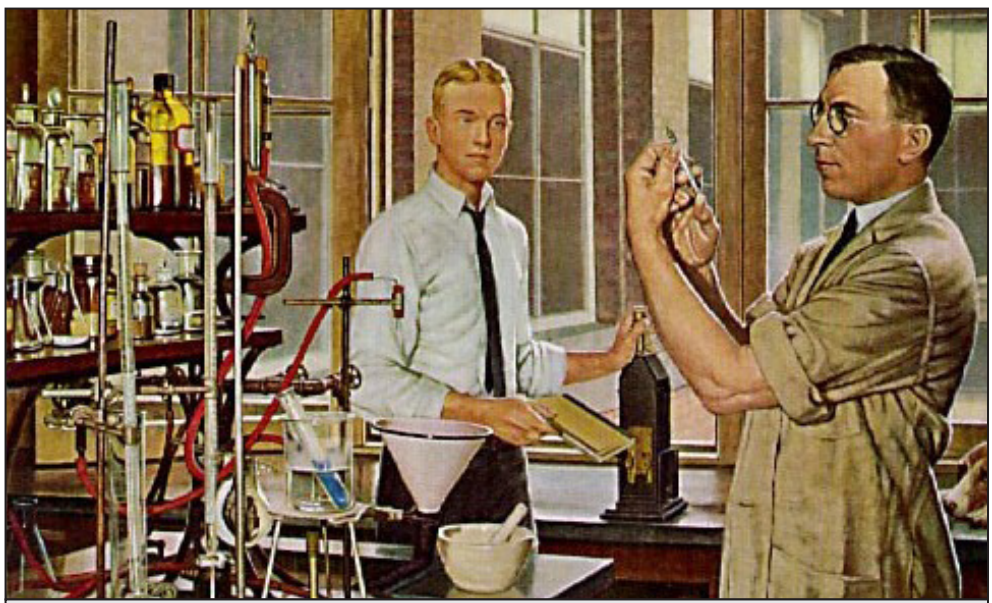


Figure 1. Banting and Best in the laboratory. Unknown artist.

Terminology and aetiology of diabetes

Diabetes is a metabolic disease affecting the carbohydrate, lipid and protein metabolism characterised by chronic hyperglycaemia due to an absolute or relative insulin deficiency. Diabetes mellitus is currently classified in four main forms (Figure 2) where this thesis will focus on type 2 diabetes.

Type 1 diabetes accounts for 5-10% of all diabetes. It is an autoimmune disease that destroys the beta cells in the pancreas, usually leading to an absolute insulin deficiency. The aetiology is not fully understood, but it is considered to be a combination of genetic predisposition and environmental factors.[9]

Type 2 diabetes accounts for 90% of all diabetes. The disease involves a successive increase in insulin resistance and a gradual decrease in beta-cell function with a relative insulin deficiency. The aetiology is complex, with the co-existence of abdominal obesity, hypertension, hyperlipidaemia, physical inactivity, smoking and a genetic predisposition.[9]

Gestational diabetes is defined as hyperglycaemia with onset during pregnancy and is present in approximately 2% of all pregnant women in Sweden.[10] Women with gestational diabetes run an increased risk of developing type 2 diabetes later in life.[9,11]

Other forms of diabetes include genetic disorders, such as defects in beta-cell function or insulin action and diseases of the exocrine pancreas (such as cystic fibrosis) or induced by drugs.[9]

Figure 2. Four main types of diabetes according to the American Diabetes Association.[9]

Impaired glucose regulation

In addition to diabetes, there are states with a higher blood glucose than normal but still not reaching the defined cut-off points for diabetes. These conditions are labelled as impaired glucose regulation and include impaired glucose tolerance (IGT= elevated postprandial blood glucose detected by an oral glucose tolerance test [OGTT]) and impaired fasting glucose (IFG= elevated fasting glucose). It is thought that IFG and IGT probably represent different abnormalities in glucose regulation with IFG more related to impaired insulin secretion and IGT to decreased insulin sensitivity[12] and the metabolic syndrome.[13] Several reports describe a gender difference, where IFG is more common among men and IGT is more common in women.[14-17] It is postulated that the gender differences are due to differences in lipid profile and other parts of the metabolic syndrome in men and women. Impaired glucose regulation is sometimes referred to as "prediabetes" as it is regarded as a condition with an increased risk of future diabetes. This is a process that takes years. The reported annual rate of type 2 diabetes varies from 1-10% in people with IFG and from 2-11% in those with IGT, depending on a diverse risk profile in different study populations.[17-20] For individuals with both IFG and IGT the risk is even higher. In a Swedish population, 14% of those with IFG and 17% of those with IGT developed diabetes after 10 years compared with 49% of those with both IFG and IGT.[17] Several years of lifestyle modification and/or pharmaceutical treatment with metformin, acarbose or rosiglitazone can prevent or delay the progression of IFG and IGT to type 2 diabetes in high-risk patients with obesity or overweight,[21-27] with more extensive

evidence for IGT than IFG. Patients with impaired glucose regulation run an increased risk of cardiovascular disease (CVD) which has been suggested by some to be stronger for IGT than IFG, possibly explained by the closer relationship to the metabolic syndrome or to the higher glucose levels that identify IGT compared with IFG.[28-30]

Classification of diabetes and diagnostic considerations

The currently used criteria for glucose abnormalities according to the WHO are presented in Table 1.[7,8] In 2011, the WHO stated for the first time that HbA1c ≥6.5 DCCT (IFCC ≥48 mmol/mol) could be used as a diagnostic test for diabetes mellitus in addition to fasting blood glucose and the OGTT, where the criteria have remained unchanged since 1999.[8] While the WHO does not state any level of HbA1c as being consistent with "prediabetes", the American Diabetes Association (ADA) has introduced 5.7-6.4% DCCT (IFCC 38-47 mmol/mol) as a cut-off point for prediabetes.[9]

Table 1. Criteria for the diagnosis of diabetes mellitus and other categories of hyperglycaemia according to the WHO in 2006 and 2011.[7,8]

	Glucose concentration (mmol/L)			
	Plasma venous	Plasma capillary	Whole blood capillary	HbA1c mmol/mol
Diabetes mellitus*				≥48
Fasting and/or	≥7.0	≥7.0	≥6.1	
two-hour post-glucose load	≥11.1	≥12.2	≥11.1	
Impaired glucose tolerance				
Fasting and	<7.0	<7.0	<6.1	
two-hour post-glucose load	7.8-11.0	8.9-12.1	7.8-11.0	
Impaired fasting glucose				
Fasting	6.1-6.9	6.1-6.9	5.6-6.0	

*If asymptomatic, an additional glucose test is required to confirm the diagnosis.

Risk factors for type 2 diabetes

The prevalence of type 2 diabetes is related to age and ethnicity. Approximately 50% of patients with type 2 diabetes are older than 60 years.[31] The prevalence of type 2 diabetes in Sweden is 4-7% compared with 50% in Pima Indians.[31,32] Other risk factors associated with diabetes include heredity, obesity (especially visceral adiposity), physical inactivity, smoking, hypertension, dyslipidaemia with hypertriglyceridaemia and low HDL cholesterol.[33,34] Patients who eventually develop type 2 diabetes usually present with several of these risk factors. The term "metabolic syndrome" is used as a state with a clustering of several of the previously listed risk factors, with and without established diabetes. There are several definitions of metabolic syndrome but it typically includes hypertension, visceral adiposity, hyperinsulinaemia, disturbed glucose regulation, increased inflammatory activity, hypofibrinolysis and dyslipidaemia.[6]

Diabetes a global disease

The global prevalence of diabetes is 8.5% in the adult population.[35] According to the International Diabetes Federation 415 million adults around the world suffered from diabetes

in 2015 and another 318 million had IGT.[32] These figures are estimated to rise to 642 million living with type 2 diabetes in 2040 due partly to increased longevity but also influenced by an unhealthy lifestyle with the overconsumption of food, an inappropriate dietary pattern and decreased physical activity. As diabetes is a major risk factor for developing premature atherosclerosis and CVD, this pandemic is of serious concern not only for the individual but also for society causing a major increase in health-care costs.

Pathophysiology and complications of diabetes

The pathophysiology of type 2 diabetes comprises a genetic predisposition to develop insulin resistance in peripheral tissues, mainly the liver and muscles, which is further enhanced by obesity and physical inactivity. To bridge this, the pancreatic beta cells are prompted to increase their production of insulin. Normoglycaemia is preserved as long as the beta cells are able to augment secretion, creating a hyperinsulinaemic state. With time, the beta-cell function becomes compromised thereby reducing the production of insulin. As a consequence, the postprandial glucose and subsequently also the fasting glucose levels are elevated. This is referred to as Starling's curve of the pancreas.[36] Studies report that patients with IGT have already lost approximately 80% of their beta-cell function.[37] The failing pancreatic beta cells combined with the enhanced insulin resistance in the skeletal muscles and liver are often referred to as "the triumvirate".[36] This concept has been further expanded to "the ominous octet", including more recently identified dysfunctional metabolic systems including the adipose tissue with accelerated lipolysis, the gastrointestinal tract with incretin deficiency and resistance, the kidney with increased glucose re-absorption, the pancreatic alpha cells with hyperglucagonaemia and the brain with insulin resistance (Figure 3).[37]

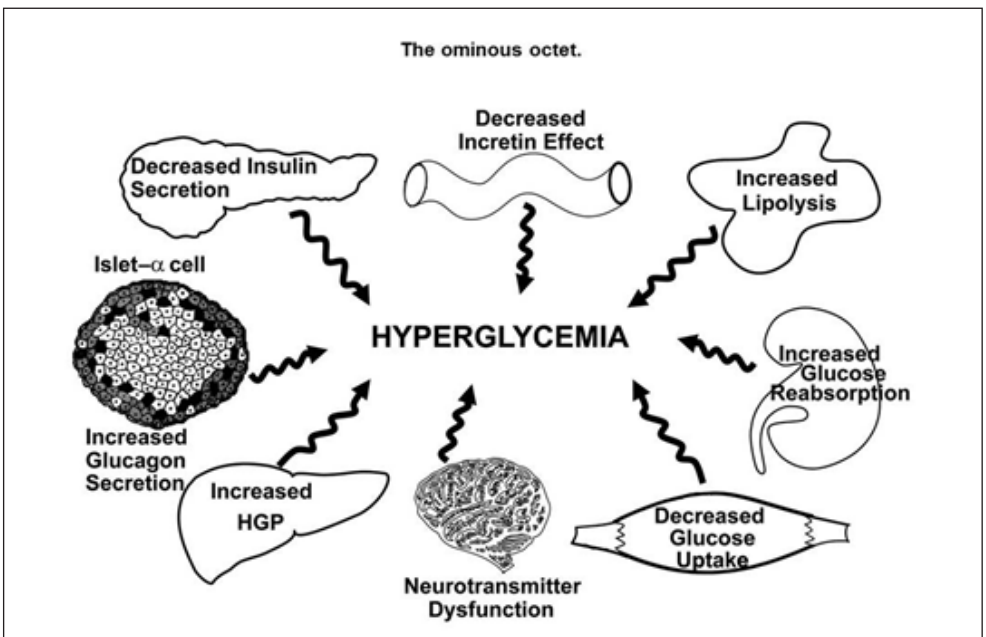


Figure 3. The ominous octet. HGP=Hepatic glucose production. Adapted with permission from DeFronzo.[37]

It is proposed that obesity and insulin resistance are complexly linked together by inflammation. In the presence of obesity, there is an imbalance between energy input and output with a state of nutrient excess triggering responses in several cell types such as vascular endothelial cells,[38] hepatocytes,[39] myocytes,[40] adipocytes,[39] and macrophages. This stimulates the production of reactive oxygen species (ROS) and proinflammatory cytokines, including tumor necrosis factor-α (TNF-α),[41,42] leptin,[43] adiponectin, interleukin-6 (IL-6),[44] resistin[45] and plasminogen activator inhibitor-1 (PAI-1),[46] eventuating the creation of oxidative stress (Figure 4).[47] Further, the endoplasmatic reticulum, which processes proteins into their mature form, becomes affected with an accumulation of fatty acid metabolites as a response.[39,40] This chain of events further enhances inflammation and increases insulin resistance through the activation of the IkappaB kinase-beta (IKKb)/ nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) pathway (where NFkB translocation leads to the increased expression of inflammatory markers and mediators) and the jun n-terminal kinase (JNK) pathway (which blocks the action of insulin by the phosphorylation of insulin receptor substrate-1).[48,49] The hypothalamic response to insulin and leptin may also be impaired due to an affected JNK pathway, resulting in an incapacity to detect the ongoing increase in adipose tissue as the brain perceives the amount of body fat to be stable.[50-52]

Hyperglycaemia and atherosclerosis

Atherosclerosis is accelerated in the presence of hyperglycaemia and it is suggested that type 2 diabetes and atherosclerotic vascular disease may share a common background, "the common soil" theory, which includes inflammation and increased oxidative stress.[53] As the antilipolytic effect of insulin is impaired in type 2 diabetes there is an excess of free fatty

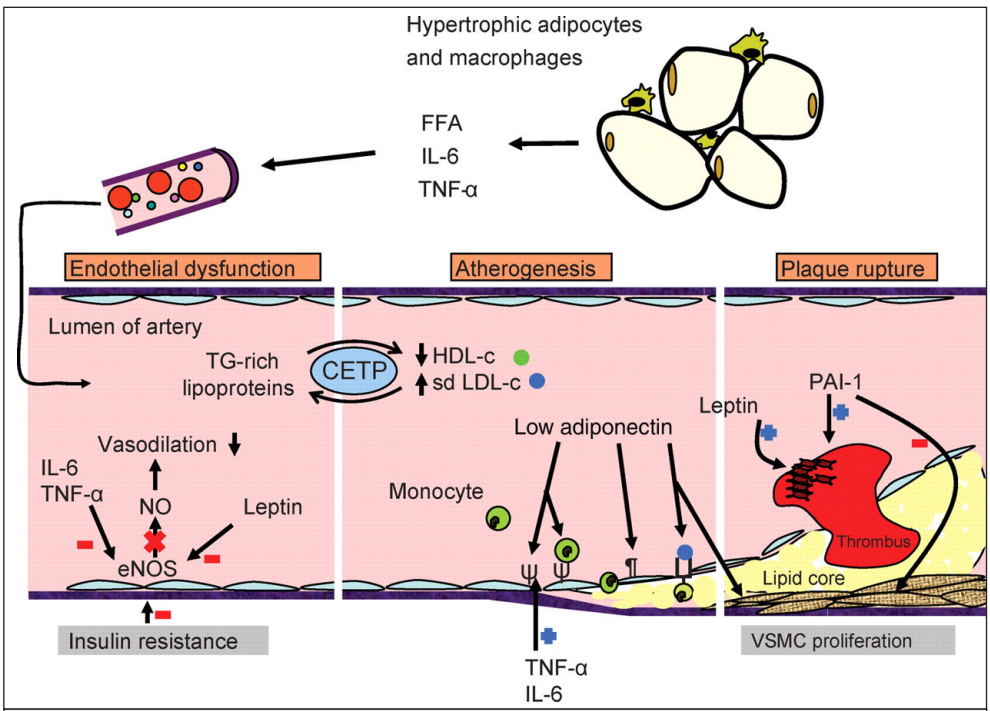


Figure 4. Hypertrophic adipocytes, cytokine-mediated inflammation and the progress of atherosclerosis. Reproduced with permission from Hajer et al.[47]

acids resulting in oxidative stress via the increased production of reactive oxygen species[54] and vasoconstrictors (such as endothelin-1)[55] and the impaired production of nitric oxide,[56] leading to a defective smooth muscle cell function with vasoconstriction. Dyslipidaemia in diabetes includes hypertriglyceridaemia, low HDL and an excess of small dense LDL particles which are prone to oxidation.[57] Oxidated LDL is consumed by macrophages with the formation of foam cells[58] in the intima, causing cytokine-mediated increased inflammation and the acceleration of the atherosclerotic process.[59] Smooth muscle cells are influenced by cytokines and migrate to form a fibrous cap which in the presence of inflammation and decreased collagen production becomes thin,[60] increasing the risk of plaque rupture. Platelet aggregation is increased with an enhanced expression of glucoprotein Ib-, IIb/IIa mediating platelet-fibrin interaction[61] and with an increased concentration of such factors as PAI-1[62] inducing a prothrombotic environment.

Adiponectin

Adiponectin is an adipokine secreted from the adipose tissue. The levels are genetically influenced, increased with age and female gender and are inversely associated with body fat percentage.[63,64] In a general population without severe or chronic disease, adiponectin ranges from 2-26 μg/ml with 1.5 times higher levels in women compared with men (mean levels of 7.3 μg/ml in men and 11.9 μg/ml in women).[65] Adiponectin assembles to form larger molecules and circulates in three isoforms: low-, medium- and high-molecular-weight adiponectin. Data on the prognostic role of the proportion of isomers are conflicting.[66-68] Adiponectin functions mainly through two receptors,[69] AdipoR1 (abundant in skeletal muscle) and AdipoR2 (abundant in liver), with the subsequent activation of AMP-activated protein kinase[70] and PPAR-α[71] resulting in improved glucose metabolism and increasing insulin sensitivity but also stimulating the oxidation of free fatty acids (FFA) and decreasing plasma triglycerides.[72] Experimental data indicate that adiponectin also has anti-inflammatory and anti-atherogenic[73] effects including the reduced expression of adhesion molecules in endothelial cells,[74] the reduced proliferation and migration of smooth-muscle cells[75,76] and the inhibited transformation of macrophages to foam cells (Figure 4).[77] Low levels of adiponectin are related to the metabolic syndrome,[78] dyslipidaemia,[79] insulin sensitivity and diabetes[80] and have been associated with coronary atherosclerosis and myocardial infarction.[81,82] However high levels are related to mortality.[83,84] That low levels predict myocardial infarction in healthy individuals while high levels are associated with increased mortality after a myocardial infarction has been referred to as “the adiponectin paradox”.[85] The mechanisms behind this paradox are not fully understood but several possibilities have been presented. Plasma brain natriuretic peptide (BNP) and cytokines have been suggested as key determinants of adiponectin by regulating its release from adipose tissue, possibly influenced by the degree of activated systemic inflammation.[86] In a state of low-grade inflammation, as in an ongoing silent atherosclerotic process without significant CVD, adiponectin may be suppressed while it is driven upwards by circulating BNP in patients with advanced CVD.[86] There are also data indicating that adiponectin may be associated with severe co-morbidity and cachexia.[87,88] Furthermore, elevated levels of adiponectin can be caused by dysfunctional or down-regulated adiponectin receptors in obesity-induced insulin resistance.[71,89] Adiponectin may be increased by physical activity and treatment with statins, PPAR γ or α agonists, RAAS blockade, some calcium channel blockers and β-blockade.[90]

Leptin

Leptin is an adipokine that is mainly expressed in adipose tissue but also in the heart, vessels, bone marrow, placenta, skeletal muscles and brain. Six isoforms of the leptin receptor have been described and they are variously expressed in different tissues.[91] If there is a balance in energy intake and output the leptin levels reflect total body fat mass. Following 24 hours of fasting, the leptin levels decrease by 30%. The levels will rise by about 50% after 12 hours of overfeeding.[92] Leptin production is decreased by statins,[93] fibrates[94] and thiazolidinediones.[95] The first detected leptin effect was regulation of body weight by decreasing food intake and increasing thermogenesis mediated via a hypothalamic influence.[96-98] It was subsequently demonstrated that leptin influenced carbohydrate and lipid metabolism and the reproductive system.[99] In addition, leptin is associated with several components of the atherosclerotic process such as endothelial dysfunction, oxidative stress, sympathetic activation and thrombogenicity.[100,101] It is not fully understood whether this is a direct pro-atherogenic effect of leptin or whether it reflects a state of leptin resistance.[102-104] It has been speculated that a selective leptin resistance may occur, explaining why appetite is not depressed in obese individuals, while autonomic and cardiovascular actions are still stimulated by hyperleptinaemia.[103] Leptin resistance has also been proposed as a mechanism behind the poor effect of recombinant leptin in obese patients.[105] High levels of leptin can inhibit the insulin receptor, resulting in impaired insulin-mediated glucose transport, hyperglycaemia and insulin resistance.[106] Hyperleptinaemia may also induce hyperinsulinaemia and insulin resistance by intensifying free fatty acid oxidation[107] which stimulates insulin secretion and impairs insulin receptor signalling.[108] Leptin levels are higher in females than males.[109] The gender differences observed in both adiponectin and leptin are not fully explained. Oestrogen stimulates leptin secretion from adipocytes[111,112] in women and there is a negative correlation between testosterone and leptin in men.[113] In addition to these sex hormone differences,[110] the distribution of body fat[114] and dissimilarities in the blood-brain barrier between men and women have been proposed.[115,116] Unlike adiponectin, leptin is associated with cerebrovascular disease.[117] Increased levels of leptin have been associated with CVD in some[118-120] but not all studies.[121-123] There are also contradictory data in patients with diabetes.[124,125] It has been speculated that the role of leptin in CVD may be as complex as that of adiponectin with a paradoxical relationship similar to the already highlighted adiponectin paradox.[126]

Microvascular complications of diabetes

Microvascular complications related to type 1 and type 2 diabetes include retinopathy, nephropathy and neuropathy. They are related both to the duration of diabetes and to the severity of hyperglycaemia. In 1993 the Diabetes Control and Complications Trial (DCCT) established that strict glucose control is of major importance in reducing microvascular complications in type 1 diabetes[127] and in 1998 the UK Prospective Diabetes Study (UKPDS) showed that glucose control reduced microvascular complications in type 2 diabetes.[128] Other important strategies to reduce microvascular complications include renal protection via blood-pressure and microalbuminuria control in order to avoid end-stage renal disease, the screening of and early laser therapy of retinopathy protecting from blindness and preventive foot care reducing the risk of amputation. The prevalence of diabetic nephropathy in patients with end-stage renal disease in Sweden is 25%.[129] Diabetes neuropathy includes autonomic dysfunction in several organ systems including the cardiovascular system, which is associated with an increased risk of silent myocardial ischaemia and sudden death.[130]

The presence of microvascular complications may therefore not only be related to small vessel disease but also have an influence on macrovascular complications.

Macrovascular complications of diabetes

The risk factors for developing macrovascular disease in type 2 diabetes are the same as for people without diabetes although more pronounced. It is estimated that 90% of the risk factors for CVD are modifiable, with diabetes as one of them, increasing the risk two to four times.[131] The risk of macrovascular complications such as coronary heart disease (CHD= acute coronary syndrome [ACS]; sudden cardiac death, angina pectoris), peripheral vascular disease and ischaemic stroke are related to insulin resistance. The risk starts several years before the diagnosis of diabetes and prior to the development of microvascular disease (Figure 5). There is a gender difference where diabetes triples the risk of incident CHD in women and doubles the risk in men.[132] The mechanism behind the higher risk for women is not fully understood. A more extensive risk factor burden already in the prediabetic state[133,134] with higher BMI in women than men[135,136] and a suboptimal management has been proposed[137] with women less likely to achieve the recommended treatment targets for cardiovascular risk factors than men.[138] In patients with diabetes the risk of developing CVD is related to fasting blood glucose and HbA1c.[139-141] There is a U-shaped relationship between the level of glycaemia and mortality with an increased risk of both low and high levels.[142-144]

Mortality causes in individuals with diabetes are to a large extent cardiovascular, while purely diabetes-related complications are less common since the introduction of insulin.[145] In Sweden, cardiovascular reasons have long been the dominant mortality cause in people both with and without diabetes. During the last twenty years, mortality due to cardiac disease has decreased by around 50% thereby increasing longevity (Figure 6). Meanwhile, cancer has become almost as common a reason for mortality as cardiovascular disease.[146] The prognosis after myocardial infarction has improved in patients both with and without diabetes but the one-year mortality is still about 30% higher in a patient with diabetes.

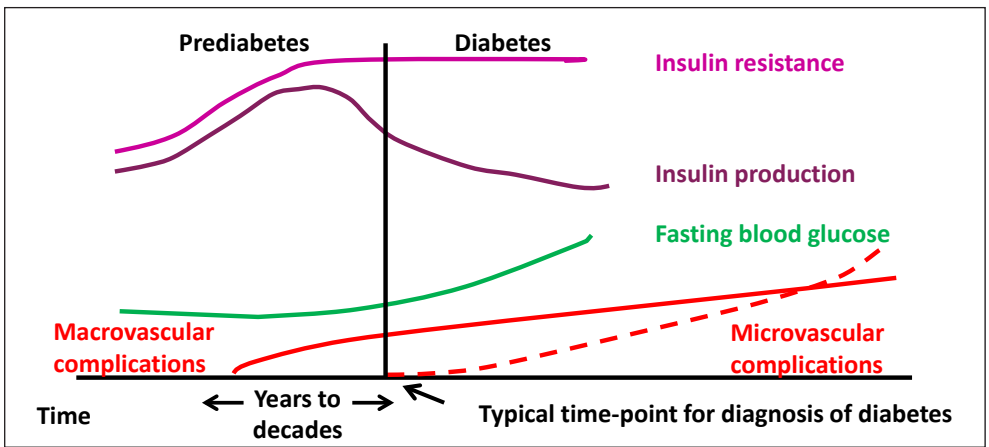


Figure 5. The natural history of dysglycaemia from prediabetes to diabetes and its relationship to macro- and microvascular complications. Importantly, macrovascular complications precede the defined point for the diagnosis of diabetes. Adapted with permission from Laakso et al.[31]

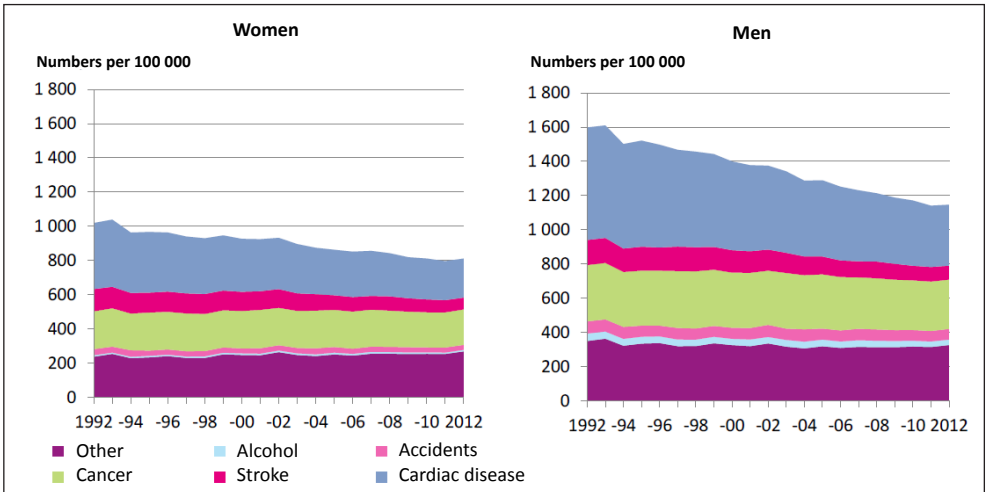


Figure 6. Trends in mortality causes in Sweden in 1992-2012. Adapted with permission from reference 146.

Glucose abnormalities in myocardial infarction

Hyperglycaemia during an acute myocardial infarction (AMI) was first described in 1929[147] and was interpreted as a result of stress,[148] related to the severity of the infarction[149] and left ventricular failure.[150] In 1966, glucose disturbances detected by an intravenous glucose tolerance test were linked with a dismal prognosis after AMI[151] and trials attempting to improve glucose tolerance with oral hypoglycaemic drugs were conducted.[152,153] These attempts were abandoned when the University Group Diabetes Program study indicated that the administration of tolbutamide was associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.[153]

Since the 1960s, many variations of a glucose tolerance test have been applied with different routes of administration, different doses of glucose and different intervals of sampling. In 1980, the OGTT was standardised by the WHO.[154] Around 20% of patients with AMI suffer from diabetes.[155] When such patients without previously known glucose perturbations were investigated with a standardised OGTT as in the GAMI study another 1/3 had previously undetected diabetes and 1/3 IGT.[156] These results have since then been repeated.[157,158] The timing of the OGTT is crucial; when tested already two days after the acute onset, the test may capture an acute stress reaction[159] which is the reason for performing the OGTT no less than four to five days after an AMI. There are indications that patients with newly detected glucose abnormalities run an increased risk of a future cardiovascular event the first year after an AMI but studies on long-term outcome are lacking.[160-163]

The cardiovascular impact of glycaemic intervention

In 1963 Sodi-Pallares proposed the use of an infusion of glucose-insulin-potassium (GIK) in patients with AMI with the aim of promoting electrical stability and preventing arrhythmias by facilitating the transportation of potassium into the myocardial cell (Figure 7).[164] Since then GIK,[165] glucose-insulin[141] or only insulin[166] has been used to impede the metabolic vicious circle in the oxygen-deficient state caused by a coronary occlusion in AMI. In addition, pain and dyspnoea enhance the sympathetic drive increasing myocardial ischemia and FFA in

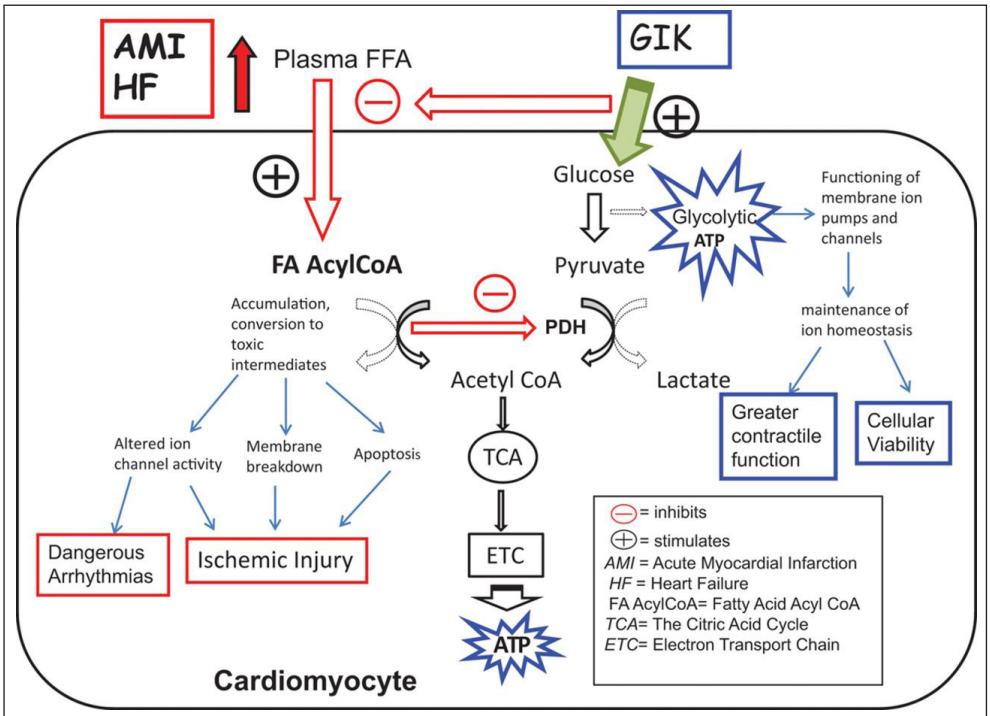


Figure 7: Metabolic pathways in the cardiomyocyte and metabolic effects of glucose-insulin-potassium (GIK). Printed with permission from Grossman et al.[167]

plasma[167] and the myocardial uptake and beta-oxidation of FFA. Via an accumulation of fatty acyl CoA, glycolysis is suppressed, with further ischaemic damage to the tissue and a risk of arrhythmia as a consequence.[167] The GIK concept was therefore introduced to improve glycolysis and reduce the more oxygen-consuming beta-oxidation.

Reducing hyperglycaemia by means of an intensified, insulin-based glycaemic control compared with conventional treatment improved survival in patients with AMI in the first DIGAMI study[141] and in some, but not all studies, in patients in general intensive care.[166,168] Further attempts to reduce cardiovascular mortality and morbidity by means of isolated glucose-lowering therapy based on insulin or oral glucose-lowering drugs were disappointing.[169-173] The UKPDS study randomised 3867 patients with newly diagnosed type 2 diabetes at low cardiovascular risk to intensified glycaemic control with insulin or sulphonylurea compared with conventional diet-based treatment studying the effect on micro- and macrovascular complications.[128] Despite an overall reduction in HbA1c of 0.9% (9.8 mmol/mol) with intensive compared with conventional therapy, there was no significant difference (p=0.052) in cardiovascular endpoints during the initial 10 years of follow-up.[128] Only obese patients on intensive therapy with metformin experienced a significant reduction in mortality and cardiovascular events.[174] However, in a further long-term follow-up, 10 years after the cessation of randomised treatment, an initial, tight glycaemic control was associated with cardiovascular benefits despite a convergence of HbA1c levels over time (the so-called “legacy effect”).[140] More recent randomised trials, Action in Diabetes and Vascular

Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[169] and Action to Control Cardiovascular Risk in Diabetes (ACCORD),[170] enrolled high-risk patients of whom approximately one third had a history of a major cardiovascular event. Intensive glycaemic control aiming at almost normal glucose levels failed to show any macrovascular benefits, despite a high event rate, and was even associated with increased mortality in the ACCORD study.[170,175] These results have further highlighted the temporal aspects of glucose control raising concern that glycaemic control may be important in the early stages of the disease but less so in cohorts with longstanding diabetes and already established CVD.[176] Furthermore, too tight glucose control has been questioned as it increases the risk of hypoglycaemia which may promote cardiovascular events.

Recent reports including new types of glucose-lowering drugs, such as an SLGT2 inhibitor in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)[177] and the GLP-1 receptor agonists liraglutide in Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)[178] and semaglutide in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)[179] trials, all including patients with type 2 diabetes at high cardiovascular risk, are promising. There was a statistically significant reduction in mortality and cardiovascular events when glucose-lowering therapies with empagliflozin,[177] liraglutid[178] and semaglutide[179] were added to standard therapy during two - three years of follow-up. These contradictory results regarding the cardiovascular outcome indicate that the choice of glucose-lowering drug is of importance when aiming for cardiovascular-safe therapies in diabetes treatment. Since 2008, the US Food and Drug Administration (FDA) has requested that all glucose-lowering drugs should be evaluated regarding not only their glucose-lowering effects but also their cardiovascular safety effects.[180]

The risk of hypoglycaemia

Hypoglycaemia, often defined as a fasting plasma glucose of <3.9mmol/L accompanied by symptoms, is classified into mild (self-treatable) and severe hypoglycaemia (an episode that requires external assistance for recovery). The potential cardiovascular effects of hypoglycaemia are described in Figure 8.[181] Hypoglycaemia activates the sympatico-adrenal system with the release of epinephrine and nor-epinephrine increasing cardiac workload while at the same time decreasing the arrhythmia threshold. Electrocardiographic changes including a lengthening of the QT interval can be seen[182] (Figure 9) and ventricular tachycardia has been described.[183] In addition, hypoglycaemia stimulates platelet activation and abnormalities in coagulation.[184] Like hyperglycaemia, hypoglycaemia also causes oxidative stress and endothelial dysfunction.[185] If recovery occurs with normoglycaemia the harmful effects are diminished. However, if hyperglycaemia succeeds hypoglycaemia the inflammatory response is enhanced and the endothelial function further impaired.[186]

The impact of coronary interventions

Important landmark events in the management of patients with coronary artery disease (CAD; Figure 10) are the development of coronary angiography by Sones in 1958,[187] coronary artery bypass grafting (CABG) by Favaloro in 1967[188] and percutaneous coronary intervention (PCI) in 1977 by Grünzig.[189] The first coronary stent implantation was performed in 1986

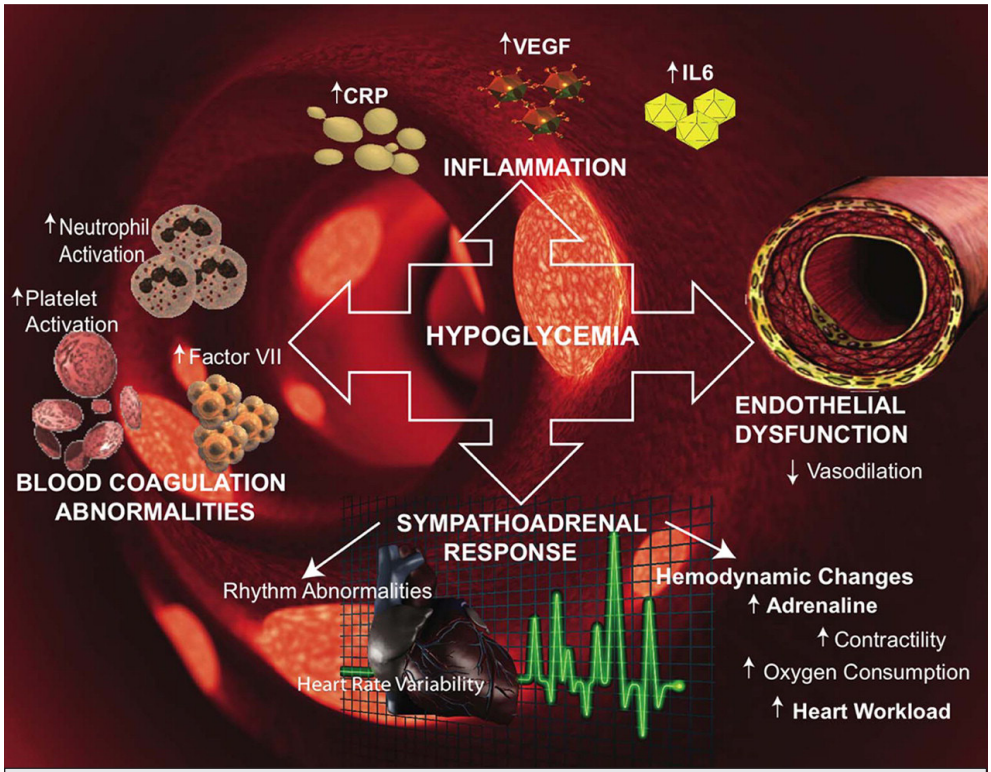


Figure 8. Overview of the potential cardiovascular effects of hypoglycaemia. Adapted with permission from Desouza et al.[181]

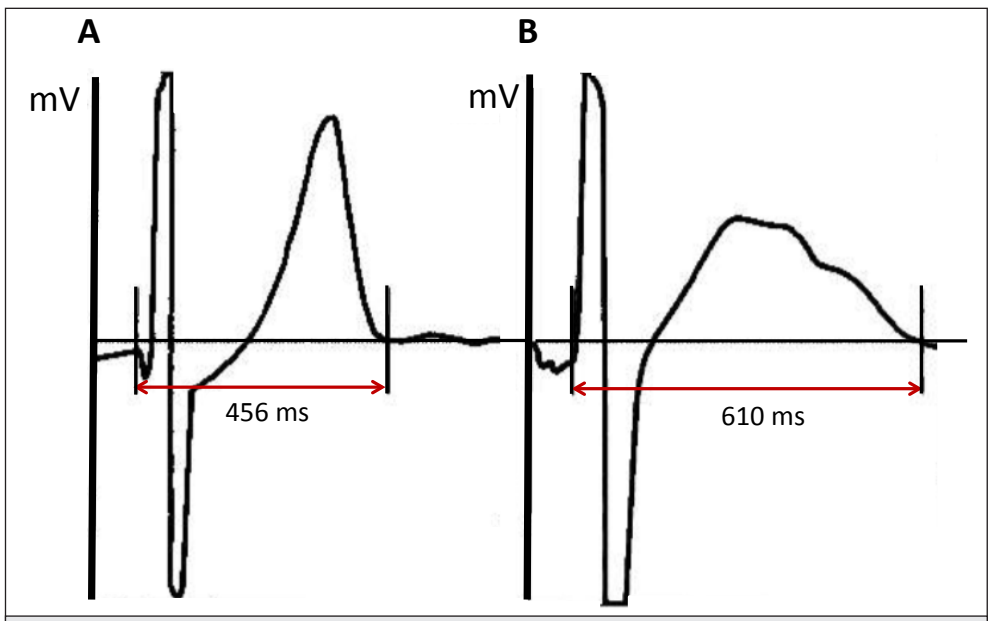


Figure 9. The QT interval during normoglycaemia (A) and induced hypoglycaemia (B). Adapted with permission from Marques et al.[182]

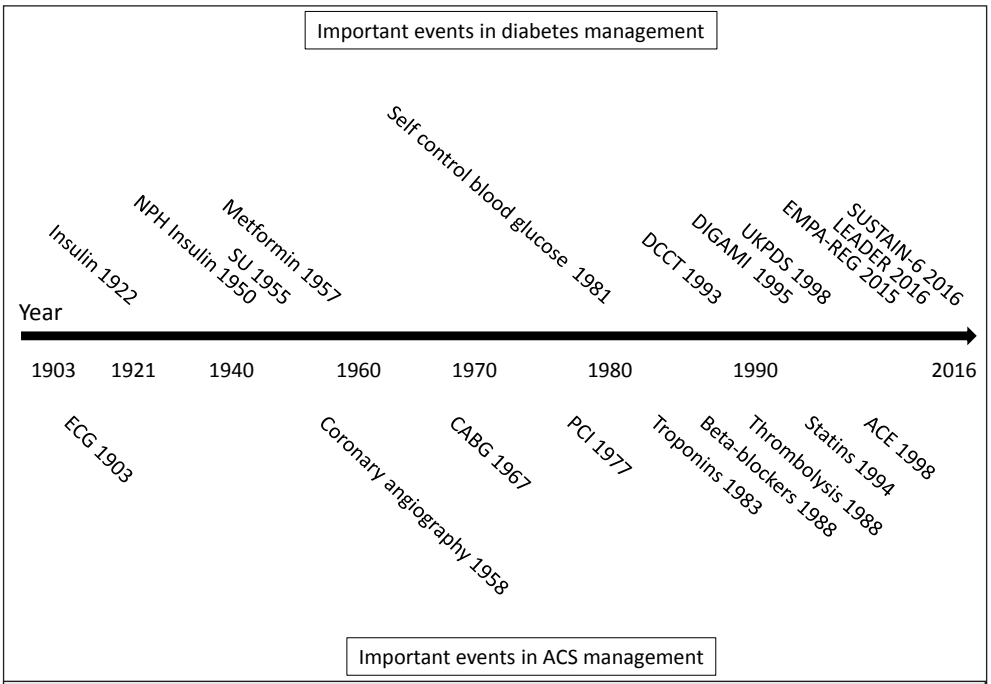


Figure 10. Landmark events in diabetes and ACS management.

by Puel,[190,191] using a self-expanding stent, while a balloon-expandable stent was first used in 1987 by Palmaz.[192] Several studies have demonstrated the superiority of coronary angioplasty over thrombolytic therapy in AMI in terms of mortality and left ventricular function, where angioplasty is associated with fewer re-infarctions and intracranial haemorrhages.[193,194] For moderate- and high-risk patients with unstable CAD there is a significantly lower mortality rate with early invasive treatment compared with non-invasive treatment.[195-197] With improved technology and treatments a lower complication rate is seen. Studies performed before the use of stents revealed a very high restenosis rate, 32-46% within one year, in patients with diabetes.[198-200] The use of bare metal stents (BMS) and drug eluting stents (DES) reduced the rate of restenosis to around 5% during the first year.[201,202] DES prevent restenosis through the suppression of tissue growth at the stent site and local modulation of the inflammatory responses and the immune system with a substantially lower restenosis rate in patients with diabetes compared with BMS.[203] In spite of this, modern technology with the use of DES has not been able to abolish the negative impact of diabetes on mortality[204] and restenosis. Due to a lower long-term mortality rate and fewer major coronary events CABG is still preferred to PCI in patients with multivessel disease, in particular in the presence of diabetes.[205-207] There may be several reasons, including that patients with diabetes respond less well to antithrombotic treatment and that hyperglycaemia during and after the intervention may be related to an increased propensity for restenosis.

Summary and gaps in knowledge

Patients with diabetes run an increased risk of CVD.[131] Despite improved management during the past twenty years the longevity after a cardiovascular event is still compromised compared with patients without diabetes.[204] In the Swedish general population, cardiovascular

mortality has decreased significantly during the last few decades.[146] The question of whether this is true for patients with diabetes is less well explored. Furthermore, the complication pattern after AMI apart from mortality is poorly evaluated. Information on mortality and complication pattern is important in order to find ways further to improve quality of life and life expectancy among patients with diabetes. Not only diabetes but also unknown glucose abnormalities, which are common in patients with AMI,[156] appear to affect the short-term prognosis.[160-163] The question of whether this is also important in the long-term perspective has not been fully explored.

The mechanism behind the cardiovascular complications related to glucose abnormalities is not completely understood. Insulin resistance and atherosclerotic vascular disease are closely linked by an unhealthy distribution of adipose tissue and an increased degree of systemic inflammation[53] with dysregulated adipokines. Both adiponectin and leptin are biomarkers that are easily available and can be measured in the setting of an acute coronary event. These biomarkers can possibly identify high-risk patients and also contribute to an understanding of the underlying pathophysiology. Data on the prognostic implications of adipokines in patients with prevalent CHD are contradictory and long-term outcome studies are lacking.

Aims

The overall aim

The overriding aim of this thesis is to increase knowledge of patterns of cardiovascular complications and mortality causes after coronary events in patients with diabetes. Moreover, the intention is to investigate the impact of undetected glucose abnormalities and glucose control on prognosis in patients with acute myocardial infarction in order to identify opportunities to improve their long-term outcome.

Specific aims

1. To investigate the lasting effect of glucose control on mortality after acute myocardial infarction in patients with diabetes randomised to intensified, insulin-based glucose control or conventional treatment **(Study I)**

2. To analyse the long-term prognosis and morbidity patterns after acute myocardial infarction in patients with and without newly discovered glucose abnormalities **(Study II)**

3. To evaluate the predictive power of HbA1c and the oral glucose tolerance test for future cardiovascular events in patients with acute myocardial infarction without previously known diabetes **(Study II)**

4. To investigate complication patterns after a first percutaneous coronary intervention in unselected patients with diabetes and to identify high-risk diabetes individuals **(Study III)**

5. To investigate mortality causes after coronary events in patients with and without diabetes or newly discovered glucose abnormalities **(Study I, II, III)**

6. To analyse the significance of adiponectin and leptin as biomarkers of long-term cardiovascular complications in patients with acute myocardial infarction and newly discovered glucose abnormalities **(Study IV)**

Material and Methods

This thesis is based on three study populations with different designs, sizes, diabetes prevalence and study periods as summarised in Table 2.

Table 2: Overview of the four studies that form the basis of this thesis.

Study	I	II	III	IV
Cohort name	DIGAMI	GAMI	SCAAR	GAMI
Study design	Randomised controlled trial	Case-control study	Register study	Cohort study
Number of patients	620	167	58 891	180
Number of controls	-	184	-	-
Age at inclusion (years, mean)	68	63 (patients) 64 (controls)	67	64
Recruitment years	1990-1993	1998-2002	2006-2010	1998-2000
Inclusion event	AMI	AMI (patients) No AMI (controls)	First PCI	AMI
Proportion with diabetes	100%	0%	19%	0%
Follow-up period (years, mean (SD))	7.3 ± 6.6	10.2 ± 3.5 (patients) 9.9 ± 1.7 (controls)	2.5 ± 1.5	9.9 ± 3.8
Outcome	Mortality	Mortality Cardiovascular events	Mortality Cardiovascular events	Mortality Cardiovascular events

Definitions

During the study period, the definition of diabetes and of myocardial infarction has changed and consequently varies in the different studies.

Diabetes mellitus and impaired glucose tolerance

In Study I, patients were defined as having diabetes if they had previously been informed of the diagnosis and prescribed treatment with diet, oral drugs or insulin. Patients without the diagnosis but with blood glucose of ≥11 mmol/L at admission were regarded as newly detected diabetes. In Study I, diabetes criteria from 1979 were used.[208]

In Studies II and IV, diabetes was defined according to the WHO criteria from 1999 (Table 1).[6]

In Study III, diabetes was considered to be present if the patient had been hospitalised for diabetes at any time in the National Patient Register or was registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) as having diabetes or was receiving treatment with diet, oral glucose-lowering treatment, or insulin according to the Prescribed Drug Register.

Abnormal glucose tolerance
Abnormal glucose tolerance (AGT) was classified as either IGT or diabetes.

Acute myocardial infarction
In Study I, the diagnosis of AMI was based on the WHO criteria from 1979.[209] At least two of the following criteria had to be fulfilled to be classified as a definite AMI: (1) chest pain for ≥15 minutes; (2) ≥2 values of serum creatine kinase (S-CK) and serum creatine kinase isoenzyme B (S-CKB) or serum lactic dehydrogenase (S-LD) above the normal range (normal+2 SD), including an LD-isoenzyme pattern typical of myocardial damage; and (3) development of new Q waves in ≥2 standard ECG leads. The diagnosis of possible AMI was used if typical chest pain was accompanied by only one S-CK or S-LD value above the normal range and/or new Q waves in one ECG lead only.

In Studies II and IV, the diagnosis of AMI was based on the joint recommendations from the ESC and ACC from 2000.[210] Acute, evolving or recent myocardial infarction was diagnosed if one of the following criteria was fulfilled: (1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischaemic symptoms; (b) development of pathological Q waves on the ECG; (c) ECG changes indicative of ischaemia (ST segment elevation or depression); or (d) coronary artery intervention (coronary angioplasty); (2) Pathological findings of an AMI. To consider established myocardial infarction, any one of the following criteria had to be satisfied: (1) Development of new pathological Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalised, depending on the length of time that has passed since the infarct developed. (2) Pathological findings of a healed or healing myocardial infarction.

In Study III, the diagnosis of myocardial infarction was set by the physician in charge based on the International Classification of Diseases (ICD-10) codes as apparent in the Swedish National Patient Register.

Re-infarction
In Studies I, II, and IV, re-infarction was defined as a new AMI >72 hours after the index infarction. In Study III, a re-infarction was based on ICD-10 codes in the Swedish National Patient Register after discharge from the index PCI.

Stroke
In Studies II and IV, stroke was classified according to the WHO as a neurological deficit observed by a physician and persisting for >24 hours without any other disease explaining the symptoms.[211] In Study III, stroke was based on ICD-10 codes in the Swedish National Patient Register after discharge from the index PCI.

Severe congestive heart failure
In Studies II and IV, severe congestive heart failure (CHF) was defined as clinician-judged heart failure necessitating hospital admission including intensified treatment. In Study III, the diagnosis of CHF was based on the ICD-10 codes in the Swedish National Patient Register.

Restenosis and stent thrombosis
Restenosis and stent thrombosis (Study III) were diagnosed if a cardiovascular event resulted in hospitalisation. A restenosis was then defined as a clinically relevant stenosis (>50%) or

as a significant reduction in fractional flow reserve (<0.80) in a previously treated vessel segment.[202]A stent thrombosis was defined as an angiographically verified occlusion or visible thrombus in a previously implanted stent.

Study subjects and protocols

Study I

Patients

Patients with diabetes or with a blood glucose concentration of >11 mmol/L admitted to the coronary care units at 19 Swedish hospitals between 1 January 1990 and 31 December 1993 with a suspected AMI in the previous 24 hours were included in the DIGAMI trial. Patients unable or unwilling to participate, living outside the catchment area, enrolled in other studies or already in DIGAMI were excluded. Of 1240 eligible patients, 620 were excluded, leaving 620 patients as the study population. Before randomisation, subjects were classified as being at high cardiovascular risk if they fulfilled two or more of the following criteria: age >70 years, previous myocardial infarction, a history of CHF and present treatment with digitalis. On the basis of this classification and if they had been prescribed insulin previously or not, the patients were divided into one of four predefined strata; I: no insulin and low risk (n=272); II: no insulin and high risk (n=129); III: insulin and low risk (n=119); or IV: insulin and high risk (n=100).

Protocol and hypothesis

DIGAMI 1 tested the hypothesis that a rapid improvement in metabolic control by insulin-glucose infusion decreases the high initial mortality and that continued strict metabolic control aiming at normoglycaemia improves the subsequent prognosis in patients with diabetes and AMI.

The study was designed as a prospective, randomised, open-label trial with blinded endpoint evaluation (PROBE). Patients were randomly assigned (1:1) to either intensified insulin-based glycaemic control for at least three months (intensified group; insulin-glucose infusion ≥24 h followed by subcutaneous multidose insulin treatment), or to serve as a control group receiving conventional glucose-lowering treatment according to the attending physician. Patients were seen at three and 12 months after randomisation. The primary endpoint was mortality after three months in the original trial and all-cause mortality in the present long-term follow-up (Study I) following all patients until 31 December 2011. Death certificates were obtained from the Swedish Cause of Death Register and mortality causes were subsequently categorised according to the ICD-9 and ICD-10 codes, as set by the physician in charge, into eight classes of mortality causes (cardiovascular, cancer, infections, renal failure, sudden death, diabetes mellitus, dementia/old age or other). All mortality causes were scrutinised and were finally classified by two research physicians blinded to randomised treatment.

Studies II and IV

Patients

Studies II and IV are based on the Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) trial. A total of 181 patients with AMI without previously known diabetes and admission capillary blood glucose of <11.1 mmol/L admitted to the coronary care units at the Karolinska and Västerås Hospitals between 1998 and 2000 were enrolled in the study. The exclusion criteria were age >80 years and serum creatinine of >200 μmol/L. One patient was lost to follow-up. In Study II, only patients whose glucose tolerance was assessed were included. Thirteen patients were not investigated with an OGTT at discharge due to death

during hospitalisation (2), refusal (2), illness (7) or technical problems (2), leaving 167 glucometabolically classified patients as the final study cohort. Study IV included all 180 patients.

Controls
Age-, gender- and catchment area-matched controls (n=185) without a prior diagnosis of diabetes or CVD (apart from mild hypertension) or any acute illness during the preceding three months were recruited between 2001-2002. One control was lost to follow-up, leaving 184 as the final study cohort in Study II. In all, 500 controls were invited by letter after matching for age and gender, of whom 80 were excluded due to previous diseases, 150 did not respond, 72 were unwilling, four died and eight were living outside the catchment area.

Protocol and hypothesis
Study II tested the hypothesis that newly identified AGT constitutes an important marker of long-term outcome, while Study IV tested the hypothesis that low levels of adiponectin but high levels of leptin were associated with a future cardiovascular event after an AMI in patients without previously known diabetes.

A prospective study design was adopted with the consecutive enrolment of patients apart from during summer vacations and weekends. All patients were treated for their AMI according to established national and international guidelines at that time which mainly included reperfusion therapy with thrombolysis. An OGTT was performed on the day of hospital discharge 4-5 days after the AMI in the patients and at the inclusion of the controls. The patients and controls were separately followed for cardiovascular events (first of cardiovascular mortality/AMI/stroke/CHF) and mortality until 31 December 2011. Information on cardiovascular events was derived from hospital and outpatient clinical records supplemented if possible by a telephone interview with the survivors (or close relatives when needed). Mortality reasons were classified according to available hospital records and to the ICD-10 codes on the death certificates obtained from the Swedish National Death Registry. The cause of death was subsequently categorised as cardiovascular (caused by AMI/stroke/aortic dissection or sudden death without any obvious reason), cancer or other after the evaluation of death certificates by two research physicians blinded to the OGTT result.

Study II comprises both patients and controls while Study IV only encompasses patients.

Study III

Patients
The patients in Study III were recruited from the SCAAR. Since the start of the registry in 1998, the SCAAR has collected data on patients undergoing coronary angiography and PCI and nowadays it includes the 29 centres performing these procedures. Details on coronary angiographies and coronary interventions in the registry are provided by the physicians who perform the coronary investigations and/or interventions. Consecutive patients with a first performed PCI, included in the SCAAR between 2006 and 2010 and with no previous revascularisation (CABG and/or PCI) and with complete information on background characteristics and treatment, were included in Study III. Due to incomplete data, 347 patients (0.6%) were excluded, leaving 58 891 patients as the final study population. Patients with a diabetes diagnosis but no prescription for glucose-lowering therapy were categorised as diet treated. Patients with a prescription for insulin were categorised as insulin treated, regardless of whether or not insulin was combined with diet or oral glucose-lowering therapy.

Protocol and hypothesis
Study III tested the hypothesis that patients with diabetes have a higher event rate after a first PCI compared with those without diabetes, despite the use of contemporary therapies. A second hypothesis was that information on the type of glucose-lowering therapy can be indicative of the prognosis following a PCI.

Patients were followed prospectively until 31 December 2010 for mortality and for hospitalisation for the following events; AMI, stroke, heart failure, renal failure, restenosis or stent thrombosis in any of the coronary vessels, CABG and new PCI. A composite cardiovascular event was defined as the first occurrence of total mortality, hospitalisation for AMI, stroke or heart failure. The long-term follow-up was obtained by merging the SCAAR database with the Prescribed Drug Register, containing data on dispensed and collected drugs, the National Patient Register, containing information on all in-patient care, and the Cause of Death Register. Causes of mortality were classified according to the main ICD-10 code on the death certificate and thereafter categorised into eight main causes of mortality (CVD, cancer, endocrine/metabolic disease, respiratory disease, gastrointestinal disease, urinary tract disease, infections or other).

No patient among those still resident in Sweden was lost to follow-up.

Laboratory investigations

Studies II and IV

Oral glucose tolerance test
A standardised OGTT with 75 g of glucose dissolved in 200 ml of water was conducted under stable conditions after 12 hours of overnight fasting without smoking or physical activity. The glucose concentration was measured in the fasting state, after 60 and 120 minutes.

Blood glucose concentrations and other biochemical measurements
Blood samples were collected on the first morning after hospital admission, at discharge and three months after the index AMI in the patients and in the fasting state during the investigation of controls. Plasma was obtained after centrifugation and stored at -70°C pending analyses.

The glucose concentration during the OGTT was measured in whole capillary blood immediately after sampling using a HemoCue® photometer (HemoCue® AB, Ängelholm, Sweden). The coefficient of variation was ≤3.5%.

HbA1c was analysed by high-performance liquid chromatography (Mono S) from whole capillary blood applied on filter paper (Boehringer-Mannheim Scandinavian AB, Bromma, Sweden).[212] The upper normal limit was 5.3%, with a coefficient of variation of <3%. The values were recalculated to the IFCC standard using the following equation: (10.11 x Mono S - 8.90).[213]

Plasma insulin and intact proinsulin were quantified with commercially available immunoassays (DAKO Ltd, Cambridgeshire, UK). The intra- and interassay coefficients of variation were 6% and 7% for insulin and 5% and 6% for proinsulin.

Insulin resistance was estimated in the fasting steady state using the homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula: HOMA-IR= (plasma insulin x blood glucose x 1.13)/(22.5x6).[214]

The insulinogenic index (IGI) was calculated as the difference between 30 and 0 minutes plasma insulin divided by the difference between 30 and 0 minutes plasma glucose.

Plasma leptin and total adiponectin were analysed with a double-antibody radioimmunoassay (Linco Res., St Louis, MO, USA). The total coefficient of variation for leptin was 4.7% at both low (2-4 ng/ml) and high (10-15 ng/ml) levels. The corresponding values for adiponectin were 15.2% at low (2-4 µg/ml) levels and 8.8% at high (26-54 µg/ml) levels.

Statistical analyses and data management

In Studies I-IV, continuous values are presented as the mean ± standard deviation (SD) or median (lower and upper quartile) and categorical variables as numbers and percentages.

In Study I, analyses were performed using the intention-to-treat principle. The significance of the differences between the groups was tested with Fisher's exact test for dichotomous variables, the χ^2 test for non-ordered categorical variables and Student's t test for continuous variables. A Cox's proportional hazard regression model was used to analyse the impact of randomised treatment. To test the proportional hazards assumption, interaction terms between log (time) and key variables were fitted into the mortality model and the possibility of a time-dependent effect of treatment was tested by means of spline curves based on Poisson models.

In Studies II-IV, Cox's proportional hazard regression models were used to analyse the univariate and multivariate prediction of a future event. In Study IV, continuous variables were log transformed before analysis to avoid the influence of extreme values. Variables considered clinically relevant and with a $p<0.05$ (Study III) or $p<0.10$ (Studies II and IV) were introduced into the multivariate model. In addition, logistic regression analysis was performed in Study IV when the association of adiponectin or leptin with future events appeared to be non-proportionally distributed. Kaplan-Meier curves were used to estimate the cumulative mortality (Studies I-IV) and time to event (Studies II-IV). In Study IV, the predictive value of log-transformed leptin and adiponectin as dichotomised by gender-specific median levels was analysed by Kaplan-Meier curves.

All p-values reported are two-tailed, with a value of <0.05 accepted as statistically significant. The analyses were conducted using the SAS statistical program (SAS version 9.2, 9.4), software from SAS Institute, Cary, NC, USA, in Studies I, II and IV and SPSS statistical program (SPSS version 20) software from SPSS Inc., Chicago, IL, USA, in Study III.

Ethical consideration

All studies were conducted in accordance with the Declaration of Helsinki. The DIGAMI protocol (Study I) was approved by the ethical boards at the Universities of Gothenburg, Linköping, Lund and Uppsala while the ethical committee at Karolinska Institutet approved the extended follow-up.

The ethical board at the Karolinska Institute approved the protocol of Studies II and IV while the board at Uppsala University approved the design of Study III.
Before enrolment in DIGAMI (Study I) and GAMI (Studies II and IV), patients gave their written, informed consent to participate in the initial study and the follow-up. All patients in Study III were informed of their participation in the SCAAR.

RESULTS

Study I

Clinical data

Apart from glucose-lowering treatment, there was no significant difference between the intensified and the control group in terms of clinical and baseline characteristics (Table 3), in-hospital or follow-up treatment during the first year. At admission, there were no significant differences in blood glucose or HbA1c. As previously reported[141] blood glucose during the first 24 hours and HbA1c after one year decreased in both groups but significantly more in the intensified group (-0.9%; SD 1.9, vs. -0.4%; SD 1.8; p=0.006), especially in stratum I (low risk-no previous insulin; -1.3%, SD 1.9, in the intensified group vs. -0.5%, SD 1.9, in controls; p=0.012). At the time of hospital discharge, 266 patients (87%) in the intensified group were on insulin compared with 135 (43%) in the control group (p<0.001). The corresponding percentages were 80% and 45% (p<0.001) after three months and 72% and 49% after one year (p<0.001). No information about treatment patterns or glucose control after one year was available.

Table 3. Baseline characteristics by randomised treatment group in Study I.

	Intensified (n=306)	Control (n=314)	p
Clinical characteristics			
Age at randomisation (years; mean ± SD)	67 (9.3)	68 (9.5)	0.371
Gender (male)	191 (62.4%)	197 (62.7%)	1.000
BMI (kg/m^2) (mean ± SD)	27.3 (4.2)	27.0 (4.4)	0.506
Previous disease			
Myocardial infarction	121 (39.5%)	117 (37.3%)	0.616
Angina pectoris	176 (57.5%)	164 (52.2%)	0.214
Hypertension	144 (47.1%)	154 (49.0%)	0.679
Heart failure	69 (22.5%)	70 (22.3%)	1.000
Diabetes			
Previously unknown	31 (10.1%)	46 (14.7%)	0.109
Duration (years; mean ± SD)	9.9 (10.7)	1.1 (10.4)	0.865
Glucose-lowering treatment			
None	32 (10.5%)	47 (15.0%)	0.083
Diet	32 (10.5%)	39 (12.5%)	
Oral	140 (45.8%)	114 (36.4%)	
Insulin	102 (33.3%)	113 (36.1%)	
Biochemical variables			
HbA1c at randomisation (% or mmol/mol, mean ± SD)	8.2 (1.9), 75 (10)	8.0 (2.0), 73 (11)	0.218
Blood glucose at randomisation (mmol/L)	15.4 (4.1)	15.7 (4.2)	0.372
Blood glucose 24 h after randomisation (mmol/L)	9.6 (3.3)	11.6 (4.1)	<0.001
Blood glucose at hospital discharge (mmol/L)	8.2 (3.1)	9.0 (3.0)	0.004

Data are the mean (SD) or n (%) unless otherwise indicated. Data are presented as Mono S standard (%) and IFCC (mmol/mol).

Mortality

During a mean follow-up period of 7.3 (range 0-22) years, 271 patients (89%) in the intensified group and 285 (91%) in the control group died. The median survival was 7.0 years (IQR 5.6-7.8) in the intensified group and 4.7 (3.8-5.7) in the control group (HR 0.83; 95% CI 0.70-0.98, p=0.027). The effect of intensified glycaemic control was apparent during eight years, increasing the mean survival by 2.3 years (Figure 11).

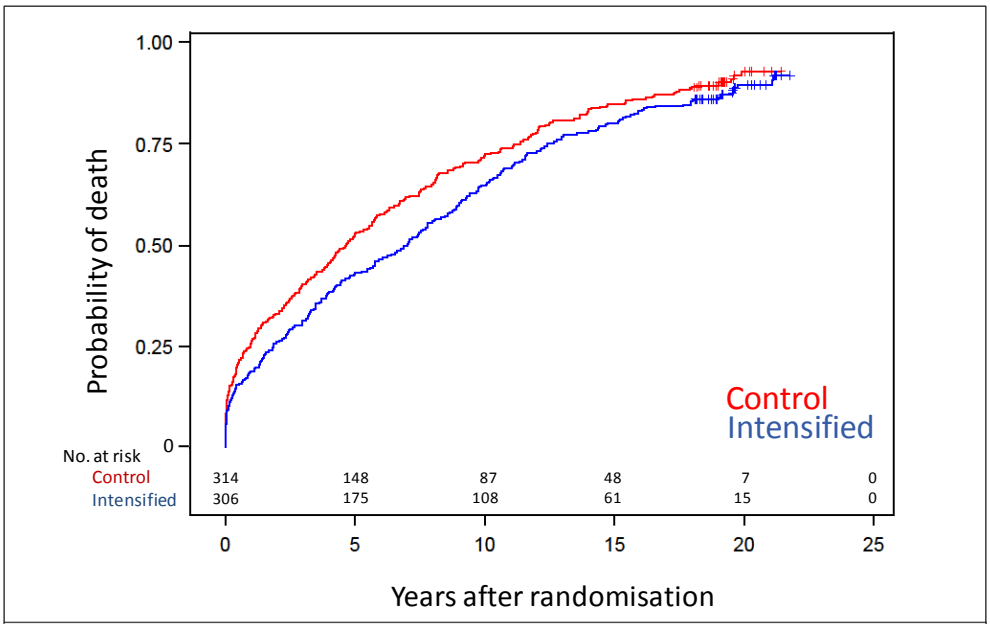


Figure 11. Time to mortality by randomised treatment group in Study I.

Patients in stratum I (low risk-no previous insulin) experienced a significant survival benefit (HR 0.77; 95% CI 0.60-1.00, p=0.048) with an average survival time of 9.4 years (95% CI 8.3-11.1) in the intensified group vs. 6.9 years (95% CI 4.8-8.2) in the control group (Figure 12 A). The corresponding HR (95% CI) for patients in stratum II (high risk-no previous insulin), III (low risk-insulin) and IV (high risk-insulin) was 1.00 (0.70-1.42, p=0.99), 0.87 (0.58-1.29, p=0.49) and 0.70 (0.47-1.06, p=0.09) as shown in Figure 12 B-D.

Glucose control at admission predicted long-term mortality in the control group (admission blood glucose; HR 1.06; 95% CI 1.02-1.09, and HbA1c; 1.10; 1.03-1.19) but not in the intensified group (1.03; 0.99-1.06 and 1.06; 0.99-1.14 respectively) after adjusting for age and gender.

Study II

Clinical data

Among 167 patients, 54 (32%) had NGT and 113 (68%) AGT (IGT=58 and diabetes=55). Patients with AGT were older (65 vs. 60 years), had more frequent previous CHF (11% vs. 2%; p=0.048) and were less often revascularised during their hospital stay (42% vs. 61%; p=0.028). Among 184 controls, 119 (65%) had NGT and 65 (35%) had AGT (IGT=45

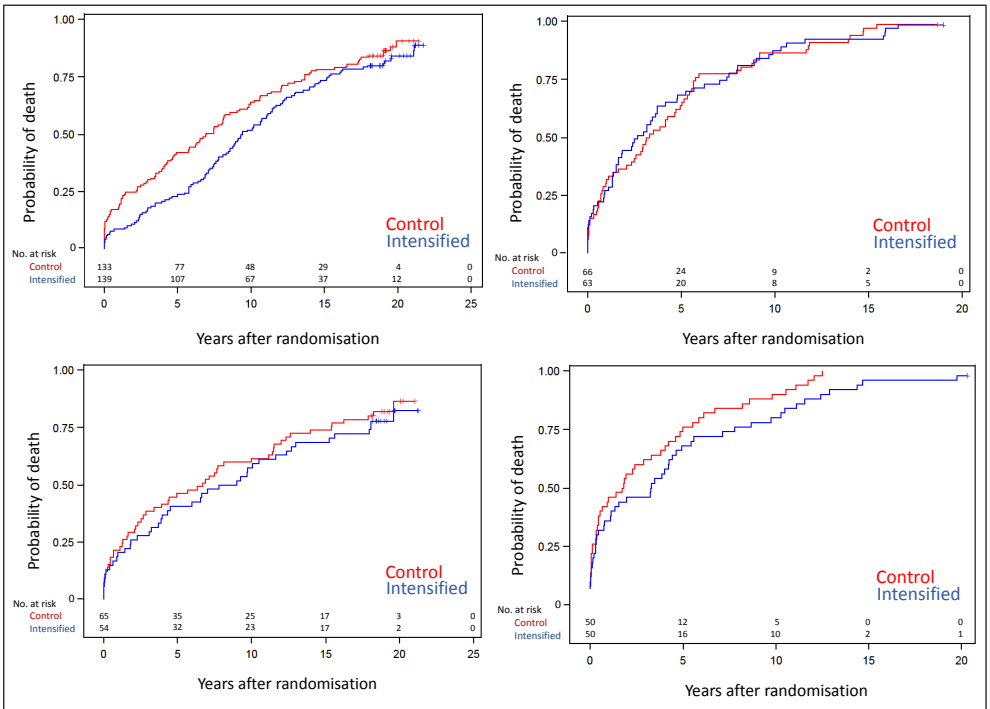


Figure 12. Time to mortality by strata in Study I. (A) Stratum I: no insulin and low risk (n=272), (B) stratum II: no insulin and high risk (n=129), (C) stratum III: insulin and low risk (n=119) and (D) stratum IV: insulin and high risk (n=100).

and diabetes=20). Controls with AGT were older (67 vs. 64 years) and had more frequent previous hypertension than those with NGT (29% vs. 12%). Baseline characteristics are presented in Tables 4 (patients) and 5 (controls).

Major cardiovascular events and mortality

Fifty-three (32%) patients and 28 (15%) controls died, while 72 (43%) patients and 29 (16%) controls suffered a major cardiovascular event during a median follow-up period of 11.6 vs. 10.4 years. The cardiovascular event rate was highest in patients with AGT while patients with NGT and controls with AGT had comparable event rates. Controls with NGT had the lowest event rate (Figure 13).

Prediction models for major cardiovascular events and mortality

Patients

In univariate analyses, AGT was related to a major cardiovascular event (HR 2.46; 95% CI 1.37-4.42, p=0.003), while fasting glucose at discharge (p=0.52) and HbA1c were not (HbA1c ≥4.7%, p=0.85; HbA1c 4.7%-5.5%, p=0.91; HbA1c ≥5.6%, p=0.74). Further, univariate variables with a p-value of <0.10 are described in Figure 14A.

In the final model (including AGT, age, BMI, previous angina pectoris/previous myocardial infarction/CHF/CABG), AGT (2.30; 1.24-4.25, p=0.008) and previous myocardial infarction (2.39; 1.31-4.35, p=0.004) remained significant predictors of a major cardiovascular event (Figure 14A).

Table 4. Clinical and laboratory characteristics in patients in Study II by glucose tolerance state. The data are presented as n (%) unless otherwise stated.

	NGT* (n=54)	AGT† (n=113)	p
Clinical characteristics			
Age (years; median (IQR))	60 (54-67)	65 (57-71)	0.006
Gender (female)	11 (20)	37 (33)	0.098
Current smokers	22 (41)	37 (33)	0.312
BMI (kg/m^2; median (IQR))	26.0 (23.1-28.1)	26.9 (24.1-29.7)	0.074
Family history of type 2 DM	8 (15)	28 (25)	0.143
Family history of CHD	30 (57)	60 (54)	0.715
Previous disease			
Myocardial infarction	7 (13)	25 (22)	0.159
Angina pectoris	17 (31)	36 (32)	0.961
Hypertension (treated)	17 (31)	38 (34)	0.783
Hyperlipidaemia (treated)	8 (15)	19 (17)	0.743
Heart failure	1 (2)	12 (11)	0.048
Stroke	1 (2)	5 (4)	0.665
CABG	3 (6)	11 (10)	0.362
Transmural myocardial infarction	20 (37)	46 (41)	0.620
Reperfusion therapy	33 (61)	48 (42)	0.028
Treatment at discharge			
Aspirin	51 (94)	102 (93)	0.680
β-blockade	50 (93)	101 (92)	0.863
ACE inhibitor	9 (17)	16 (15)	0.723
Statin	38 (86)	49 (62)	0.005
Biochemical variables, admission/day 2 median (IQR)			
Admission glucose (mmol/L)	5.9 (5.1-7.1)	6.4 (5.8-7.4)	0.002
HbA1c (%, mmol/mol)‡	4.8 (4.5-5.1), 40 (37-43)	5.0 (4.6-5.3), 42 (38-45)	0.130
Fasting blood glucose (day 2; mmol/L)	5.2 (4.6-5.7)	5.7 (5.1-6.3)	< 0.001
Creatinine (µmol/L)	92 (85-103)	90 (80-103)	0.517
Cholesterol (mmol/L)	6.0 (5.3-7.0)	5.9 (5.1-6.7)	0.215
LDL-cholesterol (mmol/L)	3.8 (3.1-4.4)	3.7 (2.9-4.4)	0.316
HDL-cholesterol (mmol/L)	1.2 (1.0-1.4)	1.1 (1.0-1.3)	0.304
Triglycerides (mmol/L)	2.4 (1.5-3.2)	2.1 (1.5-3.0)	0.415
Biochemical variables, day 4-5, median (IQR)			
hs-CRP (mg/L)	13 (6-28)	23 (9-65)	0.003
Fasting blood glucose (mmol/L)	4.8 (4.5-5.3)	5.3 (4.8-5.7)	<0.001
Two-hour glucose (mmol/L)	6.5 (5.9-7.1)	10.3 (8.8-11.9)	<0.001
Insulin at baseline (pmol/L)	52 (33-68)	56 (37-90)	0.084
Insulin 30 min (pmol/L)	314 (203-404)	265 (185-400)	0.140
Insulin 120 min (pmol/L)	240 (132-371)	554 (321-872)	<0.001
IGI§ at discharge	67 (42-98)	45 (27-68)	0.002
HOMA-IR| |, at discharge (mU mmol/L)	2.05 (1.34-2.64)	2.53 (1.52-3.97)	0.016

IQR=interquartile range. *Normal glucose tolerance. †Abnormal glucose tolerance. ‡HbA1c presented as Mono S (%) and IFCC (mmol/mol) standards. §Insulinogenic index. \| \|HOMA-IR=Homeostasis Model Assessment of Insulin Resistance.

Table 5. Clinical and laboratory characteristics in controls by glucose tolerance state in Study II. The data are presented as n (%) unless otherwise stated.

	NGT* (n=119)	AGT† (n=65)	p
Clinical characteristics			
Age (years; median (IQR))	64 (56-71)	67 (60-74)	0.012
Gender (female)	41 (34)	17 (26)	0.247
Current smokers	11 (9)	10 (15)	0.211
BMI (kg/m^2; median (IQR))	25.8 (23.6-28.2)	26.2 (23.4-30.4)	0.359
Family history of type 2 diabetes	21 (18)	12 (18)	0.911
Family history of CHD	35 (29)	16 (25)	0.487
Previous disorders			
Hypertension (treated)	14 (12)	19 (29)	0.003
Hyperlipidaemia (treated)	8 (7)	6 (9)	0.540
Treatment			
Aspirin	8 (7)	10 (15)	0.059
β-blockade	10 (8)	15 (23)	0.006
ACE inhibitor	5 (4)	5 (8)	0.318
Statin	3 (3)	4 (6)	0.246
Biochemical variables, median (IQR)			
HbA1c (% , mmol/mol)‡	4.5 (4.2-4.8), 37 (33-40)	4.8 (4.4-5.3), 40 (35-45)	<0.001
hs-CRP (mg/L)	1.6 (1.0-2.8)	2.1 (0.9-4.8)	0.003
Creatinine (µmol/L)	80 (71-88)	84 (74-92)	0.034
Cholesterol (mmol/L)	5.8 (5.3-6.6)	5.6 (5.0-6.1)	0.121
LDL-cholesterol (mmol/L)	4.1 (3.3-4.6)	3.8 (3.3-4.4)	0.076
HDL-cholesterol (mmol/L)	1.3 (1.1-1.6)	1.1 (1.0-1.5)	0.071
Triglycerides (mmol/L)	1.1 (0.9-1.5)	1.3 (1.0-2.0)	0.023
Biochemical variables at OGTT, median (IQR)			
Fasting blood glucose (mmol/L)	4.8 (4.5-5.2)	5.4 (4.8-5.8)	<0.001
Two-hour glucose (mmol/L)	6.2 (5.5-7.0)	9.1 (8.1-10.9)	<0.001
Insulin at baseline (pmol/L)	45 (31-67)	53 (36-89)	0.118
Insulin 120 min (pmol/L)	194 (120-293)	349 (224-555)	<0.001
Proinsulin baseline (pmol/L)	2.1 (1.2-4.0)	2.9 (1.7-6.8)	0.013
HOMA-IR| | at discharge (mU mmol/L)	1.83 (1.28-2.64)	2.38 (1.51-4.11)	0.011

IQR=interquartile range.*Normal glucose tolerance. †Abnormal glucose tolerance. ‡HbA1c presented as Mono S (%) and IFCC (mmol/mol) standards. \| \|HOMA-IR=Homeostasis Model Assessment of Insulin Resistance.

Controls
In controls, AGT was related to a major cardiovascular event (HR 2.13; 95% CI 1.03-4.41, p=0.042), while fasting blood glucose (p=0.81) and HbA1c were not (HbA1c ≥4.7%, p=0.77; HbA1c 4.7%-5.5%, p=0.70; HbA1c ≥5.6%, p=0.94). Further, univariate variables with a p-value of <0.10 are described in Figure 14B.

The final Cox regression model, including age, gender, hypertension and AGT, identified age (1.09; 1.04-1.14, p<0.001), female gender (0.11; 0.03-0.46, p=0.003) and hypertension (3.05; 1.36-6.85, p=0.007) as remaining predictors of a major cardiovascular event, while AGT did not remain as an independent predictor (Figure 14B).

Study III

Clinical data

Of 58 891 patients, 19% had diabetes, whereof 27% were on diet only and 33% had been prescribed oral glucose-lowering drugs and 40% insulin treatment. ACS (unstable angina pectoris and AMI) was the most common indication for the PCI. Cardiovascular risk factors, multiple coronary vessel disease and left main stem disease were more frequent in patients with diabetes, particularly if insulin treated, and their revascularisation was less often complete (Table 6). There was no significant difference in the numbers of stents implanted in the different groups, although patients with diabetes more frequently received DES than those without (33% vs. 24%). Furthermore, there was only a minor difference in pre- and per-operative treatment between the two groups.

Cardiovascular events and mortality

In all 1619 (14%) of the patients with diabetes (322 [10.5%] in the diet group, 412 [11%] in the oral glucose-lowering group and 885 [19%] in the insulin group) and 3825 (8%) of the patients without diabetes died during a mean follow-up period of 920 (SD 530, range 0-1825) days (estimated cumulative mortality rate presented in Figure 15).

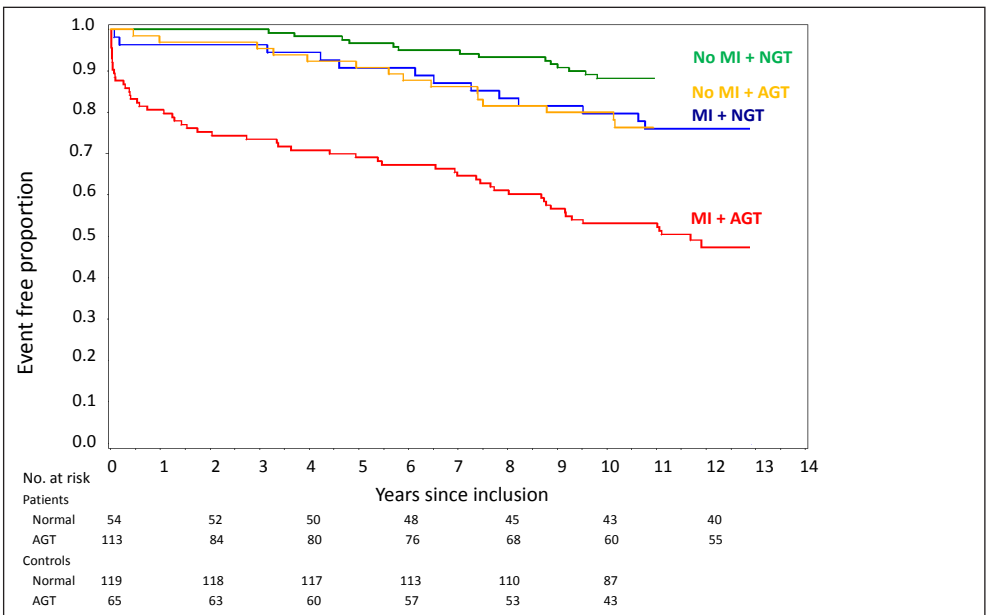
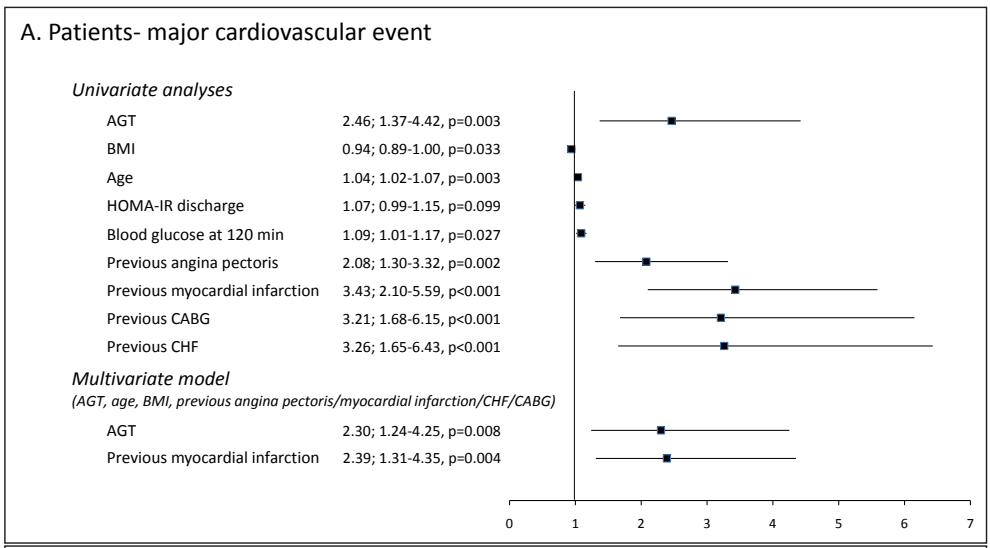


Figure 13. Time to major cardiovascular events in patients and controls. Log-rank test p=0.002 for patients with AGT vs. NGT. Log-rank test p=0.037 for controls with AGT vs. NGT.

The composite cardiovascular event (total mortality, AMI, stroke or heart failure) was more frequent in patients on insulin followed by those on oral glucose-lowering drugs and diet and lowest in patients without diabetes (Figure 16). Following adjustment, the risk of developing a composite cardiovascular event was increased in patients on insulin (HR 1.63; 95% CI 1.55-1.72), on oral treatment (1.23; 1.15-1.31) and on diet only (1.21; 1.12-1.29) compared with patients without diabetes. The unadjusted and adjusted risk of a future event is presented in Table 7.

The presence of diabetes increased the risk of future non-fatal events, in particular heart failure and renal failure. Insulin-treated patients had a substantially increased risk of restenosis (1.54; 1.39-1.71) and stent thrombosis (1.56; 1.25-1.96).



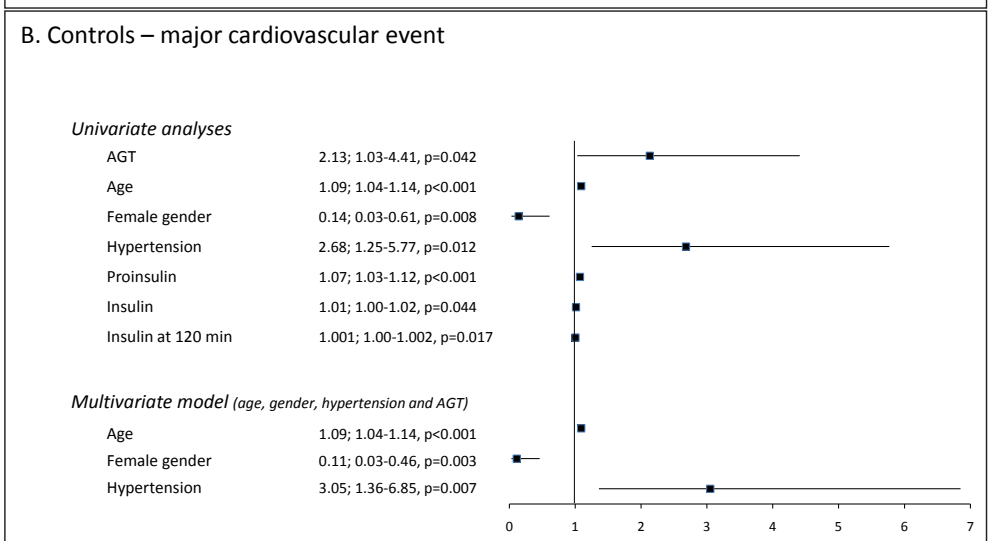
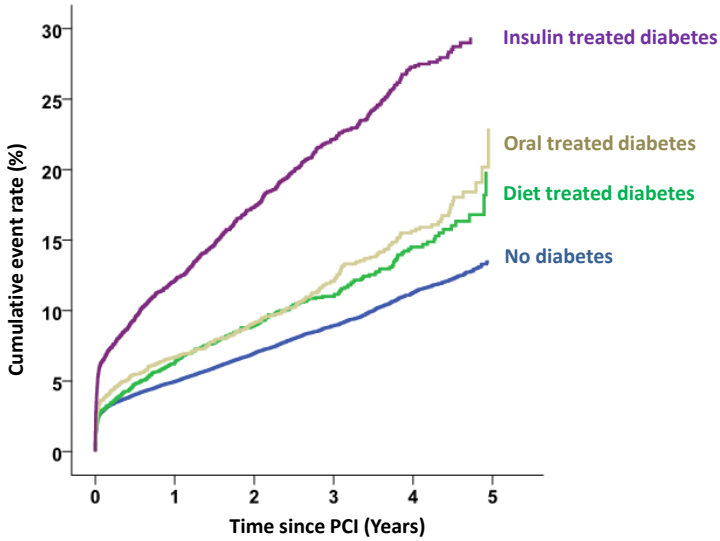


Figure 14. Variables related to major cardiovascular events in patients (A) and controls (B) in univariate and multivariate analyses.

Table 6. Baseline characteristics by diabetes status and treatment at first PCI. The data are presented as n (%) unless otherwise stated.

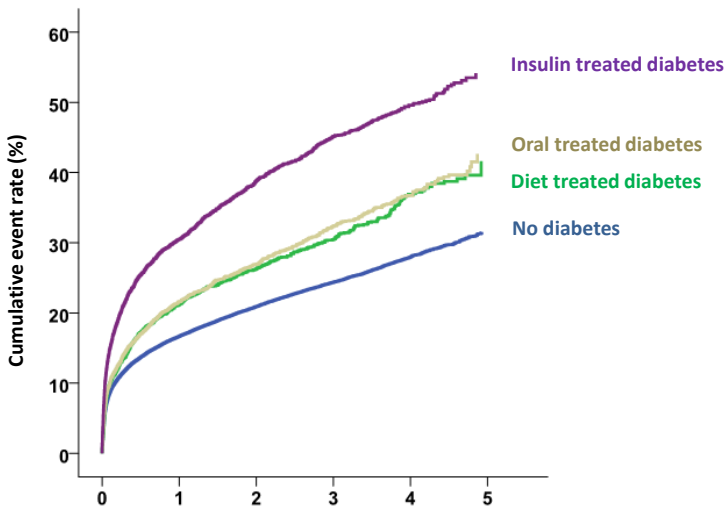
	No diabetes n=47454 n (%)	Diabetes n=11437 n (%)	Diet n=3061 n (%)	Oral n=3771 n (%)	Insulin n=4605 n (%)	P overall
Clinical characteristics						
Age; years, mean (SD)	66 (11)	68 (11)	67 (11)	68 (10)	67 (11)	<0.001
Male	33816 (71)	7639 (67)	2122 (69)	2626 (70)	2891 (63)	<0.001
Smoker (yes)	11158 (24)	2160 (19)	725 (24)	683 (18)	752 (16)	<0.001
Previous diseases						
Hypertension (treated)	20468 (43)	7744 (68)	1777 (58)	2671 (71)	3296 (72)	<0.001
Hyperlipidaemia (treated)	15847 (33)	6275 (55)	1258 (41)	2130 (57)	2887 (63)	<0.001
Myocardial infarction	4456 (9)	1906 (17)	382 (13)	573 (15)	951 (21)	<0.001
Heart failure	1708 (4)	1006 (9)	176 (6)	232 (6)	598 (13)	<0.001
Stroke	2367 (5)	1073 (9)	197 (6)	321 (9)	555 (12)	<0.001
Renal insufficiency	472 (1)	392 (3)	69 (2)	34 (1)	289 (6)	<0.001
Peripheral artery disease	1105 (2)	356 (3)	100 (3)	123 (3)	333 (7)	<0.001
Indication for PCI						
Stable CAD disease	7460 (16)	2107 (18)	402 (13)	791 (21)	914 (20)	<0.001
Non-ST-elevation ACS*	22333 (47)	5675 (50)	1460 (48)	1855 (49)	2360 (51)	<0.001
STEMI	16633 (35)	3383 (30)	1150 (38)	1034 (27)	1199 (26)	<0.001
PCI result						
Complete revascularisation	30288 (64)	6388 (56)	1799 (59)	2163 (57)	2426 (53)	<0.001
Angiographic finding						
Normal/atheromatosis	588 (1)	152 (1)	46 (2)	48 (1)	58 (1)	<0.001
One-vessel disease	24679 (52)	4853 (42)	1423 (47)	1638 (43)	1792 (39)	<0.001
Two-vessel disease	14273 (30)	3728 (33)	949 (31)	1262 (34)	1517 (33)	<0.001
Three-vessel disease	6520 (14)	2260 (20)	531 (17)	704 (19)	1025 (22)	<0.001
Left main stem disease	1345 (3)	419 (4)	107 (4)	108 (3)	204 (4)	<0.001
Stent implantation						
Stents/patient; mean (SD)	1.5 (0.9)	1.5 (1.0)	1.5 (0.9)	1.5 (0.9)	1.5 (1.0)	0.441
Drug-eluting stent (%)	11545 (24)	3802 (33)	823 (27)	1279 (34)	1700 (37)	<0.001
Only bare metal stent (%)	32937 (69)	6677 (58)	2022 (66)	2194 (58)	2461 (53)	<0.001
No stent (%)	2972 (6)	742 (7)	216 (7)	298 (8)	444 (10)	<0.001
Treatment at PCI						
Aspirin (before)	43257 (91)	10521 (92)	2807 (92)	3492 (93)	4222 (92)	0.059
Clopidogrel (before)	38768 (82)	9291 (81)	2528 (83)	3081 (82)	3682 (80)	0.042
Bivalirudin (during)	10093 (21)	2355 (21)	635 (21)	785 (21)	935 (20)	<0.001
GP2B/3A inhibitor (during)	12531 (26)	2721 (24)	891 (29)	835 (22)	995 (22)	<0.001

* Non-ST-elevation ACS: unstable angina or non-ST-elevation myocardial infarction.



No. at risk						
No diabetes	47454	36155	26752	17596	8658	10
Diet	3061	2351	1712	1129	547	3
PO	3771	2770	2015	1321	639	2
Insulin	4605	3231	2278	1429	665	2

Figure 15. Estimated cumulative rate of mortality after a first PCI in patients with and without diabetes and by glucose treatment.



No. at risk						
No diabetes	47454	31719	22801	14673	7005	8
Diet	3061	1967	1370	876	395	1
PO	3771	2325	1611	1026	492	2
Insulin	4605	2549	1675	995	441	2

Figure 16. Estimated cumulative rate of the composite endpoint (total mortality, AMI, stroke or heart failure) after a first PCI in patients with and without diabetes and by glucose treatment.

Table 7. Unadjusted and adjusted risk of a first event after PCI in patients with diabetes by glucose-lowering treatment in comparison with patients without diabetes.

Event	Unadjusted HR (95% CI)	p	Adjusted† HR (95% CI)	p
All-cause mortality				
No diabetes	1		1	
Diet	1.30 (1.16-1.46)	<0.001	1.22 (1.09-1.37)	<0.001
Oral	1.40 (1.26-1.55)	<0.001	1.22 (1.10-1.35)	<0.001
Insulin	2.59 (2.41-2.79)	<0.001	1.91 (1.77-2.07)	<0.001
AMI				
No diabetes	1		1	
Diet	1.23 (1.11-1.37)	<0.001	1.11 (0.99-1.23)	0.064
Oral	1.17 (1.06-1.29)	0.002	1.09 (0.98-1.20)	0.108
Insulin	1.69 (1.57-1.83)	<0.001	1.40 (1.29-1.53)	<0.001
Heart failure				
No diabetes	1		1	
Diet	1.65 (1.49-1.82)	<0.001	1.47 (1.33-1.63)	<0.001
Oral	1.63 (1.49-1.79)	<0.001	1.41 (1.28-1.55)	<0.001
Insulin	2.64 (2.45-2.83)	<0.001	1.90 (1.76-2.05)	<0.001
Stroke				
No diabetes	1		1	
Diet	1.45 (1.19-1.75)	<0.001	1.33 (1.09-1.61)	0.004
Oral	1.65 (1.40-1.95)	<0.001	1.38 (1.16-1.64)	<0.001
Insulin	2.02 (1.74-2.33)	<0.001	1.54 (1.33-1.80)	<0.001
Renal failure				
No diabetes	1		1	
Diet	2.07 (1.72-2.48)	<0.001	1.67 (1.39-2.00)	<0.001
Oral	1.82 (1.52-2.18)	<0.001	1.47 (1.23-1.77)	<0.001
Insulin	5.15 (4.60-5.77)	<0.001	2.70 (2.38-3.06)	<0.001
Restenosis				
No diabetes	1		1	
Diet	1.09 (0.95-1.25)	0.232	1.07 (0.93-1.23)	0.320
Oral	1.16 (1.03-1.31)	0.016	1.16 (1.03-1.31)	0.019
Insulin	1.64 (1.48-1.81)	<0.001	1.54 (1.39-1.71)	<0.001
Stent thrombosis				
No diabetes	1		1	
Diet	1.01 (0.74-1.38)	0.943	1.01 (0.74-1.38)	0.934
Oral	0.97 (0.73-1.30)	0.849	1.00 (0.75-1.34)	0.983
Insulin	1.66 (1.34-2.06)	<0.001	1.56 (1.25-1.96)	<0.001
CABG				
No diabetes	1		1	
Diet	1.11 (0.90-1.37)	0.331	0.98 (0.79-1.21)	0.834
Oral	1.49 (1.26-1.77)	<0.001	1.37 (1.16-1.63)	<0.001
Insulin	1.44 (1.23-1.69)	<0.001	1.26 (1.07-1.49)	0.006
Re-PCI				
No diabetes	1		1	
Diet	1.16 (1.06-1.27)	0.001	1.09 (0.99-1.20)	0.067
Oral	1.14 (1.04-1.24)	0.003	1.05 (0.96-1.14)	0.295
Insulin	1.29 (1.20-1.39)	<0.001	1.10 (1.02-1.19)	0.014
Combined cardiovascular event (mortality/AMI/stroke/HF*)				
No diabetes	1		1	
Diet	1.32 (1.23-1.41)	<0.001	1.21 (1.12-1.29)	<0.001
Oral	1.36 (1.28-1.45)	<0.001	1.23 (1.15-1.31)	<0.001
Insulin	2.05 (1.95-2.16)	<0.001	1.63 (1.55-1.72)	<0.001

*Heart failure (HF). †Adjusted for age, indication, gender, hospital, admission year, previous myocardial infarction, previous heart failure, previous renal insufficiency, previous stroke, hypertension, hyperlipidaemia, dementia, cancer diagnosis within three years, dialysis, chronic obstructive pulmonary disease, peripheral artery disease, smoking, angiographic findings, complete revascularisation, treated stenosis at bifurcation, treated chronic occlusion, BMS, DES or balloon, numbers of stents, aspirin, clopidogrel or warfarin before PCI, GP2B3A-inhibitor, heparin or bivalirudin treatment during PCI.

Study IV

Clinical data related to adiponectin

The median level of adiponectin on day 2 was 10.2 mg/L for men (IQR 6.7-14.5) and 16.6 mg/L (IQR 12.2-24.1) for women and at discharge 8.6 mg/L (IQR 5.9-14.4) for men and 16.3 mg/L (IQR 10.2-21.7) for women. The clinical and laboratory characteristics of patients above and below the median level of adiponectin at discharge are presented in Table 8. Patients with adiponectin levels above median were older, with a lower BMI and HOMA index and had a more frequent history of heart failure. The cut-off level for the highest quartile of adiponectin at discharge was 14.4 mg/L in men and 21.7 mg/L in women.

Adiponectin and mortality risk

During a median follow-up period of 11.6 years (IQR 9.6-12.1), 34% (n=61) of the patients died and 80 (44%) experienced a major cardiovascular event. Patients that died showed increasing levels of adiponectin during hospitalisation (median 0.2 mg/L (IQR -2.7 to 2.7), compared with survivors whose levels were decreasing (-0.2, -3.6 to 0.5; p=0.011). Adiponectin levels above the median at discharge were associated with higher mortality ($p<0.001$; Figure 17), with gradually separating curves over time, while the rate of major cardiovascular events did not differ between those above/below the median levels of adiponectin (log-rank p=0.234).

After adjustments for age, adiponectin levels on day 2 did not predict mortality or major cardiovascular events, while high adiponectin levels at discharge remained a predictor of total mortality (1.69; 1.07-2.68, p=0.026) and cancer mortality (3.87; 1.43-10.48, p=0.008). After further adjustment for previous myocardial infarction, previous CHF and BMI, adiponectin still predicted total mortality (1.67; 1.04-2.68, p=0.035) and remained even when gender was forced into the model (1.79; 1.07-3.00, p=0.027). When adiponectin was categorised as gender-specific median values, it did not substantially change the predictive value (data not shown). High levels of adiponectin at discharge corresponding to the highest quartile (men: >14.4 mg/L; women: >21.7 mg/L) were strongly associated (age adjusted) with total mortality (3.57; 1.30-9.82, p=0.014). Mortality by quartiles of adiponectin at discharge is presented in Figure 18.

Clinical data related to leptin

The median level of leptin was 8.9 ng/ml for men and 22.6 ng/ml for women on day 2 and 6.7 ng/L for men and 22.2 ng/ml for women at discharge. The clinical and laboratory characteristics of patients by the median level of leptin on day 2 are presented in Table 9. Patients with leptin levels above median had a higher BMI, HOMA-IR, CRP, triglycerides and more frequent AGT and previous hypertension but a less frequent history of cancer.

Leptin and cardiovascular risk

Leptin levels on day 2 or at discharge with or without categorisation by gender-specific medians did not predict total mortality or any major cardiovascular events during the complete follow-up period. Leptin levels above the median on day 2 did however predict major cardiovascular events during the first seven years following the index AMI (unadjusted HR; 95% CI by year: 1: 1.70; 1.10-2.63, year 2: 1.70; 1.15-2.53, year 3: 1.55; 1.06-2.28, year 4: 1.57; 1.09-2.26, year 5: 1.52; 1.07-2.15, year 6: 1.48; 1.05-2.07, year 7: 1.39; 1.01-1.91), as illustrated by the converging Kaplan-Meier curves (Figure 19).

Table 8. Clinical and laboratory characteristics in patients divided into those above and below the median (men 8.6 mg/L, women 16.3 mg/L) for adiponectin at discharge. The data presented are n (%) unless otherwise stated.

	Adiponectin ≤median (n=81) n (%) or median (IQR)	Adiponectin >median (n=81) n (%) or median (IQR)	p
Clinical characteristics			
Age (years), median (IQR)	60 (54-67)	67 (60-74)	<0.001
Gender (male)	57 (70)	57(70)	1.000
Current smoker	33 (41)	24 (30)	0.139
BMI (kg/m^2), median (IQR)	28.2 (25.2-30.4)	24.6 (22.3-26.8)	<0.001
Blood pressure (mm/Hg), median (IQR)			
Systolic	156 (133-177)	146 (135-160)	0.073
Diastolic	94 (83-105)	90 (80-100)	0.195
Medication prior to admission			
Aspirin	23 (28)	47 (58)	0.594
β-blockade	26 (32)	28 (35)	0.739
ACE inhibitor	8 (10)	7 (9)	0.786
Statin	10 (12)	9 (11)	0.807
Transmural myocardial infarction	35 (43)	28 (35)	0.509
Reperfusion therapy	41 (51)	39 (48)	0.694
Medication at discharge			
Aspirin	73 (90)	75 (93)	0.738
β-blockade	75 (93)	70 (86)	0.098
ACE inhibitor	9 (11)	15 (19)	0.195
Statin	47 (58)	40 (49)	0.204
Previous disease			
Myocardial infarction	16 (20)	15 (19)	0.842
Heart failure	3 (4)	10 (12)	0.043
Hypertension	29 (36)	23 (28)	0.313
Hyperlipidaemia	16 (20)	9 (11)	0.128
Stroke	3 (4)	3 (4)	1.000
Cancer	1 (1)	3 (4)	0.620
Biochemistry, median (IQR) or n (%)			
Fasting blood glucose (mmol/L) day 2	5.6 (5.0-6.1)	5.4 (4.8-6.1)	0.365
HbA1c (%), (mmol/mol)* day 2	4.9 (4.5-5.3), 41 (36-45)	4.9 (4.6-5.2), 41 (37-44)	0.928
Creatinine (mmol/L) at admission	92 (81-102)	89 (82-103)	0.902
hs-CRP day 2 (mg/L)	11 (4-26)	12 (5-25)	0.657
Cortisol day 2 (nmol/L)	442 (342-574)	489 (347-586)	0.363
Cholesterol day 2 (mmol/L)	6.0 (5.2-7.2)	5.9 (5.1-6.6)	0.150
LDL day 2 (mmol/L)	3.7 (3.1-4.6)	3.9 (3.1-4.4)	0.694
HDL day 2 (mmol/L)	1.1 (0.9-1.3)	1.2 (1.1-1.4)	<0.001
Triglycerides day 2 (mmol/L)	2.6 (1.8-3.2)	1.7 (1.4-2.4)	<0.001
Abnormal glucose tolerance at OGTT	55 (68)	51 (63)	0.737
IGI† at discharge	49 (33-80)	50 (26-87)	0.906
HOMA-IR‡ at discharge (mU mmol/L)	2.73 (1.69-4.20)	1.93 (1.20-2.67)	<0.001
Leptin at discharge (ng/ml)	11.4 (7.0-20.7)	6.4 (4.2-15.2)	0.003

IQR=interquartile range. *HbA1c presented as Mono S standard (%) and IFCC (mmol/mol). †IGI=Insulinogenic Index. ‡HOMA-IR=Homeostasis Model Assessment of Insulin Resistance.

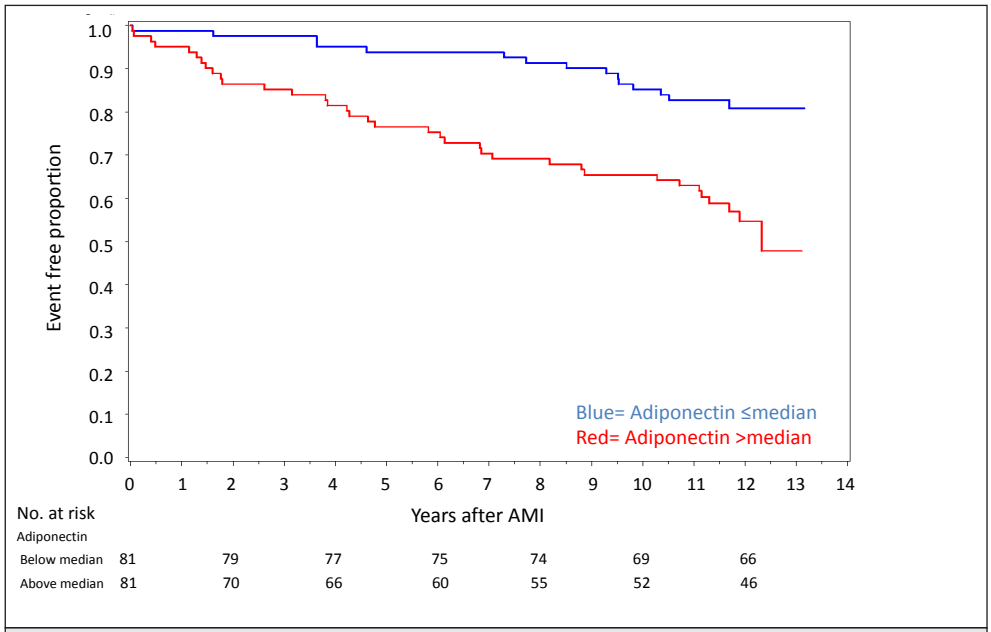


Figure 17. Kaplan-Meier curves for adiponectin at discharge divided into patients above and below the median (men 8.6 mg/L), women 16.3 mg/L) related to all-cause mortality, log-rank (p<0.001).

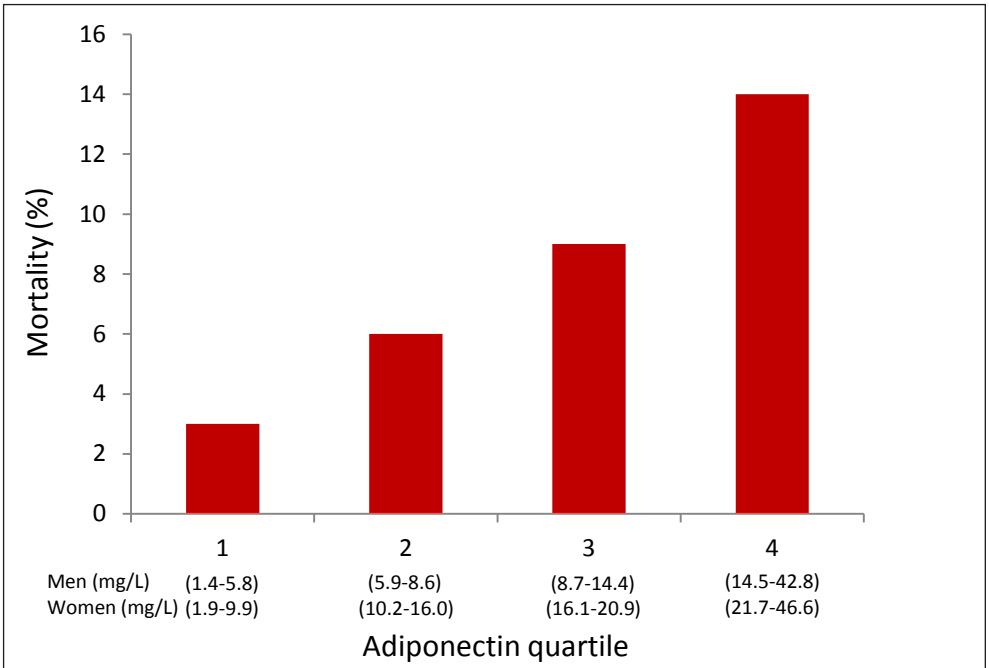


Figure 18. Mortality percentages (%) by quartiles of adiponectin at discharge.

Table 9. Clinical and laboratory characteristics of patients divided into those above and below the median (men 8.9 ng/ml and women 22.6 ng/ml) for leptin on day 2. The data presented are n (%) unless otherwise stated.

	Leptin ≤median (n=91) n (%) or median (IQR)	Leptin >median (n=89) n (%) or median (IQR)	p
Clinical characteristics			
Age (years), median (IQR)	62 (56-70)	64 (57-72)	0.130
Male gender	28 (31)	28 (31)	0.920
Current smoker	36 (40)	25 (28)	0.243
BMI (kg/m^2), median (IQR)	24.1 (22.3-26.2)	28.6 (26.0-31.1)	<0.001
Blood pressure (mm/Hg), median (IQR)			
Systolic	150 (130-170)	150 (133-172)	0.391
Diastolic	90 (80-101)	93 (80-100)	0.629
Medication prior to admission			
Aspirin	22 (24)	29 (33)	0.211
β-blockade	26 (29)	32 (36)	0.289
ACE inhibitor	6 (7)	10 (11)	0.274
Statin	9 (10)	11 (12)	0.598
Transmural myocardial infarction	34 (37)	35 (39)	0.761
Reperfusion therapy	51 (56)	35 (39)	0.029
Medication at discharge			
Aspirin	83 (92)	77 (93)	0.891
β-blockade	79 (88)	79 (95)	0.084
ACE inhibitor	12 (13)	14 (17)	0.516
Statin	52 (76)	41 (66)	0.192
Previous disease			
Myocardial infarction	14 (15)	22 (25)	0.118
Heart failure	8 (9)	6 (7)	0.608
Hypertension	19 (21)	38 (43)	0.002
Hyperlipidaemia	12 (13)	15 (17)	0.491
Stroke	2 (2)	4 (4)	0.441
Cancer	5 (5)	0 (0)	0.059
Biochemistry, median (IQR) or n (%)			
Fasting blood glucose (mmol/L) day 2	5.3 (4.8-5.8)	5.7 (5.2-6.7)	<0.001
HbA1c (%), (mmol/mol)* day 2	4.9 (4.6-5.2), 41 (37-44)	5.0 (4.5-5.4), 42 (36-46)	0.414
Creatinine (mmol/L) at admission	89 (81-101)	94 (81-106)	0.263
hs-CRP day 2 (mg/L)	10.0 (3.6-18.2)	14.9 (5.7-38.6)	0.032
Cortisol day 2 (nmol/L)	487 (353-617)	463 (334-584)	0.395
Cholesterol day 2 (mmol/L)	6.0 (5.2-6.7)	6.0 (5.2-7.4)	0.317
LDL day 2 (mmol/L)	3.9 (3.1-4.4)	3.7 (3.0-4.7)	0.038
HDL day 2 (mmol/L)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	0.735
Triglycerides day 2 (mmol/L)	1.95 (1.40-2.85)	2.50 (1.75-3.30)	0.004
Adiponectin day 2 (mg/L)	13.5 (9.4-20.9)	10.9 (6.8-15.1)	0.002
Abnormal glucose tolerance at OGTT	47 (56)	66 (80)	0.001
IGI† at discharge	47 (27-70)	50 (35-83)	0.217
HOMA-IR‡ at discharge (mU mmol/L)	1.78 (1.17-2.44)	3.00 (2.19-4.57)	<0.001

IQR=interquartile range. *HbA1c presented as Mono S standard (%) and IFCC (mmol/mol). †IGI=Insulinogenic Index. ‡HOMA=Homeostasis Model Assessment of Insulin Resistance.

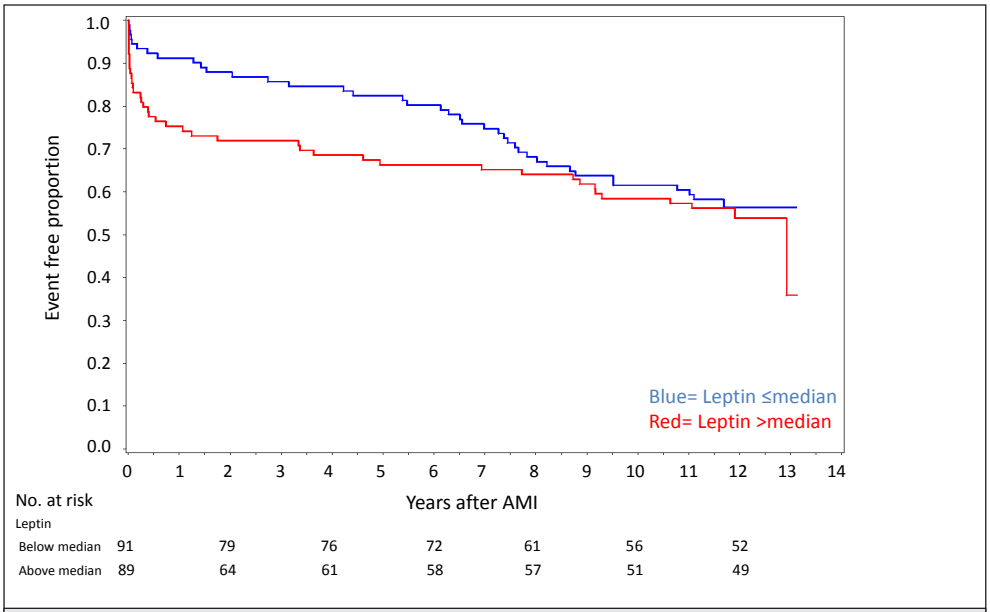


Figure 19. Kaplan-Meier curves for leptin on day 2 divided into patients above and below the median (men 8.9 ng/ml; women 22.6 ng/ml) related to cardiovascular events (log-rank p=0.422).

Studies II and IV

Outcome

Overview for events and patients and controls in the GAMI cohort by glucose tolerance state and medians of adiponectin and leptin (Table 10).

Table 10. Events in the GAMI cohort during follow-up (patients 11.6 years and controls 10.4 years).

	All patients n=180 n (%)	Patients with NGT n=54 n (%)	Patients with AGT n=113 n (%)	Patients with adiponectin ≤median n=81 n (%)	Patients with adiponectin >median n=81 n (%)	All controls n=184 n (%)	Controls with NGT n=119 n (%)	Controls with AGT n=65 n (%)
Total mortality	61 (34)	14 (26)	39 (35)	15 (19)	36 (44)	28 (15)	13 (11)	15 (23)
Cardiovascular death	35 (19)	5 (9)	26 (23)	10 (67)	21 (58)	12 (7)	4 (3)	8 (12)
Cancer death	18 (10)	9 (17)	6 (5)	4 (27)	10 (28)	11 (6)	7 (6)	4 (6)
Miscellaneous death*	7 (4)	0 (0)	6 (5)	1 (7)	5 (14)	5 (3)	2 (2)	3 (5)
Non-fatal stroke	15 (8)	3 (6)	11 (10)	7 (9)	7 (9)	7 (4)	3 (3)	4 (6)
Non-fatal myocardial infarction	34 (19)	5 (9)	26 (23)	16 (20)	14 (17)	10 (5)	6 (5)	4 (6)
Severe heart failure	23 (13)	3 (6)	20 (18)	6 (7)	17 (21)	6 (3)	4 (3)	2 (3)
Major cardiovascular event	80 (44)	14 (26)	58 (49)	31 (38)	40 (49)	29 (16)	14 (12)	15 (23)

*Death due to infections, accidents etc. One patient could not be classified according to death cause. Each event is recorded only once.

Studies I-IV

Mortality causes

Mortality causes in the three different study populations are presented in Table 11. Cardiovascular reasons were behind 80% of the mortality causes in the patients with diabetes and myocardial infarction in the DIGAMI cohort and 64% among individuals with diabetes compared with 67% without diabetes in the SCAAR cohort. There were no major differences in mortality causes between the intensified and the control group in Study I (DIGAMI). In the GAMI cohort (Studies II and IV) cardiovascular death was more common in patients and cancer was more frequent in controls. In Study III (SCAAR) death due to cancer was more common among patients without diabetes while endocrine/metabolic diseases were a more prevalent cause of death in patients with diabetes.

Table 11. Mortality causes (%) by study cohort. Data presented are the proportion of the total mortality within each cohort.

	DIGAMI (I)		GAMI (II, IV)		SCAAR (III)	
	Intensified	Control	Patients	Controls	No Diabetes	Diabetes
Cardiovascular	79	81	57	43	67	64
Ischaemic	48	43	41	18	56	54
Heart failure	7	9	10	7	2	2
Cerebrovascular	5	12	2	4	6	5
Cancer	8	7	30	39	18	12
Other	13	12	11	18	15	24

Other=infection, renal disease, respiratory disease, gastrointestinal disease or endocrine/metabolic disease.

General Discussion

Diabetes and previously undetected glucose abnormalities are common in patients with AMI and affect the subsequent prognosis. Despite improvements in the management of acute coronary events during the last decades patients with diabetes are still at increased risk in terms of mortality and new cardiovascular events. The focus of the present thesis is to characterise patterns of complications, mortality causes and the impact of glucose control after AMI with the aim to identify potential ways to improve the prognosis. Both patients with established diabetes and newly detected glucose abnormalities were studied.

Glucose control and cardiovascular outcome

Both an extensive use of evidence based therapy in the acute setting and a carefully conducted secondary prevention are important to improve the prognosis after AMI in patients with diabetes.[204] In addition primary prevention and multifactorial risk factor control are of importance to reduce cardiovascular complications.[215-218] The UKPDS found that LDL, blood pressure and HbA1c were the strongest predictors for CHD in patients with type 2 diabetes at low cardiovascular risk.[215-217] The Steno-2 study underlined the importance of a multifactorial intervention to reduce mortality and decrease micro- as well as macrovascular complications in patients with type 2 diabetes and microalbuminuria.[218] The investigators behind the Steno 2 study analysed the relative contribution of lipid, blood pressure and glucose control to the observed cardiovascular benefits. They noted that lipid control (73% of the benefit) was considerably more important than blood pressure (11%) and glucose control (13%).[219] The capability of glucose control to reduce macrovascular complications has after the DIGAMI 2, ACCORD, ADVANCE and Veteran's Affairs Diabetes Trial (VADT) studies been questioned, especially in patients with longstanding diabetes and established CVD. One exception is the use of metformin, which reduced total mortality and myocardial infarction in overweight newly diagnosed diabetes patients in the UKPDS study and the major reason behind the recommendations of metformin as first-line therapy.[174]

Study I demonstrates that intensified, insulin-based glycaemic control in patients with AMI and clearly deranged blood glucose is of importance, increasing longevity by almost 50%.[220] These results from a cohort with established CAD extends the results from primary prevention as in the long-term follow-up of DCCT and UKPDS.[140,221] In these studies the positive impact of intensified glycaemic control on mortality and macrovascular events was not noted until 22 and 30 years of follow-up respectively while the impact on microvascular complications was seen already earlier. The benefit was seen despite a convergence of HbA1c levels over time giving rise to the discussion of a glycaemic memory, "the legacy effect", first in type 1 diabetes (DCCT) and thereafter in type 2 diabetes (UKPDS).[140,221] The background for this legacy effect has been debated and it has been proposed that it does not only apply to improved glucose levels but also to control of other vascular risk factors as blood lipids[222] and hypertension.[223,224] Mechanisms for the glycaemic memory may include formation of superoxide anions,[225] reduced NO availability,[226] changes in glycation which may alter the function of proteins,[227] and activation of NFkB pathway mediating inflammation.[226] Furthermore gene expression may be modified through changes in microRNA[228] and epigenetic changes where the up-regulation of Pin1 has been suggested crucial.[226] As the legacy effect

comprises factors that are important during a lifetime, affecting on outcome seen later in life, it highlights the importance of early instituted glucose- and risk factor control. Moreover it underlines the relevance of long-term follow-up of trials studying such interventions as in the 20 years report of the first DIGAMI cohort, which followed patients towards 90% mortality. A too short study period may explain why the ACCORD[170] study, terminated prematurely after 3.5 years because of a rising mortality rate in the intensified group, or ADVANCE[169] with 5 years of follow-up was not able to show any cardiovascular benefit despite high event rates. Compared to DCCT[127] and UKPDS,[128] ACCORD,[170] ADVANCE[169] and VADT[173] included patients at high cardiovascular risk. In Study I intensified insulin-based glycaemic control had the most pronounced effect in patients with low cardiovascular risk without previous insulin treatment while it did not seem to improve the outcome in patients at high risk without previous insulin. This supports the conclusions from the ACCORD and ADVANCE trials that intensified glycaemic control in patients with longstanding diabetes and advanced CVD does not seem to improve mortality. There are several explanations to the discrepant findings in Study I compared to the ACCORD and ADVANCE trials. It must be kept in mind that in the DIGAMI cohort (Study I) secondary prevention was considerably less well developed compared to such studies as ACCORD and ADVANCE, for instance, angiotensin-converting enzyme inhibitors were only prescribed to a third of the patients and none received statins as the integration of statins in secondary prevention was started after 1994.[229] Moreover glycaemic control at hospital admission was considerably worse and the subsequent mortality higher when Study I was conducted compared to the conditions when the more recent studies were initiated. The proportionate impact of the intensified glycaemic control might therefore have been much more apparent.

It has been debated which glycaemic level to aim for and likewise what choice of glucose lowering therapy that is most beneficial. The intensified insulin-based treatment in DIGAMI, aimed for a blood glucose of 7-10 mmol/L during the period of intensive care and a fasting level <7 mmol/L during follow-up. In ACCORD the intensified target, an HbA1c <6.0% (IFCC <42 mmol/mol), was lower than in previous studies while the standard target was an HbA1c of 7.0-7.9% (IFCC 53-63 mmol/mol). To reach these goals several glucose lowering drugs were allowed introducing a potential for complex drug interactions and risk for hypoglycaemia. For instance 91% in the intensified group vs. 58% in the standard group were treated with rosiglitazone, a drug that was withdrawn from the market in 2010 due to a suspicion of increased cardiovascular risk.[170] In ADVANCE all patients in the intensified group were treated with sulphonylurea among other glucose lowering therapy to achieve HbA1c ≤6.5 (IFCC ≤48 mmol/mol) with potential increased risks for hypoglycaemia.[169] In DIGAMI 10% of the patients in the intensified group had to stop insulin treatment during hospitalisation because of hypoglycaemic episodes. In ACCORD, ADVANCE and VADT hypoglycaemia was at least twice as common in the intensive compared to the control arm (intensive vs. standard group; 10.5 vs. 3.5, 2.7 vs. 1.5 and 21.2 vs. 9.9%).[169,170,173] However, although an association of hypoglycaemia and increased cardiovascular mortality risk has been described, it is not clearly established that pharmacologically induced hypoglycaemic episodes are related to increased cardiovascular risk and if this may have contributed to the increased mortality in the ACCORD study.[230,231] Both in the NICE-SUGAR[232] and in the ORIGIN study[233] there was a stronger association between hypoglycaemia and cardiovascular mortality in the control than in the insulin arm respectively. If there is a causality link between hypoglycaemia and adverse events or if a hypoglycaemic event identifies patients that are vulnerable due to other reasons is not fully elucidated as mortality from other causes than

cardiovascular are dominant the following year after a severe hypoglycaemia.[234]
Study I is not able to answer whether the gain in life expectancy relates to the initial glucose insulin infusion or the continued long-term glucose control. DIGAMI 2[171] was designed to clarify this but did not show any mortality benefit during the period of hospitalisation or the three years of follow-up. In fact the first DIGAMI study is the only study that have showed reduced mortality with intensified glucose control after AMI.[171] One reason for this may be that no significant difference in glucose levels between the intensified insulin-based and the control group was achieved in DIGAMI 2. Another explanation is that blood glucose and HbA1c at admission were substantially higher in DIGAMI 1 than DIGAMI 2 (mean blood glucose 15.4 mmol/L ±SD 4.1 vs. 12.8 mmol/L ±SD 4.5 and HbA1c 8.2% ±SD 1.9 vs. 7.2% ±SD 1.7).[171]

In summary there are five major reasons why only the first DIGAMI study and few other studies succeed to show benefits of intensive glucose lowering on cardiovascular outcome. First, inclusion of high-risk patients with long-standing type 2 diabetes and increased incidence of advanced vascular damage with less possibilities to influence already existing damage.[235] Secondly extensive use of concomitant treatment of other cardiovascular risk factors.[235] Third, aggressive glucose lowering therapy may be associated with risk of hypoglycaemia and weight gain but also direct harmful drug interactions.[128,235,236] Fourth, as in DIGAMI 2, that no significant difference was achieved in glucose control between the intensive and standard arm.[171,235] Finally it should be considered if the most appropriate outcome was studied. Currently the most common initial manifestation of macrovascular disease in patients with diabetes include peripheral arterial disease and heart failure while cardiovascular mortality and the incidence of AMI and stroke has declined.[139,237] These endpoints may have made sense when the UKPDS and the first DIGAMI trials were initiated but perhaps not in the contemporary environment. Still most clinical trials continued to use a composite of cardiovascular mortality, non-fatal AMI or stroke as the primary outcome. As demonstrated in Study III heart failure was the most common adverse event (19%) among patients with diabetes treated with a first PCI.[238] Hospitalisation for heart failure might thus be a previous neglected but a more appropriate primary outcome to address when studying cardiovascular morbidity in patients with diabetes.[239] Furthermore, other approaches than tight glucose control to reduce cardiovascular complications might be beneficial although studied in a limited extent. In this respect the recent EMPA-REG OUTCOME study, the LEADER trial and the SUSTAIN-6 trial are of interest. There was a statistically significant reduction of cardiovascular and total mortality as well as for hospitalisation for heart failure (35%) in the EMPA-REG OUTCOME study[177] and cardiovascular and total mortality in the LEADER trial[178] when adding the SGLT-2-inbhibitor empagliflozin[177] or the GLP-1 receptor agonist liraglutid[178] to standard therapy in patients with type 2 diabetes. In SUSTAIN-6 the rate of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke was significantly lower among patients receiving the long-acting GLP-1 receptor agonist semaglutide compared to those receiving placebo, principally driven by a significant (39%) decrease in the rate of non-fatal stroke.[179] Only modest improvements in glycaemic control were detected in these trials why other mechanisms than strict glucose lowering seem to be crucial to improve outcome.

Long-term outcome after coronary artery disease and revascularisation

Multifactorial treatment in patients with diabetes and coronary heart disease also comprises interventional therapy as PCI and CABG if signs of coronary ischaemia.[240] In a modern

unselected nationwide cohort as the SCAAR population in Study III a significant proportion of patients with diabetes are naive to coronary interventions despite suffering a previous AMI (17% compared to 9% in patients without diabetes). This indicates an underuse of revascularisation especially among patients with diabetes. For patients with diabetes and multivessel disease CABG has been documented as a better revascularisation alternative than PCI due to lower mortality and less coronary events during follow-up.[205-207] Still 15% (20% of those with diabetes vs. 14% of those without) of the patients in Study III undergoing a first PCI have three-vessel disease. It can only be speculative if those patients rather should have been subjected to a CABG rather than a PCI and if that would have altered their prognosis. Furthermore the decision might have been influenced by the patient preference and/or the doctor's recommendation to avoid open surgery due to comorbidities. Patients treated with insulin are at a particularly high risk including stent occlusions and restenosis. In Study III 45% of insulin treated patients had a new cardiovascular event (total mortality, stroke, myocardial infarction and heart failure) within three years. The strikingly high event rate in a modern setting advocates a close follow-up of patients with diabetes in order to reduce the complication rate. The event rate from this unselected cohort is higher than in the randomised controlled Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial in which the subgroup on insulin had a five-year event rate (all-cause mortality, stroke, myocardial infarction) of 32% after PCI.[241] In this context it is of interest that the event rate was significantly reduced, regardless of insulin or coronary lesion complexity (estimated as SYNTAX score) in patients randomised to CABG.[241] Unfortunately the assessment of SYNTAX score was not feasible in Study III, but such information could have given further details on the complexity of the CAD in individuals with diabetes with or without insulin treatment and its eventual influence on outcome. Reasons why the insulin treated patients are especially prone to future cardiovascular event cannot be explained in Study III but only be speculative since treatment was not randomised. The increased proportion of restenosis and stent occlusions can only explain some events. Prescription of insulin can reasonably be considered as a proxy for long standing diabetes where the insulin treated group may reflect a more severe disease that may not be possible to adjust for. The results from Study I and from the ORIGIN study, the first with reduced mortality with insulin-based glucose control and the latter with a neutral effect on cardiovascular outcome in the insulin group, contradicts that insulin per se should be harmful compared to the standard therapies available at that time.[220,242]

Impact of undetected glucose abnormalities on long-term outcome

Around twenty per cent of the patients suffering from an AMI have previously known diabetes,[155] another two thirds have unknown glucose abnormalities which can be identified by an OGTT.[156] Several investigations studied the prognostic implication of newly detected glucose abnormalities in a short-term perspective up to three years following an AMI.[160-163] However the long-term follow-up of the GAMI cohort (Study II) reveals that newly detected AGT constitute an important, independent and long-lasting prognostic factor during at least a decade after an AMI.[243] Neither fasting glucose nor HbA1c had the predictive power as categorisation of AGT from 2-hour post load glucose levels.[243] Our findings contrasts those presented by Kuhl et al. They studied 750 patients with ACS from a single Swedish center during four years without finding any difference in terms of mortality and re-infarction between those with NGT and AGT.[244] This discrepancy is confusing but an explanation might be a difference in the methodological follow-up of the OGTT results. Kuhl et al. communicated the result of the OGTT to the patients and glucose lowering treatment was initiated if diabetes

was detected which might have influenced long-term outcome.[244] George et al. did on the other hand present results similar to those in the GAMI study and demonstrated that IGT and newly detected diabetes in patients with AMI were independently associated with an increase in cardiovascular events and mortality two years after an AMI.[245] This was found despite advisements of lifestyle modifications and referral to a diabetologist.[245] However there was no data on type of glucose lowering treatment or adherence to such lifestyle modifications. In the GAMI cohort (Study II) patients were referred to their ordinary physician for further management if the OGTT at three months indicated diabetes. None of the patients received information on the OGTT results at discharge.

It has been debated if and how to best screen for dysglycaemia. The WHO criteria for an appropriate screening test were first published by Wilson and Jungner in 1968[246] and further modified in 2008 by Andermann et al.[247] The criteria include a recognised need of screening with a target population, a predefined objective and a scientific evidence of effectiveness.[246,247] In addition the overall benefits of screening should outweigh the potential harm. An OGTT at discharge of an AMI meet all these criteria, with a target AMI-population, finding increased cardiovascular risk to a low cost by a test with no other harm other than discomfort by the glucose liquid in some cases. The criteria also comprise an accepted treatment for the patients with the newly detected disease in this case AGT. Apart from patients with type 2 diabetes, there are to date few studies demonstrating prognostic advantages with glucose lowering treatment in patients with IGT and AMI.[248]

The timing of the OGTT following an AMI is however of importance to consider. Wallander et al. demonstrated by repeating tests up to one year following the AMI that OGTT performed 4-5 days after AMI is a reliable tool for assessment of the glucometabolic state with limited influence by stress in the acute setting.[249] Knudsen et al. found OGTT to be a non-robust marker of glucometabolic disturbance when it was performed within the first two days after onset of symptoms suggesting that OGTT should be performed first day 4-5 to avoid the influence of stress.[159] With the current shorter hospital stays this implicates a logistical concern where the most reasonable may be to analyse HbA1c and fasting glucose during hospital stay and to schedule the OGTT at the first follow-up two weeks after the index event. A great proportion of patients with glucose abnormalities would remain undetected using only fasting blood glucose or HbA1c as a screening procedure compared to OGTT.[156,250-255] In a report from EUROASPIRE IV OGTT had the greatest probability to identify undetected diabetes in stable CAD (detected 96%) compared to the combination of Hba1c and fasting plasma glucose (detected 81%).[252] HbA1c has been emphasised to be more convenient than OGTT as it can be performed at any time of the day without fasting or stable situations and requires less resources.[8] However there are limitations with HbA1c as it can be affected by other comorbidities and genetic factors.[8] Taken together Study II supports the inclusion of OGTT as a screening tool, at least if prevalent CVD, not only for diagnosing diabetes but also for identifying individuals at high cardiovascular risk.

Adiponectin and leptin as biomarkers for identifying high risk patients

As discussed the combination of CVD and glucose abnormalities has serious prognostic consequences. Although this thesis cannot determine any direct causation dysregulated adipokines as adiponectin and leptin may be one mechanism of importance since dysglycaemia often co-exists with the metabolic syndrome including central obesity. In Study IV elevated

levels of adiponectin at discharge were associated with an increased risk of mortality the coming 12 years after an AMI.[256] The risk tended to increase with time and cannot be explained by traditional risk factors such as age and obesity.[256] These results were somewhat surprising considering that high rather than low levels of adiponectin predicted mortality, supporting the existence of an "adiponectin paradox". The mechanism behind the increased risk of mortality associated with elevated levels of adiponectin after AMI is not fully understood and may seem contradictory, as adiponectin has been attributed anti-inflammatory and anti-atherogenic properties. High levels of adiponectin during an acute coronary event may be indicative of a natural defence in a severe situation where adiponectin is upregulated in a compensatory manner. Patients that succumbed during the total follow-up time in Study IV but who survived until hospital discharge had increasing levels of adiponectin during hospitalisation. This might be a response to oxidative stress and inflammation from the acute event, and a warning sign for an inability to cellular adaptation to stress. It may be a possible reason why adiponectin at discharge (where adiponectin levels had raised) but not at day 2 reflects total mortality. Patients with high adiponectin at discharge in Study IV were older, with a more frequent history of heart failure and a lower BMI implying that adiponectin can be indicative of other comorbidities or reflect cachexia and general catabolism. Antonopoulos et al. suggested that BNP and upstream pro inflammatory cytokines are key determinants of adiponectin by regulating the release of adiponectin from the adipose tissue.[86] Adiponectin would then reflect the grade of systemic inflammation and is driven upward by circulating BNP levels.[86] This cannot be further assessed in Study IV as NT-proBNP was not measured in the GAMI cohort, however only a minority (8%) of the patients had a previous diagnosed heart failure.

Another important finding in Study IV is that leptin is associated with cardiovascular events up to seven years after the myocardial infarction. Plausible mechanisms could be the previous described association with increased levels of leptin and the atherosclerotic process including endothelial dysfunction, sympathetic activation, acute thrombosis and plaque rupture.[100,101] In the GAMI cohort with only slightly obese patients but with a high proportion of AGT, which is closely associated with leptin, it is likely that adipose tissue is redistributed to intra-abdominal locations contributing to the increased risk of cardiovascular events.[101] Contrary to adiponectin, levels of leptin did not predict total mortality.

In summary, adiponectin captures patients with a high, long-term mortality risk (Study IV) while elevated levels of leptin and also a pathological OGTT (Study II) captures patients with increased risk for future cardiovascular events. Accordingly these markers may not necessarily reflect the same risk groups. Further research is needed to understand this discrepancy of these biomarkers, all easily available and measured in the acute setting of an acute coronary event, to further understand the underlying causes for the observed long-term risk.

Mortality causes

In Study III the underlying cause of mortality in patients with established CAD was shown to have a similar pattern for those with and without diabetes although occurring at an earlier stage in those with known diabetes. Cardiovascular mortality was around 80% in the 1990s in the DIGAMI cohort (Study I) and about 60% in those with diabetes mellitus in a population as the SCAAR cohort (Study III). Therefore it seems to have been a reduction in

causes of mortality from CVD probably explained by a longer life-expectancy for patients with diabetes resulting in other causes of mortality, such as endocrine and microvascular complications. This is in accordance with other reports, showing a decline in cardiovascular death related to diabetes with accompanying increase in deaths from other causes as cancer, endocrine and respiratory disorders.[257, 258] However, one has to bear in mind that a greater proportion of the patients are followed until death in Study I compared to Study III and therefore proportion of mortality causes when all patients in Study III have been followed to mortality will be of interest to explore.

Strengths and limitations of Studies I-IV

A major strength in Studies I, II and IV is the exceptional long follow-up time with no (Study I) or only one patient lost to follow-up (Studies II and IV) including almost all mortality in Study I. Study I is a randomised controlled trial allowing the investigation of a causal association between the intervention, an intensified insulin-based glycaemic control, and mortality. The relatively small sample size does, however, limit the statistical modelling where the outcome analyses of the predefined strata should mainly be regarded as indicative. Another limitation is that the type of glucose-lowering treatment was only known during the first year of follow-up. A cross-over may have taken place thereafter, with more insulin prescribed to patients in the control group by time. Moreover generalising of the results of Study I to present-day practice is difficult as the beneficial effect of glucose lowering on mortality may be less apparent with a modern secondary prevention strategy including statins and a greater proportion of angiotensin-converting enzyme inhibitors as previously discussed.

The limited number of patients in Studies II and IV provides an opportunity to get complete information on each individual and enables a careful ascertainment of cardiovascular events based on direct information from the patients, hospital records and national registries. However, the small sample size and limited number of events reduces the statistical power. Another limitation is that no information on treatment, possibly influencing prognosis, during follow-up is available.

A major strength in Study III is the recruitment of a large and unselected cohort mirroring an everyday life setting. This provides more appropriate information on event types and rates after a PCI compared to trials performed on selected populations. However, as discussed, more detailed information on the extent and distribution of the CAD apart from in the affected arteries had been advantageous. Presently this important variable is not possible to adjust for as SYNTAX score or equivalent data are not included in SCAAR. A major limitation is the lack of diabetes related variables like type of diabetes, its duration and the actual glycaemic control which could further give insights on reasons for the high event rate in the insulin treated patients. Another limitation is the lack of information on long-term treatment after the PCI, like dual antiplatelet treatment and compliance to secondary prevention with statins and other drugs that may influence the prognosis.

Future directions

CVD is common in patients with diabetes and despite improved management longevity is still compromised compared with patients without diabetes. This refers both to diabetes in general and to those with prevalent cardiovascular disease. However today, in Sweden, the

underlying causes of mortality after myocardial infarction does not seem to differ between patients with or without diabetes mellitus although they occur at an earlier time point in the latter group. This illustrates the importance of preventing both development of diabetes, thereby reducing duration of overt diabetes and its adverse outcome including cardiovascular complications following an established event. Until recently focus has been on the impact of glucose lowering therapies. This approach had limited effects on cardiovascular mortality and morbidity unless the glycaemic control was very poorly controlled as in the DIGAMI study. In the future other preventive approaches than glucose control should be more prioritised. An attractive strategy could for instance be a multifactorial treatment targeting several components of the metabolic syndrome including an elevated state of inflammation. The ALECARDIO study was one such broad approach but was terminated due to lack of futility and drug related problems.[259] Other novel therapies of interest are for instance PCSK9-inhibitors and new pharmacological compounds reducing inflammation. Recent studies on PCSK9-inhibitors have shown promising reduction of LDL levels in diabetes.[260] Ongoing trials will provide additional data if PCSK9 inhibition will have cardiovascular benefits not the least in the diabetes cohort. In patients with autoimmune diseases as rheumatoid arthritis methotrexate reduces the incidence of CVD.[261] There are ongoing randomised studies to further explore if also patients with diabetes would benefit from anti-inflammatory treatment with methotrexate or IL-1 inhibitors. Bariatric surgery is another promising area with weight reduction and improvements of glycaemic control and dyslipidaemia in obese patients with dysregulated diabetes.[262,263] In the 15 year follow-up of the non-randomised controlled Swedish Obesity Subjects study bariatric surgery was associated with a higher diabetes remission rate and less microvascular and macrovascular complications compared to controls.[264] Bariatric surgery is currently recommended by ADA in individuals with BMI $\geq$35 kg/m^2 plus an obesity related comorbidity as diabetes as well as by IDF in patients with BMI >30 kg/m^2 not achieving treatment targets with optimal medical therapy.[265,266] Larger randomised controlled trials with longer follow-up time are needed to further analyse the cardiovascular benefit in patients with type 2 diabetes.

This thesis supports the inclusion of an OGTT as a screening tool after an AMI not only for diagnosing diabetes but also for identifying individuals at high cardiovascular risk. It strengthens the recommendation of OGTT as an important screening option in the ESC/EASD guidelines.[240] This is however not recommended in the most recent Swedish national cardiology guidelines.[267] The question of whether an interventional program in patients with prediabetes and myocardial infarction would reduce cardiovascular complications is less well explored and future studies need to investigate this.

Furthermore the substantially high event rate after a first PCI demonstrated in this thesis advocates a close follow-up to reduce the complication rate where cardiology units should consider a special follow-up program in patients with diabetes exceeding the usually eight weeks visit, preferably including a follow-up time during at least 12 months.

CONCLUSIONS

1. Intensified insulin-based glycaemic control improves long-term survival after an acute myocardial infarction in patients with diabetes and substantially deranged glucose control.

2. Newly detected glucose abnormalities by OGTT are common in patients with acute myocardial infarction and constitute an independent predictor of future cardiovascular mortality and morbidity during the coming decade. Patients with normal glucose tolerance have a very low event rate after an acute myocardial infarction.

3. HbA1c is not an independent predictor of future cardiovascular events following a myocardial infarction either analysed as a continuous variable or when categorised according to recommended cut-off points for prediabetes or diabetes.

4. Patients with diabetes run a high risk of mortality and new cardiovascular events after a first PCI, such as myocardial infarction, heart failure and renewed PCI. Patients treated with insulin run a particularly high risk, including stent occlusions and restenosis.

5. In patients with diabetes and established coronary artery disease, cardiovascular mortality is still the most common cause of death, with a proportion comparable to that in patients without diabetes.

6. In patients with acute myocardial infarction but without previously known diabetes, high levels of adiponectin constitute an independent predictor of long-term mortality, while high leptin levels are associated with future cardiovascular events.

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