Aspects of Abnormal Glucose Regulation in Various Manifestations of Coronary Artery Disease

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"It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories instead of theories to suit facts."

Sherlock Holmes

CONTENTS

ABSTRACT

Background
Diabetes is common among patients with coronary artery disease (CAD) and is associated with an approximate doubling of the mortality risk in this patient population. Prediabetes, an intermediate glycometabolic state between normal and diabetic glucose homeostasis, is also prevalent in patients with CAD but its prognostic impact has not been studied in detail. The optimal glucose-lowering treatment in CAD patients has been the subject of debate.

Aims
1. To evaluate the association between admission glycaemia and future disturbance in glucose regulation, and mortality in patients with acute coronary syndrome (ACS).
2. To describe the association between diabetes and outcome after in-hospital cardiac arrest.
3. To evaluate the prevalence and the prognostic impact of abnormal glucose regulation after coronary artery bypass grafting (CABG).
4. To investigate whether increased mortality rates in insulin treated patients with type 2 diabetes and CAD can be explained by comorbidities.

Study population
This thesis is based on observational studies of four different study populations. To evaluate the association between admission glycaemia and future disturbance in glucose regulation (Study I) and mortality (Study II) we used data from the PRACSIS study comprising patients with ACS admitted to the coronary care unit at Sahlgrenska University Hospital, Gothenburg, between 1995 and 2001. Data on 1,810 patients, treated for in-hospital cardiac arrest between 1994 and 2006 at Sahlgrenska University Hospital and nine other hospitals in Sweden were used to analyse the association between diabetes and outcome (Study III). The prevalence and impact of abnormal glucose regulation were assessed in 276 patients undergoing CABG at Sahlgrenska University Hospital between 2003 and 2006 (Study IV). Data on 12,515 patients with type 2 diabetes undergoing coronary angiography between 2001 and 2009 were obtained from the NDR and the SCAAR registries and the association between glucose-lowering treatment and long-term mortality was analysed (Study V).

Admission hyperglycaemia in patients with ACS
In 762 ACS patients without known diabetes, the prevalence of diabetes at the 2.5 year follow-up increased with rising admission glucose, from 5% in those with plasma glucose of <6.1 mmol/l to 24% in those with plasma glucose of ≥7.0 mmol/l.
Among 1,957 patients with ACS, admission hyperglycaemia defined as plasma glucose >9.4 mmol/l, was found to be an independent predictor of both 30-day mortality (HR 4.13, 95% CI: 2.54-6.70, *p*<0.0001) and late mortality (HR 1.57, 95% CI: 1.02-2.41, *p*=0.04) in patients without known diabetes. In patients with diabetes admission hyperglycaemia was an independent predictor of late mortality (HR 2.14, 95% CI: 1.21 to 3.78, *p*=0.009).

Diabetes and survival after in-hospital cardiac arrest
The in-hospital mortality rate was higher among patients with diabetes than among those without (70.7% vs 62.4%, *p*=0.001). The adjusted odds ratio of being discharged alive for patients with diabetes was 0.57 (95% CI: 0.40-0.79).

Abnormal glucose regulation and prognosis after **CABG**
Two-thirds (65%) of the patients undergoing CABG had either prediabetes or diabetes. During a mean follow-up period of 5.3 years there was a successive increase in the primary endpoint rate (a composite of all-cause mortality and hospitalisation for a cardiovascular event) from normoglycaemia through prediabetes to diabetes (adjusted HR 1.40; 95% CI, 1.01 to 1.96; *p*=0.045).

Glucose-lowering treatment and prognosis
Compared with diet treatment alone, insulin in combination with oral glucose-lowering treatment (adjusted HR 1.22; CI 1.06 to 1.40; *p*<0.005) and treatment with insulin alone (adjusted HR 1.17; CI 1.02 to 1.35; *p*<0.01) were independent predictors of long-term mortality in patients with type 2 diabetes undergoing coronary angiography.

Conclusions
These observational studies show that abnormal glucose regulation is prevalent and predicts a poor prognosis in patients with various manifestations of coronary artery disease. Not only patients with diabetes but also patients with acute phase hyperglycaemia and hyperglycaemia in the non-diabetic range appear to run an increased risk of unfavourable outcome. Treatment with insulin in type 2 diabetic patients undergoing coronary angiography predicts long-term mortality risk even after adjustment for comorbidities. Whether or not this association is causal remains to be clarified.

SAMMANFATTNING

Bakgrund
Diabetes är en vanligt förekommande sjukdom hos patienter med kranskärlssjukdom och medför en fördubblad risk för tidig död. Prediabetes är ett förstadium till typ 2 diabetes som också är ett vanligt tillstånd bland patienter med kranskärlssjukdom men dess betydelse för överlevnad är inte lika väl studerad. Det är inte helt klarlagt vilken glukossänkande behandling som är mest lämplig för patienter med diabetes och kranskärlssjukdom.

Syfte
1. Att undersöka sambandet mellan högt blodsocker vid akut koronart syndrom (AKS) och dels senare utveckling av störning i sockeromsättningen och dels överlevnad.
2. Att beskriva betydelsen av diabetes för överlevnad efter hjärtstopp på sjukhus.
3. Att studera förekomsten och den prognostiska betydelsen av störningar i sockeromsättningen hos patienter som genomgått kranskärlskirurgi.
4. Att utforska till vilken grad insulin behandling hos patienter med typ 2 diabetes och kranskärlssjukdom är associerad med överlevnaden.

Studiepopulation
Denna avhandling bygger på data från fyra observationsstudier. De första två studierna, där vi undersöker sambanden mellan högt blodsocker och senare störningar i sockermetabolismen (Studie I) och överlevnad (Studie II), omfattar patienter som ingick i PRACSIS studien och vårdades för AKS på Sahlgrenska Universitetssjukhuset Göteborg mellan 1995 och 2001. För att studera betydelsen av diabetes för överlevnad efter hjärtstopp på sjukhus (Studie III) använde vi data från 1810 patienter som drabbades av hjärtstopp på Sahlgrenska Universitetssjukhuset Göteborg och nio andra svenska sjukhus under perioden 1994 till 2006. Utvärdering av förekomsten och betydelsen av störningar i sockeromsättningen efter kranskärlskirurgi (Studie IV) gjordes på 276 patienter som genomgick kranskärlskirurgi på Sahlgrenska Universitetssjukhuset Göteborg 2003 till 2006. Associationen mellan olika blodsockersänkande behandlingar och prognos för överlevnad (Studie V) undersöktes med hjälp av data från 12515 patienter med typ 2 diabetes som genomgick kranskärlsröntgen under perioden 2001 till 2009 och samtidigt var registrerade i två nationella kvalitetsregister (NDR och SCAAR).

Högt ankomstblodsocker hos patienter med AKS
Bland 762 patienter utan tidigare känd diabetes, ökade förekomsten av diabetes efter 2½ år i korrelation med ökat ankomstblodsocker, dvs från 5% av dem med plasmaglukos <6.1 mmol/l till 24% av dem med plasmaglukos ≥7.0 mmol/l. Bland 1957 patienter med AKS visade sig plasmaglukos vid ankomst >9.4 mmol/l vara en oberoende prediktor för både 30 dagars dödlighet (HR 4.13, 95% CI: 2.54-6.70, *p*<0.0001) och långtidsdödlighet (HR 1.57, 95% CI: 1.02-2.41, *p*=0.04) hos patienter utan tidigare känd diabetes. Hos patienter med känd diabetes var plasmaglukos >9.4 mmol/l en oberoende prediktor enbart för långtidsdödlighet (HR 2.14, 95% CI: 1.21-3.78, *p*=0.009).

Diabetes och överlevnad efter hjärtstopp på sjukhus
Sjukhusdödligheten var högre bland patienter med jämfört med utan diabetes (70.7% vs 62.4%, *p*=0.001). Justerat odds ratio för patienter med diabetes att skrivas ut levande från sjukhus var 0.57 (95% CI: 0.40-0.79).

Störningar i sockeromsättningen och prognos efter kranskärlskirurgi
Av 274 patienter som genomgick kranskärlskirurgi hade 178 (65%) antigen prediabetes eller diabetes. Efter en medeluppföljningstid av 5.3 år var den observerade risken för död eller sjukhusvård pga hjärt-kärlsjukdom stigande i följande ordning: normal sockeromsättning, prediabetes, diabetes (justerat HR 1.40; 95% CI, 1.01-1.96; *p*=0.045).

Blodsockersänkande behandling och prognos
Jämfört med kostbehandling var kombinationsbehandling med insulin och tabletter (justerat HR 1.22; CI 1.06-1.40; *p*<0.005) och behandling med enbart insulin (justerat HR 1.17; CI 1.02-1.35; *p*<0.01) oberoende prediktorer för långtids dödlighet hos patienter med typ 2 diabetes som genomgått kranskärlsröntgen.

Slutsatser
Dessa observationsstudier visar att störningar i sockeromsättningen är vanliga och predikterar sämre prognos bland patienter med olika manifestationer av kranskärlssjukdom. Även prediabetes och högt blodsocker i samband med insjuknande i AKS förefaller vara förknippade med ogynnsam prognos. Insulinbehandling hos patienter med typ 2 diabetes som genomgått kranskärlsröntgen predikterar långtidsdödlighet även efter att hänsyn tagits till andra sjukdomar. Eventuellt orsakssamband återstår att fastställa.

LIST OF ORIGINAL PAPERS

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

I.   Petursson P, Herlitz J, Caidahl K, et al. Association between glycometabolic status in the acute phase and 21/2 years after an acute coronary syndrome. Scandinavian cardiovascular journal 2006;40:145-51.

II. Petursson P, Herlitz J, Caidahl K, et al. Admission glycaemia and outcome after acute coronary syndrome. International journal of cardiology 2007;116:315-20.

III. Petursson P, Gudbjornsdottir S, Aune S, et al. Patients with a history of diabetes have a lower survival rate after in-hospital cardiac arrest. Resuscitation 2008;76:37-42.

IV. Petursson P, Herlitz J, Lindqvist J, Sjöland H, Gudbjornsdottir S. Prevalence of abnormal glucose regulation and its relation to prognosis after CABG. Submitted.

V.   Saleh N, Petursson P, Lagerqvist B, Skuladottir H, Svensson A, Eliasson B, Gudbjornsdottir S, Eeg-Olofsson K, Norhammar A. Long-term Mortality in Patients with Type 2 Diabetes undergoing Coronary Angiography – The Impact of Glucose-Lowering Treatment. Submitted.

LIST OF ABBREVIATIONS

ADA   American Diabetes Association

ACS   Acute coronary syndrome

AGR   Abnormal glucose regulation

AMI   Acute myocardial infarction

CABG   Coronary artery bypass grafting

CAD   Coronary artery disease

DCCT   Diabetes Control and Complication Trial

FPG   Fasting plasma glucose

HbA1c   Haemoglobin A1c

IFCC   International Federation of Clinical Chemistry

IFG   Impaired fasting glycaemia

IGT   Impaired glucose tolerance

NDR   National Diabetes Register

NGSP   National Glycohemoglobin Standardization Program

NSTEMI   Non-ST-segment elevation myocardial infarction

OGTT   Oral glucose tolerance test

PCI   Percutaneous coronary intervention

SCAAR   Swedish Coronary Angiography and Angioplasty Register

SCD   Sudden cardiac death

STEMI   ST-segment elevation myocardial infarction

WHO   World Health Organization

INTRODUCTION

Coronary Artery Disease

Coronary artery disease (CAD) is the most common form of cardiovascular disease which is the leading cause of morbidity and mortality in the developed world. Although age-adjusted CAD mortality rates have declined markedly during the past few decades, CAD still accounts for approximately 20% of all deaths [1].

The hallmark of CAD is atherosclerosis of the coronary arteries, where lipid-filled plaques develop in the inner lining of the arteries to form blood flow-limiting stenoses that lead to myocardial ischaemia (stable angina). These atherosclerotic plaques can rupture and trigger thrombosis with the subsequent interruption of blood flow and myocardial ischaemia (acute coronary syndrome) [2].

The most important risk factors associated with CAD are diabetes, age, male gender, adverse lipid profile, smoking, hypertension, psychosocial factors and abdominal obesity [3].

The clinical presentations of CAD include silent ischaemia, stable angina pectoris, acute coronary syndrome (ASC), heart failure, and sudden cardiac death. An ACS may take the form of an ST-elevation myocardial infarction (STEMI), a non-ST-elevation myocardial infarction (NSTEMI), or unstable angina.

The mainstay of the treatment of CAD is medical therapy with or without revascularisation. For most patients percutaneous coronary intervention (PCI) is the revascularisation treatment of choice. In general coronary artery bypass grafting (CABG) is recommended for patients with more advanced coronary disease or multivessel disease, especially if they have concomitant diabetes [4]. When compared with PCI or medical therapy alone, CABG has been associated with an improved outcome in patients with diabetes and multivessel disease [5, 6].

Abnormal Glucose Regulation

Definition and epidemiology
The term abnormal glucose regulation (AGR) includes two glycometabolic states, i.e. diabetes mellitus and prediabetes.

Diabetes is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in the secretion and/or action of insulin. The definition of diabetes is primarily based on the level of hyperglycaemia giving rise to a risk of microvascular complications such as retinopathy, nephropathy and neuropathy. Type 2 diabetes is the most common form and accounts for ~ 90-95% of those with diabetes. Individuals with type 2 diabetes have insulin resistance and usually have relative insulin deficiency [7].

Prediabetes refers to the intermediate glycometabolic state between normal and diabetic glucose homeostasis and comprises two distinct states, impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT) or a combination of the two.

The prevalence of the different states of AGR is dependent on what diagnostic test and criteria that are chosen for the diagnosis. According to a recently published study the number of patients with diabetes worldwide increased from 153 million in 1980, to 347 million in 2008. In the same study the estimated age standardised prevalence of diabetes was 9.8% in adult men and 9.2% in adult women in 2008. The corresponding numbers for Swedish men and women were 8.1% and 6.0% respectively [8]. It is estimated that up to 50% of individuals with diabetes are undiagnosed. The prevalence increases with age and is less than 10% among subjects below the age of 60 years, approximately 15% in those between the ages of 60 and 69 years and over 20% in subjects aged 70 years and older [9].

The prevalence of IFG varies between age groups and populations. Based on the World Health Organisation (WHO) criteria the overall prevalence in Europe is more than 5% and IFG is more common in men than women [9]. The prevalence is two to three times higher if the American Diabetes Association (ADA) criteria from 2003 are used [10].

As with IFG the prevalence of IGT varies between populations and across age groups. A reported prevalence of 10% or more is common and it is typically more common among women than men. The prevalence increases with age [9].

Diagnostic criteria
Currently, two diagnostic criteria (ADA and WHO criteria) are mainly used for diabetes and prediabetes [7, 11-13]. The criteria are fairly concordant, apart from the definition of IFG.

	WHO	**ADA**
Diabetes		
Fasting plasma glucose	≥7.0 mmol/l	≥7.0 mmol/l
	or	**or**
2-h glucose*	≥11.1 mmol/l	≥11.1 mmol/l
	or	**or**
HbA1c (DCCT)	≥6.5%	≥6.5%
Impaired Glucose Tolerance (IGT)		
Fasting plasma glucose	<7.0 mmol/l	
	and	
2-h glucose*	≥7.8 and <11.1 mmol/l	≥7.8 and <11.1 mmol/l
Impaired Fasting Glycaemia (IFG)		
Fasting plasma glucose	≥6.1 and <7.0 mmol/l	≥5.6 and <7.0 mmol/l

Table 1. Comparison of WHO and ADA diagnostic criteria for diabetes and intermediate hyperglycaemia.
*Plasma glucose 2 hours after the ingestion of a 75g oral glucose load

The ADA defines IFG as fasting plasma glucose (FPG) of 5.6-6.9 mmol/l, while the WHO criterion for IFG is FPG 6.1-6.9 mmol/l. The criteria are summarised in Table 1. Apart from symptomatic hyperglycaemia (random plasma glucose of ≥11.1 mmol/l), a single elevated test is not enough to establish the diagnosis, but it should be confirmed by a second test.

Glucose measurements

Glucose can be measured in several different ways but venous plasma glucose is the standard method for measuring and reporting glucose concentration in blood [12]. The advantages of plasma glucose measurements include inexpensive assays that are widely available. One of the main limitations of FPG measurements is the significant variability in the test results. A reproducibility of only 70% has been reported [14]. Numerous biological and analytical factors can influence the FPG measurements; they include large biological variability, medications, acute stress, duration of fasting and glycolysis in the blood sample [15]. Glucose measured in plasma is approximately 11% higher than glucose measured in whole blood. However, the conversion of whole blood glucose to plasma glucose is problematic because this difference of 11% is not a constant, i.e. the difference increases with rising haematocrit levels [16]. The site of collection of the blood sample is also important, i.e. capillary samples will give higher results than venous samples in a non-fasting state. Table 2 summarises the different methods and values for the diagnosis of diabetes and intermediate hyperglycaemia according to the WHO criteria.

Oral Glucose Tolerance Test - OGTT

The Oral Glucose Tolerance Test (OGTT) measures the ability of the body to metabolise glucose. After an overnight fast the subject to be tested drinks 75g of glucose dissolved in water. Blood samples for glucose measurements are obtained before and two hours after glucose load. The definition of the different categories of hyperglycaemia based on an OGTT is shown in Table 2.

	Plasma glucose venous	Whole blood glucose venous	Whole blood glucose capillary
Diabetes			
Fasting plasma glucose	≥7.0 mmol/l	≥6.1 mmol/l	≥6.1 mmol/l
	or	**or**	**or**
2-h glucose*	≥11.1 mmol/l	≥10.0 mmol/l	≥11.1 mmol/l
IGT			
Fasting plasma glucose	<7.0 mmol/l	<6.1 mmol/l	<6.1 mmol/l
	and	**and**	**and**
2-h glucose*	≥7.8 and <11.1 mmol/l	≥6.7 and <10.0 mmol/l	≥7.8 and <11.1 mmol/l
IFG			
Fasting plasma glucose	≥6.1 and <7.0 mmol/l	≥5.6 and <6.1 mmol/l	≥5.6 and <6.1 mmol/l

Table 2. WHO values for the diagnosis of diabetes and intermediate hyperglycaemia. Modified from reference [11]. IGT; impaired glucose tolerance, IFG; impaired fasting glycaemia.
*Plasma glucose 2 hours after the ingestion of a 75g oral glucose load

The OGTT is the gold standard for identifying people with AGR. Postprandial hyperglycaemia usually occurs before fasting hyperglycaemia. Postprandial glucose is therefore an early marker of impaired glucose homeostasis. The DECODE study showed that among individuals with newly diagnosed diabetes, 52% met only the 2-h plasma glucose criterion but not the FPG criterion [17]. In the Euro Heart Survey [18] and the China Heart Survey [19] the percentage of patients with newly diagnosed diabetes who only fulfilled the 2-h criterion was approximately 75%, i.e. only a quarter of the patients were diagnosed on the basis of FPG. In other words, by using only FPG, up to 75% of individuals with undetected diabetes could remain undiagnosed. This may be of significant clinical importance as studies have consistently shown a poorer outcome in patients with diabetes diagnosed on the basis of the 2-h plasma glucose compared with those diagnosed with FPG [20-22]. In other words, 2-h plasma glucose has been shown to be a stronger predictor of mortality (all-cause and cardiovascular) than FPG.

One of the main drawbacks of the OGTT is the low reproducibility of <50% for the classification of prediabetes (IFG and IGT) and approximately 60% for diabetes [23-28]. Compared with FPG measurement the OGTT is inconvenient and more expensive.

HbA1c

Plasma glucose binds irreversibly to the haemoglobin in the red blood cells and forms a glycosylated haemoglobin molecule known as Haemoglobin A1c (HbA1c). Since red blood cells have about a 120 day life span, HbA1c reflects mean glycaemia for the previous two to three months [29]. HbA1c is regarded as the golden standard for assessment of long-term glycaemic control in patients with diabetes. Both HbA1c and plasma glucose correlate well with retinopathy [30]. The HbA1c assay has several advantages over plasma glucose measurements, including lower biological variability and the test results are not affected by fasting and acute stress. The major disadvantages of HbA1c are the lack of standardisation of the measurement and the fact that the results can be influenced by several factors such as anaemia, haemoglobinopathies and uraemia. Compared with the OGTT lack of sensitivity and specificity affects its suitability for diagnostic purposes [31].

Until recently lack of standardisation of HbA1c measurements has been problematic. Many methods are available for the measurement of HbA1c and these methods are based on different analytical principles (e.g. immunoassays, affinity chromatography and ion-exchange chromatography). These methods not only produce different results, there are also variations between laboratories using the same analytical principles. In Sweden the Mono S method (ion-exchange chromatography) has been chosen for the harmonisation of HbA1c results. In general this method produces almost 1% lower HbA1c results than the more widely used National Glycohemoglobin Standardization Program (NGSP) method (sometimes referred to as the DCCT method) which is standardised to the reference method from the Diabetes Control and Complication Trial (DCCT). For example, an HbA1c value of 6.5% according to the NGSP method is equivalent to 5.6% measured with the Mono S method [32]. In order to achieve the uniform international standardisation of HbA1c measurements, the International Federation of Clinical Chemistry (IFCC) has developed a reference system for HbA1c [32].

The IFCC-HbA1c values are expressed as mmol/mol instead of %. An NGSP-HbA1c of 6.5% is equivalent to an IFCC-HbA1c value of 48 mmol/mol. The following equations describe the relationship between the different reference methods [32]:

$$\text{NGSP-HbA1c (\%)} = [0.923 \times \text{Mono-S-HbA1c (\%)}] + 1.345$$

$$\text{IFCC-HbA1c (mmol/mol)} = [\text{NGSP-HbA1c (\%)} - 2.15] \times 10.929$$

With advances in instrumentation and standardisation, HbA1c assays have become at least as reliable as glucose assays. It is now recommended that HbA1c can be used for the diagnosis of diabetes with a diagnostic cut-off point of 6.5% (NGSP) [7, 13, 30]. However, an HbA1c value of <6.5% does not exclude diabetes diagnosed using glucose tests. The HbA1c cut-off point of 6.5% identifies one-third fewer cases of undiagnosed diabetes than an FPG cut point of 7.0 mmol/l [33].

Is prediabetes a pre-diabetic state?
According to the ADA, IFG and IGT should not be viewed as clinical entities but rather as risk factors for diabetes as well as cardiovascular disease [7]. IFG is probably the result of impaired insulin secretion and increased hepatic gluconeogenesis, whereas IGT is a marker of early insulin resistance. A systematic review from The McMaster University recently reported that the annualised relative risk of people with prediabetes progressing to diabetes was increased 5 to 12-fold compared with normoglycaemic people. Those with both IGF and IGT ran the highest risk [34]. Soderberg et al. reported that in people with IGT at baseline, 24% had normoglycaemia, 26% still had IGT, 4% had IFG and 46% had developed diabetes after follow up period of 11 years. The corresponding percentages after 11 years for those with IFG at baseline were, 38% normoglycaemia, 17% IGT, 7% IFG, and 38% diabetes [35]. A pooled analysis of 10 studies with a follow up period of two to eight years showed that approximately one third of those with IGT reverted to normoglycaemic status at follow up [34]. Because many people with prediabetes do not progress to diabetes the term *intermediate hyperglycaemia* has been recommended instead of *prediabetes* [12].

Glucose Regulation in Coronary Artery Disease

Prevalence and prognosis of AGR in CAD
In patients with coronary artery disease (CAD) 25-30% have known diabetes. Of those without known diabetes, approximately 20-25% have diabetes, 35-40% have IFG and/or IGT, and 35-45% have normal glucose regulation. The prevalence of the different glycometabolic states is similar in patients with stable angina and ACS [19, 36]. As a result, more than 70% of all CAD patients may have AGR.

Diabetes is an important risk factor for CAD [3, 37]. Further, diabetes is a strong predictor of poor outcome in patients with CAD and has been associated with as much as a doubling of the mortality risk [38-40]. Studies have shown that patients who have diabetes but not a previous

history of CAD run a similarly high risk of fatal CAD as patients without diabetes who have established CAD and the combination of diabetes and CAD is associated with the most unfavourable prognosis [41-43]. The hypothesis that diabetes is a CAD equivalent in terms of risk has recently been questioned. A recent meta-analysis of 13 studies revealed that patients with diabetes without prior myocardial infarction ran a 43% lower risk of fatal and non-fatal myocardial infarction as compared with those without diabetes who had a previous history of myocardial infarction [44].

IGT and to a lesser degree IFG have been related to increased CAD risk. The DECODE study, a pooled analysis of 10 prospective European cohort studies comprising >15 000 people, showed that compared with normoglycaemia, IGT but not IFG was an independent predictor of all-cause and CAD mortality [22].

How should hyperglycaemia be defined in patients with ACS?
Based on fasting glucose measurements it is logical to define hyperglycaemia as glucose levels above the normal range (Table 1). Patients with hyperglycaemia can therefore have either FPG in the diabetic range (≥7.0 mmol/l) or IFG with FPG of < 7.0 mmol/l. The lower IFG cut-off point is not well defined and there is disagreement between diagnostic criteria from the ADA and the WHO. The ADA defines IFG as FPG of 5.6-6.9 mmol/l [7], while, in the WHO criteria IFG is defined as 6.1-6.9 mmol/l [11].

There is currently no consensus about how hyperglycaemia on admission to hospital should be defined. Admission glucose is usually regarded as random (non-fasting) glucose. For random glucose, a cut-off point equivalent to the OGTT criteria for IGT and diabetes may be the most appropriate definition of hyperglycaemia (i.e. plasma glucose ≥7.8 mmol/l). Recently, the American Scientific Statement on Hyperglycemia and Acute Coronary Syndrome suggested a random plasma glucose level ≥7.8 mmol/l as the definition of hyperglycaemia in patients hospitalised for ACS [45]. Random plasma glucose of ≥7.8 mmol/l can therefore be regarded as hyperglycaemia. However, the correlation between admission glucose and 2-h post challenge glucose is low [46].

Prevalence of hyperglycaemia on admission in ACS
The reported prevalence of admission hyperglycaemia in patients with ACS varies widely from study to study, partly due to different definitions of hyperglycaemia in the individual studies. In a meta-analysis of stress hyperglycaemia and outcome after myocardial infarction the prevalence of hyperglycaemia ranged from 3-71% in non-diabetics and 46-84% in diabetics [22, 47]. In a recent study of 3,750 patients with acute myocardial infarction (AMI) the prevalence of plasma glucose levels above ≥ 9.0 mmol/l was 30% among non-diabetics and 74% among diabetics [48]. Kosiborod et al. reported that in a study of 141,680 elderly patients with AMI the prevalence of admission plasma glucose ≥ 7.8 mmol/l (≥140 mg/dl) was 58%. The corresponding prevalence of plasma glucose ≥ 9.4 mmol/l (≥170 mg/dl) was 40% [49].

To summarise, admission hyperglycaemia is common in patients with ACS but the prevalence is obviously dependent on how hyperglycaemia is defined.

Admission, fasting and persistent hyperglycaemia in ACS

Many studies have demonstrated that admission hyperglycaemia is a strong predictor of an adverse outcome in patients with ACS [47-54]. The predictive value of fasting glucose for the prognosis after ACS has been less well studied. Kolman et al. recently reported that elevated fasting glucose of ≥126 mg/dl (≥7.0 mmol/l) in patients with ACS was associated with in-hospital adverse events, and fasting glucose of ≥100 mg/dl (≥5.6 mmol/l) was associated with an increased risk of six-month mortality in non-diabetics but not diabetics [55]. Otten et al. reported that FPG of ≥5.6 mmol/l was associated with an adverse in-hospital outcome [56]. Data from the GRACE registry revealed that a higher fasting glucose level was related to a higher probability of in-hospital death, without detectable threshold and independent of diabetes status [57].

The respective contributions of admission and fasting glucose level to predicting outcome in ACS are unclear. Suleiman et al. have found that fasting glucose is superior to admission glucose in the assessment of short term risk in non-diabetic patients with AMI [58]. The study showed that although elevations of both fasting and admission blood glucose concentrations were significant and independent predictors of outcome, fasting glucose was a better predictor of 30-day mortality and heart failure than admission glucose. Sinnaeve et al. reported that in contrast to fasting glucose level, admission glucose level was not predictive of six-month post-discharge outcome in patients with STEMI (ST-elevation myocardial infarction) and non-STEMI [57].

Other studies have shown that persisting hyperglycaemia after admission may predict poor outcome. Kosuge et al. demonstrated that hyperglycaemia that persisted 24 hours after symptom onset in patients with AMI is associated with left ventricular dysfunction before discharge [59]. Goyal et al. studied 1,469 patients with AMI and found that both higher baseline glucose and the failure of glucose levels to decrease in the first 24 hours after admission predict higher mortality in non-diabetics [60]. In an observational study of 417 patients undergoing primary PCI, persisting hyperglycaemia was an independent predictor of major adverse cardiac events at the 30-day follow-up and was a stronger predictor than admission glycaemia [61]. This observation was confirmed in a study of 16,871 patients with AMI, where three measurements of glucose control were compared with admission glycaemia for their ability to predict in-hospital mortality [62]. In that study persistent hyperglycaemia was a better predictor of mortality than admission hyperglycaemia. Further, there was a J-shaped relationship between average glucose and mortality with both persistent hypoglycaemia and hyperglycaemia associated with a poor prognosis.

Diabetes and sudden cardiac death

Sudden cardiac death (SCD) is usually defined as an unexpected death due to cardiac causes generally occurring within one hour of symptom onset. Most cases of SCD are related to cardiac arrhythmias such as ventricular fibrillation or ventricular tachycardia. Approximately half of all deaths due to CAD can be classified as SCDs [63]. CAD is one of the most important risk factors for SCD [64-66] and the majority of patients suffering from cardiac arrest have CAD [67]. CAD and SCD therefore share the same risk factors. In fact, in several

prospective studies, diabetes has been associated with a higher risk of SCD [66, 68-70] and lower survival rates after out-of-hospital cardiac arrest compared with patients without diabetes [71, 72].

Glucose-lowering treatment

The mainstay of diabetes treatment is the management of hyperglycaemia, even though the treatment of other coincident micro- and macrovascular risk factors such as dyslipidaemia, hypertension and obesity, has been the subject of increasing interest in recent years. Maintaining glycaemic levels as close to normal as possible has been shown to have beneficial effects not only on microvascular complications (including nephropathy, neuropathy and retinopathy) [73-76] but also on macrovascular complication [77, 78].

Lifestyle intervention A sedentary lifestyle and overnutrition are the major environmental risk factors for type 2 diabetes [79]. Lifestyle intervention to increase physical activity and decrease weight have been shown to improve glycaemic control in patients with established type 2 diabetes [80]. The expected decrease in HbA1c as a result of lifestyle intervention is 1-2% (absolute units measured with the NGSP method) [81].

Metformin is a biguanide and its glucose-lowering effects are mediated through reduced hepatic glucose output (i.e. the inhibition of gluconeogenesis and glycolysis in the liver), and increased peripheral glucose uptake (i.e. improved insulin sensitivity in peripheral tissue). Metformin monotherapy lowers HbA1c levels by ~1% [82]. In the UK Prospective Diabetes Study, metformin treatment in overweight patients with newly diagnosed type 2 diabetes was associated with lower rate of cardiovascular events and death compared with conventional treatment [76, 78].

Sulfonylureas stimulate insulin secretion and have effects similar to those of metformin on long-term glycaemia, lowering HbA1c levels by ~1.25% [82].

Glinides have a mechanism similar to that of the sulfonylureas and lower glycaemia by enhancing insulin secretion. Glinides reduce HbA1c levels by ~0.75% [82].

α-Glucosidase inhibitors reduce the rate of absorption of polysaccharides in the small intestine. α-Glucosidase inhibitors lower the HbA1c level by ~1% [82]. In the STOPP-NIDDM trial 1,429 patients with IGT were randomised to receive either placebo or acarbose. Acarbose was associated with a 49% relative risk reduction and a 2.5% absolute risk reduction in the development of cardiovascular events after a mean follow-up of 3.3 years [83].

Thiazolidinediones (glitazones or TZDs) are peroxisome proliferator-activated receptor γ modulators that increase the insulin sensitivity of adipose tissue, liver and muscle [84]. TZDs have been shown to reduce HbA1c levels by ~1.25% [82]. TZDs have been associated with an increased risk of cardiovascular complications. A meta-analysis demonstrated that rosiglitazone was associated with an increased risk of myocardial infarction (OR,1.28;95%

CI,1.02-1.63; *p*=0.04) [85]. Another meta-analysis found that pioglitazone lowered the risk for the composite endpoint of death, myocardial infarction, and stroke (HR, 0.82; 95% CI,0.72-0.94; *p*=0.005) but increased the risk of serious heart failure (HR,1.41; 95% CI,1.14-1.76; *p*=0.002) [86].

Dipeptidyl peptidase 4 (DPP-4) inhibitors increase glucose-mediated insulin secretion by inhibiting the degradation of intestinal incretin hormones (GLP-1 and GIP). DPP-4 inhibitors lower HbA1c levels by ~0.75% [82].

Insulin is the most effective treatment when it comes to lowering glycaemia and, in adequate doses, it can reduce almost any level of elevated HbA1c to the therapeutic level. Because of its potency insulin is associated with a risk of hypoglycaemia. In the DCCT the incidence of severe hypoglycaemic episodes was 62 per 100 patient-years in patients with type 1 diabetes [87]. The reported frequency of severe hypoglycaemia in patients with type 2 diabetes is much lower [88]. The results of registry studies and subgroup analyses of clinical trials have raised concerns about the possibly harmful effects of exogenous insulin treatment in patients with CAD [40, 89, 90].

Glucagon-like peptide 1 (GLP-1) agonists binds to the GLP-1 receptor on the pancreatic beta cell and potentiates glucose-stimulated insulin secretion. Like insulin the drug is administered subcutaneously and reduces HbA1c levels by 0.5-1% [81]

AIMS

1. To evaluate the association between admission glycaemia and future disturbance in glucose regulation in patients with acute coronary syndrome (Study I)

2. To determine the predictive value of admission glycaemia in terms of mortality in patients with acute coronary syndrome (Study II)

3. To describe the association between diabetes and outcome after in-hospital cardiac arrest (Study III)

4. To evaluate the prevalence and prognostic impact of abnormal glucose regulation after coronary artery bypass grafting (CABG) (Study IV)

5. To investigate whether increased mortality rates in insulin treated patients with type 2 diabetes and coronary artery disease can be explained by comorbidities (Study V)

MATERALS & METHODS

Study population

Studies I & II

All patients with ACS admitted to the coronary care unit at Sahlgrenska University Hospital in Gothenburg, Sweden, were evaluated for participation in a study of prognosis and its prediction in ACS. In Paper I patients were included in the study between 15 September 1995 and 15 September 1999. In Paper II the inclusion period was between 15 September 1995 and 15 March 2001. Only patients under the age of 80 and living within the hospital's catchment area were eligible. Patients with an obvious AMI, chest pain or other symptoms suggestive of myocardial ischaemia were eligible for inclusion. The suspicion of myocardial ischemia had to be supported by ECG changes on admission, biochemical markers above the upper reference level (creatine-kinase (CK)-MB 5 μg/l and/or troponin T 0.05 μg/l) or previously recognised coronary artery disease. The exclusion criteria were severe non-cardiac disease with an expected survival of less than one year and unwillingness to participate.

Study I

A total of 1,854 patients were included in the study. Of these patients 110 did not fulfil the criteria for ACS. Of the remaining 1,744 patients, 332 had known diabetes, information on diabetic status was not available for 4 patients, 212 died during follow-up and 11 patients did not participate in the follow-up. At follow-up, plasma glucose was available for 954 patients of the remaining 1,185. Among those 954 patients, measurements of admission plasma glucose and HbA1c were available for 762 (80%) and 521 (55%) respectively.

Study II

In all, 2,481 patients were included in the study. Of these, 150 were finally discharged with a diagnosis other than ACS. In four patients, information on diabetic status was missing and glucose values were not available in a further 370 patients, leaving 1,957 patients for this analysis.

Study III

Between 1 November 1994 and 30 November 2006, all patients suffering an in-hospital cardiac arrest for whom the resuscitation team was alerted were evaluated prospectively at Sahlgrenska University Hospital, Gothenburg, Sweden. Between 1 February 2006 and 30 November 2006, patients who suffered an in-hospital cardiac arrest at a further nine hospitals in Sweden were also included in the survey. A total of 1,810 patients were eligible for this analysis.

Study IV

In this prospective study we enrolled 276 patients scheduled for isolated CABG at Sahlgrenska University Hospital, Gothenburg, Sweden, during the period from September

2003 to December 2006. The hospital is a large tertiary cardiothoracic centre taking referrals from western Sweden. Only patients living within the hospital's catchment area were eligible. The exclusion criteria were prior cardiac surgery, unwillingness to participate and language problems.

Study V

This is a retrospective analysis of merged data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and the Swedish National Diabetes Register (NDR) for all patients with type 2 diabetes, registered in the NDR, who underwent coronary angiography between 1 January 2001 and 31 December 2009. Follow-up data on mortality and any hospitalisations were obtained by merging the data with the Swedish National Population Registry and the Swedish Registry on Hospital Diagnosis until 31 December 2009. The epidemiological definition of type 1 diabetes used in this study and thus excluded from the present analyses was: a patients treated with insulin and diabetes diagnosed before the age of 30 years. Patients with onset age 30-39 years and insulin treatment were excluded from this study, as it was difficult to epidemiologically classify them as type 1 diabetes, LADA or type 2 diabetes. In all, data on 14,080 patients were available in both registries. The final study population consisted of 12,515 patients for whom complete data were available.

The SCAAR collects data on all consecutive patients undergoing coronary angiography and PCI at all 29 centres that perform coronary angiography and PCI in Sweden. The data have been monitored and verified at all hospitals since 2001 by annually comparing 50 entered variables in 20 randomly selected interventions per hospital with the patients' hospital records. The overall correspondence in data during the study period was 95.2%.

The NDR was initiated in 1996 as a tool for local quality assurance in diabetes care at national level. Reporting to the register is not mandatory, but all hospital diabetes outpatient clinics and primary healthcare centres are encouraged to do so. More than 260,000 patients were reported to the registry in 2009, which is estimated to be approximately 70% of all patients with diabetes in Sweden. Annual reporting of 24 variables is carried out by trained physicians and nurses via the internet or via clinical records databases, with information collected during patient visits to hospital outpatient clinics and primary healthcare centres nationwide.

Definition of ACS

Studies I and II
Based on ECG and biochemical markers of myocardial injury, patients were diagnosed with STEMI (ECG with ST-segment elevation or left bundle branch block and CK-MB >10 μg/l and/or troponin T≥0.15 μg/l), NSTEMI (CK-MB >10 μg/l and/or troponin T≥0.15 μg/l) or unstable angina (CK-MB ≤10 μg/l and troponin T<0.15 μg/l).

Study IV
ACS included myocardial infarction and unstable angina. Myocardial infarction was diagnosed according to the joint guidelines of the ESC and ACC [91]. Patients were therefore

diagnosed as having an acute myocardial infarction if they had elevated troponin T/I or CK-MB with at least one of the following: ischemic symptoms; ischemic ECG changes (development of pathological Q wave, ST segment elevation or depression); or coronary artery intervention.

Classification of admission glycaemia and glycaemic state

Study I
For descriptive purposes patients were divided into three groups defined by admission plasma glucose values of <6.1, 6.1-6.9 and ≥7.0 mmol/l. At the 2.5-year follow-up we classified patients as having diabetes if, during the follow-up period, they had been given the diagnosis of diabetes mellitus (self-reported or according to medical records or were receiving glucose lowering therapy) or if they had FPG values in the diabetic range (FPG ≥7.0 mmol/l). Patients were defined as having disturbed metabolic status if they had IFG (i.e. plasma glucose 6.1-6.9 mmol/l, according to the WHO classification [11]) or diabetes at follow-up.

Study II
Patients were stratified into quartile groups defined by admission plasma glucose. Admission hyperglycaemia was defined as plasma glucose of >9.4 mmol/l, which was the cut-off value for the 4th quartile.

Study IV
Glycaemic state was classified according to the WHO diagnostic criteria from 1998 for capillary blood glucose [11]. Diabetes was defined as fasting blood glucose of ≥6.1 mmol/l and/or 2-h blood glucose of ≥11.1 mmol/l. Impaired Glucose Tolerance (IGT) was defined as fasting blood glucose <6.1 mmol/l and 2-h blood glucose of 7.8-11.0 mmol/l. Isolated Impaired Fasting Glycaemia (IFG) was defined as fasting blood glucose of 5.6-6.0 mmol/l and 2-h blood glucose of <7.8 mmol/l. Prediabetes was defined as hyperglycaemia in the non-diabetic range, i.e. IGT and/or IGF. Normoglycaemia was defined as fasting blood glucose of <5.6 mmol/l and 2-h blood glucose of <7.8 mmol/l.

Measurement of glycaemia

Glucose
In *Studies I and II* casual (non-fasting) plasma glucose was analysed at admission. Before 4 May 1998, glucose measurements were made in whole blood. After that date, measurements were made in plasma. A constant factor of 1.11 was used to convert measured glucose concentrations in whole blood to the equivalent concentration in plasma [92].
In *Study IV* a standardised OGTT with 75g of glucose was performed and glucose concentrations were measured in capillary whole blood.

HbA1c

HbA1c measurements were made at the local hospital laboratory with an HbA1c assay calibrated to the HPLC Mono-S standard. In *Study V,* all HbA1c values were converted to the DCCT standard levels using the formula: HbA1c (DCCT) = (0.923×HbA1c (Mono-S)) + 1.345; $R2=0.998$ [32].

Statistical methods

Continuous variables are expressed as means and categorical variables as percentages. For two-group comparisons Fisher's exact test or the chi-square were used for proportions and the Mann-Whitney U test or Fisher's non-parametric permutation test for ordered and continuous variables. In *Study IV*, the Mann-Whitney U test was used to test for association between dichotomous variables and the ordered variable normoglycaemia-prediabetes-diabetes. The association of this ordered degree of glycaemic state and continuous variables was tested using Spearman's rank order statistic. In *Study V*, baseline characteristics were compared using the chi-square for categorical variables and ANOVA for continuous variables.

In *Studies I and III,* adjusted odds ratios were calculated using logistic regression. Adjustments were made for all variables that differed ($p<0.20$ in *Study I* and $p<0.05$ in *Study III*) at baseline between groups.

In *Studies II, IV and V,* Cox's proportional hazards model was used for calculation of hazard ratios. In *Study V*, Cox's proportional hazards model was used to estimate unadjusted and adjusted mortality rates.

In *Studies II and IV*, cumulative event probability was estimated using the Kaplan-Meier method, and the log-rank test was used for univariate comparisons of mortality rates in *Study II*.

All tests are two-sided and *p*-values below 0.05 were considered statistically significant.

Ethical approval

All the studies were approved by the ethics committee at the University of Gothenburg.

RESULTS

Study I

Association between glycometabolic status in the acute phase and 2½ years after an acute coronary syndrome

The aim of this study was to evaluate the association between admission glycaemia and glycometabolic status 2½ years after an ACS.

Results

Of a total of 762 ACS patients without known diabetes at admission, 13% had diabetes at the 2.5-year follow-up and 16% had IFG. The prevalence of diabetes at the 2.5-year follow-up increased with rising admission glucose, from 5% in those with plasma glucose of <6.1 mmol/l to 24% of those with plasma glucose of ≥7.0 mmol/l. The corresponding prevalence of IFG at follow-up was 14% and 18% (Figure 1).

Figure 1. Glycometabolic status at the 2.5-year follow-up, according to admission plasma glucose level
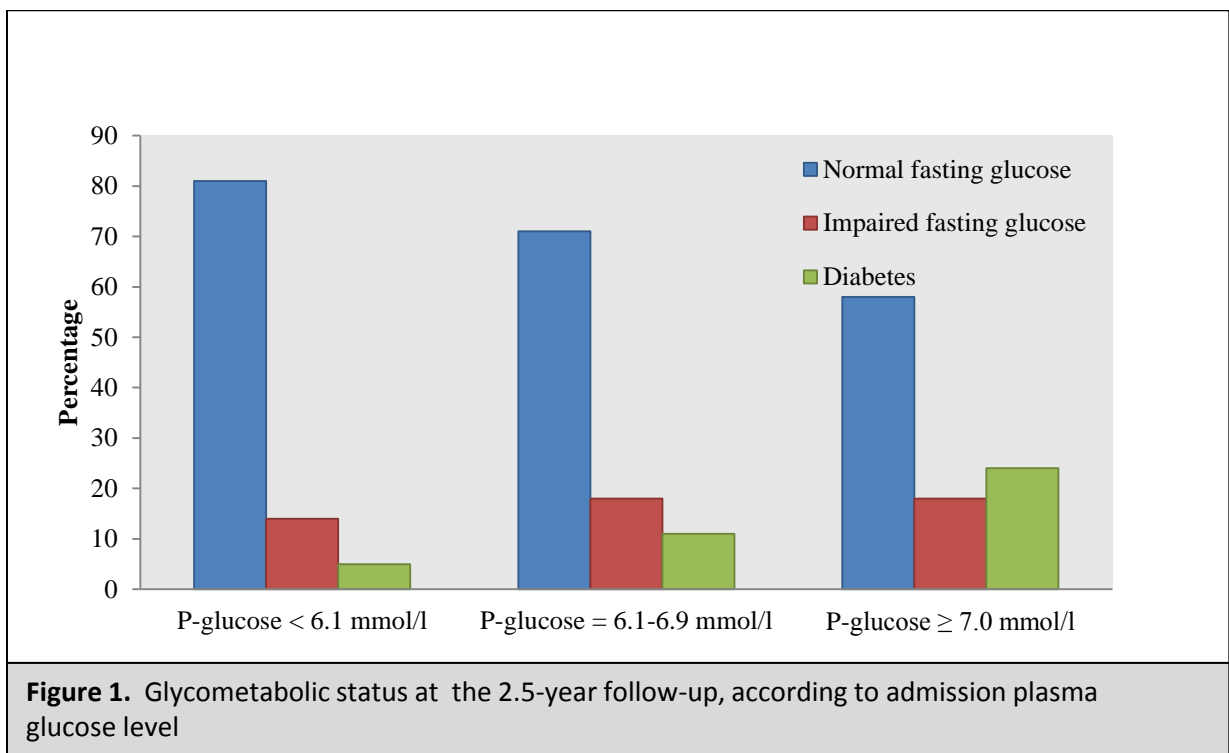
At admission HbA1c was measured in 521 patients. Of those with HbA1c of ≥5.5%, 49% had developed diabetes after 2½ years, compared with 8% of those with HbA1c of 4.6-5.4 and 5% of those with HbA1c of ≤4.5% (Figure 2). The adjusted odds ratio for patients with admission HbA1c of ≥5.5% in relation to those with <5.5% was 13.1 (95% CI: 7.1-24.2, $p<0.0001$). The corresponding prevalence of IFG at follow-up was 12% in those with HbA1c of ≥5.5%, 19% in those with HbA1c of 4.6-5.4 and 13% in those with HbA1c of ≤4.5%. The adjusted odds

ratio for disturbed glycometabolic status for patients with HbA1c of ≥5.5% in relation to those with <5.5% was 4.5 (95% CI: 2.7-7.4, $p<0.0001$).

Figure 2. Glycometabolic status at the 2.5-year follow-up, according to HbA1c level at admission
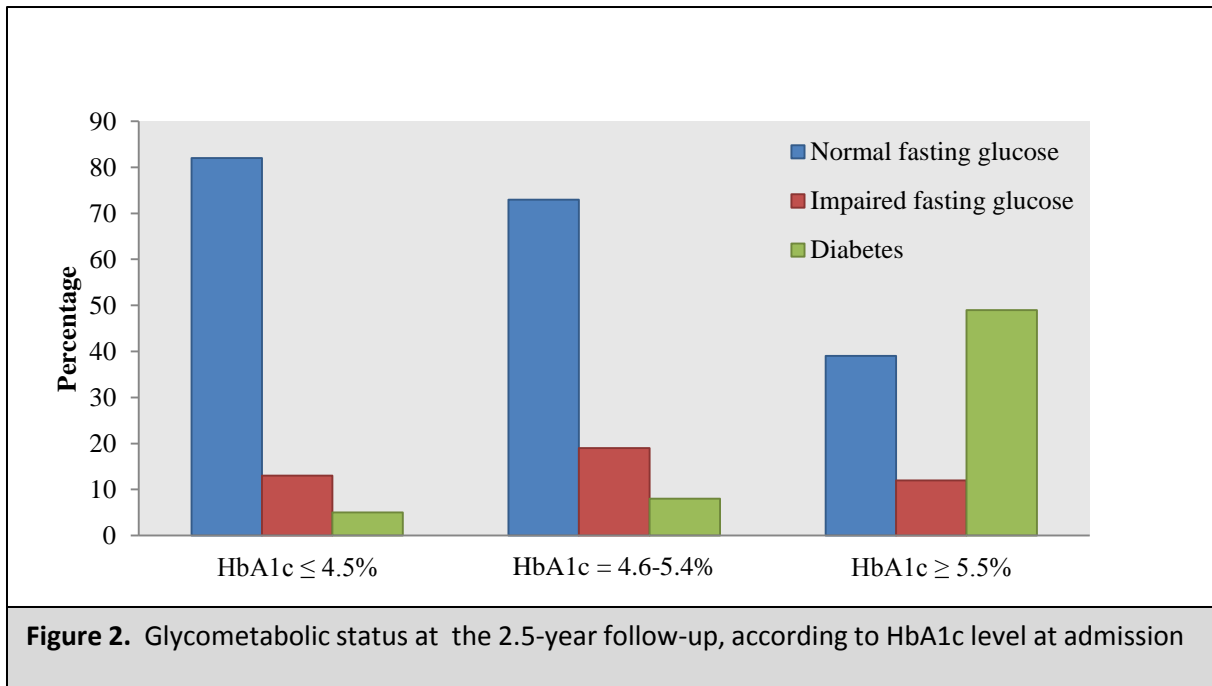
Measurements of both admission plasma glucose and HbA1c as well as fasting plasma glucose at follow-up were available for 439 patients, of which 15% had diabetes at follow-up and 16% had IFG. Among 46 patients who had both admission plasma glucose of ≥7.0 mmol/l and HbA1c of ≥5.5%, the prevalence of diabetes and IFG at follow-up was 67% and 13% respectively.

Conclusion

Non-diabetic patients with ACS and elevated admission plasma glucose levels should be regarded as running a high risk of developing glycometabolic disturbance. The patients at the highest risk are those with the combination of admission hyperglycaemia and elevated HbA1c levels.

Study II

Admission glycaemia and outcome after acute coronary syndrome

In this study, we investigated the association between admission glycaemia and outcome in patients with ACS, with the emphasis on prior diabetic status.
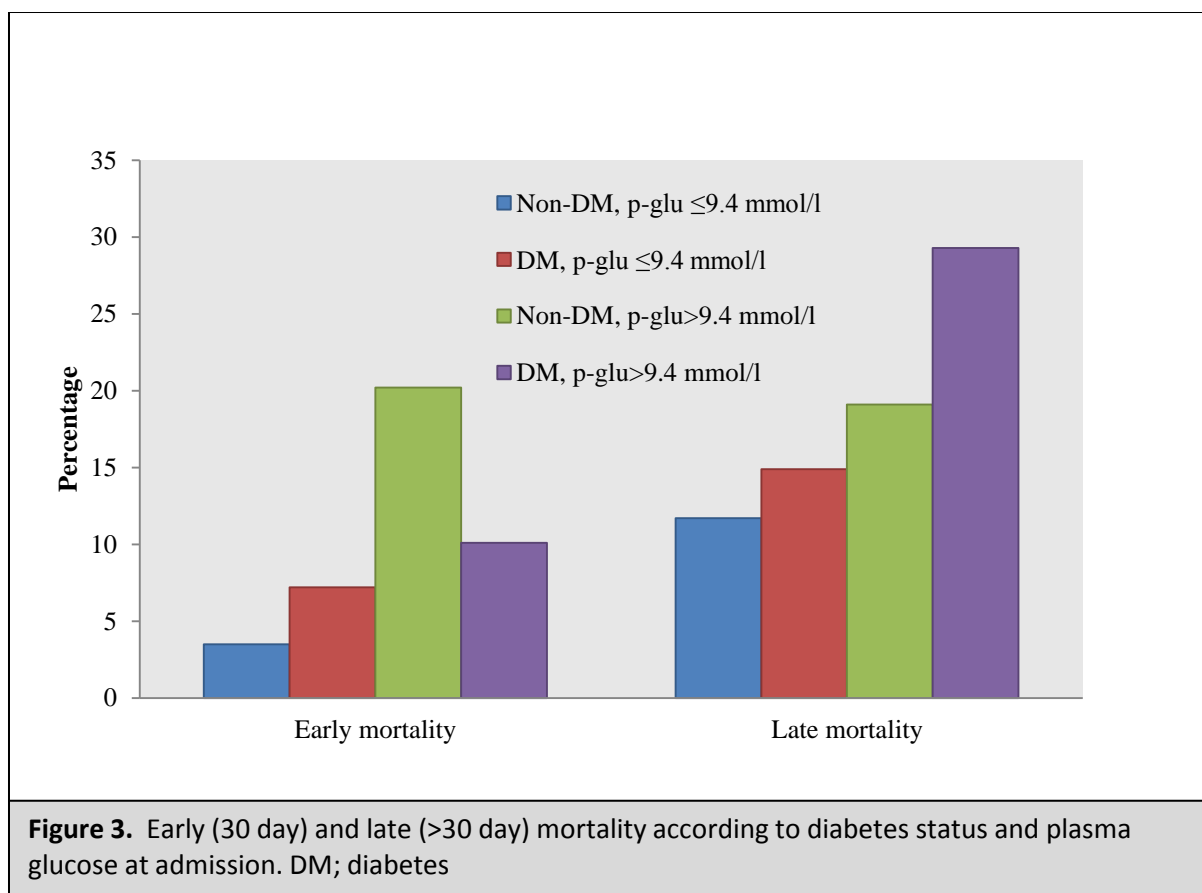
Results

Of the 1,957 enrolled patients, 22% had a history of diabetes. Compared with the diabetic group, proportionally fewer patients in the non-diabetic group had admission plasma glucose of >9.4 mmol, 65% and 13% respectively. Of patients with plasma glucose of >9.4 mmol/l,

those with diabetes had a lower 30-day mortality rate compared with those without diabetes (10.1% vs 20.2%, *p*=0.002). However, late mortality (>30 days) was higher among diabetic patients (*p*=0.01) (Figure 3).

The 30-day mortality rate for patients without diabetes was 6%. Non-diabetic patients with admission plasma glucose of >9.4 mmol/l had a significantly higher 30-day mortality rate compared with those with plasma glucose of ≤9.4 mmol/l, 20.2% and 3.5%, respectively (*p*<0.0001). The late mortality rate (>30 days) was significantly higher in the hyperglycaemic group, 19.1% vs. 11.7% (*p*=0.007) (Figure 3). After adjustment for potential confounders, plasma glucose of >9.4 mmol/l remained an independent predictor of both 30-day mortality (HR 4.13, 95% CI: 2.54-6.70, *p*<0.0001) and late mortality (HR 1.57, 95% CI: 1.02-2.41, *p*=0.04).

The 30-day mortality rate for diabetic patients was 9%. There was no statistically significant difference (*p*=0.31) in the 30-day mortality rate between those with admission plasma glucose of >9.4 mmol/l and those with plasma glucose of ≤9.4 mmol/l. The late mortality rate (>30 days) was significantly higher in patients with admission plasma glucose levels of > 9.4 mmol/l compared with patients with plasma glucose of ≤9.4 mmol/l, 29.3% vs. 14.9%, respectively (*p*=0.001) (Figure 3). After adjustment for potential confounders, plasma glucose of >9.4 mmol/l still did not predict 30-day mortality (*p*=0.56) but remained an independent predictor of late mortality (HR 2.14, 95% CI: 1.21 to 3.78, *p*=0.009).

Figure 3. Early (30 day) and late (>30 day) mortality according to diabetes status and plasma glucose at admission. DM; diabetes

The overall 45-month mortality was higher among patients with plasma glucose of >9.4 mmol/l, both for patients with previously known diabetes (*p*=0.001) and for those without (*p*<0.0001) (Figure 4).
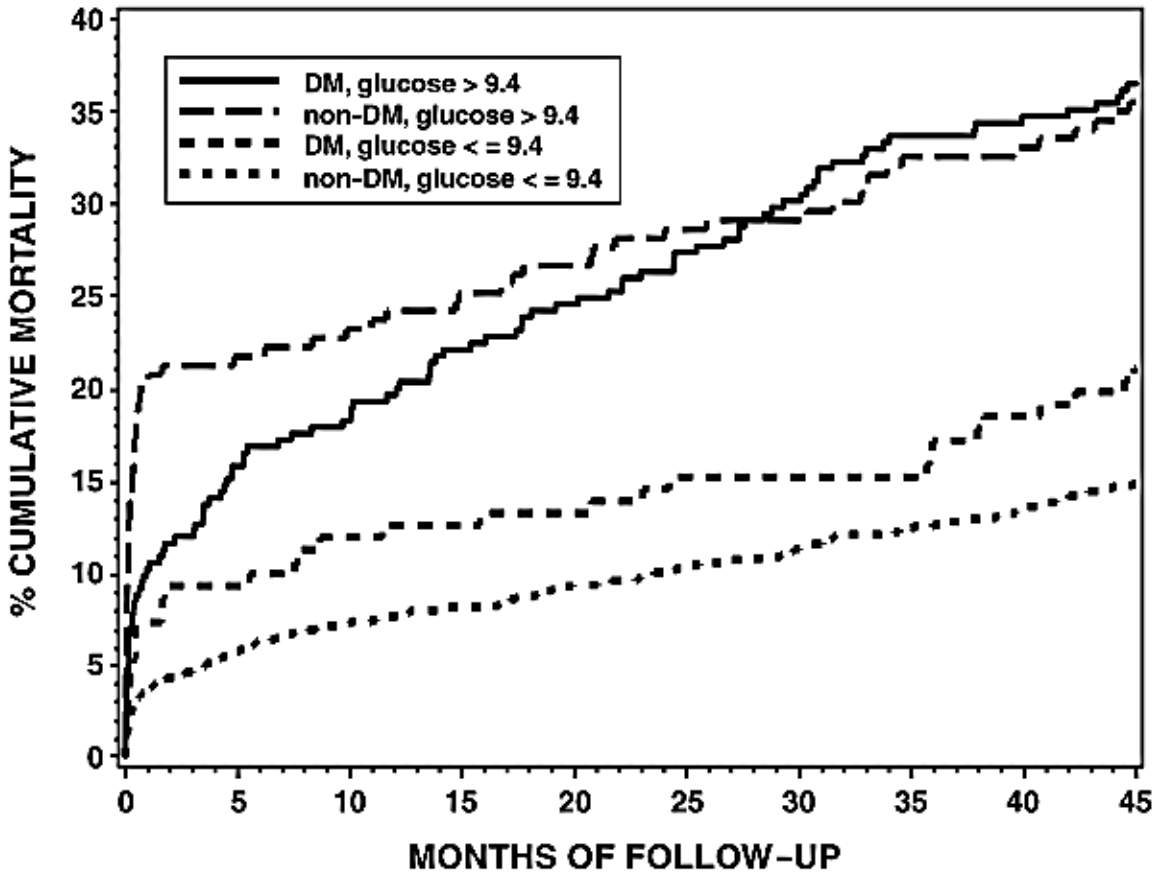

Figure 4. Kaplan-Meier curves for cumulative mortality proportion according to diabetes status and plasma glucose at admission

Conclusion
Admission plasma glucose is a strong predictor of mortality after ACS. Hyperglycaemic patients without known diabetes have a higher short-term mortality risk than hyperglycaemic patients with known diabetes.

Study III

Patients with a history of diabetes have a lower survival rate after in-hospital cardiac arrest

Diabetes is associated with an adverse outcome after out-of-hospital cardiac arrest. The aim of this study was to assess the impact of diabetic status on outcome in patients suffering an in-hospital cardiac arrest.

Results

Of 1,810 cases of in-hospital cardiac arrest, 22% had previously known diabetes. In general patients with diabetes had more comorbidity. A higher percentage of patients in the diabetic group were treated with anti-arrhythmic agents after collapse. Otherwise, the resuscitation treatment was similar in patients with and without diabetes. The immediate survival rate was similar between patients with and without diabetes, 51.7% and 53.1%, respectively. However, a significantly lower percentage of patients with diabetes were discharged alive from hospital, 29.3% and 37.6%, respectively ($p= 0.001$). The adjusted odds ratio of being discharged alive for patients with diabetes was 0.57 (95% CI: 0.40-0.79). Among patients who were discharged alive from hospital, the estimated cerebral function did not differ between the two groups according to CPC score.

Conclusion

Diabetes is prevalent among patients suffering an in-hospital cardiac arrest. In these patients diabetes is a strong independent predictor of mortality.

Study IV

Prevalence of abnormal glucose regulation and its relation to prognosis after CABG

The prevalence of prediabetes and its impact on prognosis after CABG is not well described. In this study we evaluate the prevalence and prognostic impact of the different states of AGR after CABG.

Results

We enrolled 276 patients, of whom 172 underwent an OGTT and 72 had previously known diabetes. Thirty two patients did not attend the OGTT visit. Eighty-six (35%) patients were normoglycaemic, 58 (24%) had prediabetes and 100 (41%) had diabetes, of whom 28 (28%) had newly diagnosed diabetes on the basis of the OGTT. Table 3 shows the baseline characteristics according to glycaemic state. During a mean follow-up period of 5.3 years, 25% of the study population suffered the primary endpoint. There was a successive increase in the primary endpoint rate (a composite of all-cause mortality and hospitalisation for a cardiovascular event) from normoglycaemia through prediabetes to diabetes (HR 1.51; 95% CI, 1.11 to 2.05; $p=0.009$). This pattern remained after adjustment for dissimilarities in baseline variables (HR 1.40; 95% CI, 1.01 to 1.96; $p=0.045$). Figure 5 shows cumulative event probability according to glycaemic state.

Conclusion

Given the high prevalence of AGR and its prognostic impact after CABG, we assume that systematic screening for AGR in patients undergoing CABG is reasonable in order to identify these high risk individuals.

	Normoglycaemia n=86	Prediabetes n=58	Diabetes n=100	*p*-value
Age – yrs	63.8	67.5	64.8	0.47
Male gender - %	89.5	79.3	83.0	0.25
Previous history of - %				
Heart failure	2.3	6.9	16.0	0.001
Hyperlipidemia	37.2	48.3	44.0	0.38
Hypertension	41.9	58.6	71.0	<0.0001
Myocardial infarction	29.1	22.4	32.0	0.61
Pulmonary disease	5.8	1.7	16.0	0.01
Stroke/TIA	11.6	13.8	11.0	0.87
Malignancy	5.8	12.1	7.0	0.83
Renal disease	7.0	6.9	5.0	0.57
PCI	17.7	13.8	21.4	0.48
Indications for CABG - %				
Stable angina	28.6	25.9	26.3	0.74
Unstable angina	38.1	46.6	43.3	0.50
Myocardial infarction	31.0	25.9	25.3	0.40
No of diseased coronary vessels - %				
1 or 2	21.2	29.6	17.8	0.59
3	51.5	52.3	58.9	0.38
Left main	27.7	18.2	23.3	0.61

Table 3. Baseline characteristics according to glycaemic state
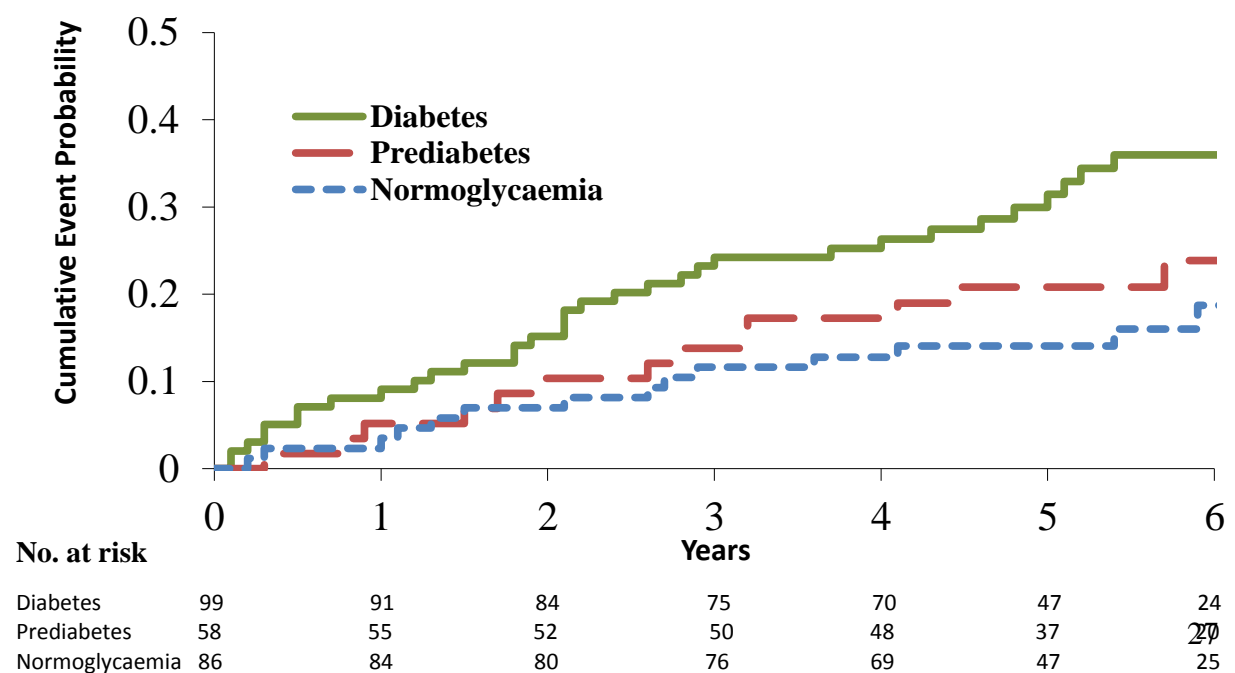
No. at risk							
Diabetes	99	91	84	75	70	47	24
Prediabetes	58	55	52	50	48	37	27
Normoglycaemia	86	84	80	76	69	47	25

Long-term mortality in patients with type 2 diabetes undergoing coronary angiography: the impact of glucose-lowering treatment

Reports have indicated that insulin treatment may possibly be harmful. The aim of this study was to investigate the impact of insulin treatment on long-term mortality in patients with type 2 diabetes and suspected CAD.

Results

A total of 12,515 patients with type 2 diabetes who underwent coronary angiography in 2001-2009 were stratified into four groups according to glucose-lowering treatment. The baseline characteristics are summarised in Table 4. Patients receiving insulin (with or without oral treatment) generally had more frequently established cardiovascular disease, longer diabetes duration, higher prevalence of diabetes complications and poorer glucose control. Further, insulin treatment was associated with more advanced CAD. During a mean follow-up period of 4.14 (SD 2.0) years there were 3,093 (22%) deaths from any cause. The absolute mortality rates were 19.2%, 17.4%, 22.9% and 28.1%, in patients treated with diet alone, oral therapy alone, insulin in combination with oral glucose-lowering drugs and insulin only.

Figure 6. Adjusted long-term mortality after angiography in patients with type 2 diabetes by glucose-lowering treatment
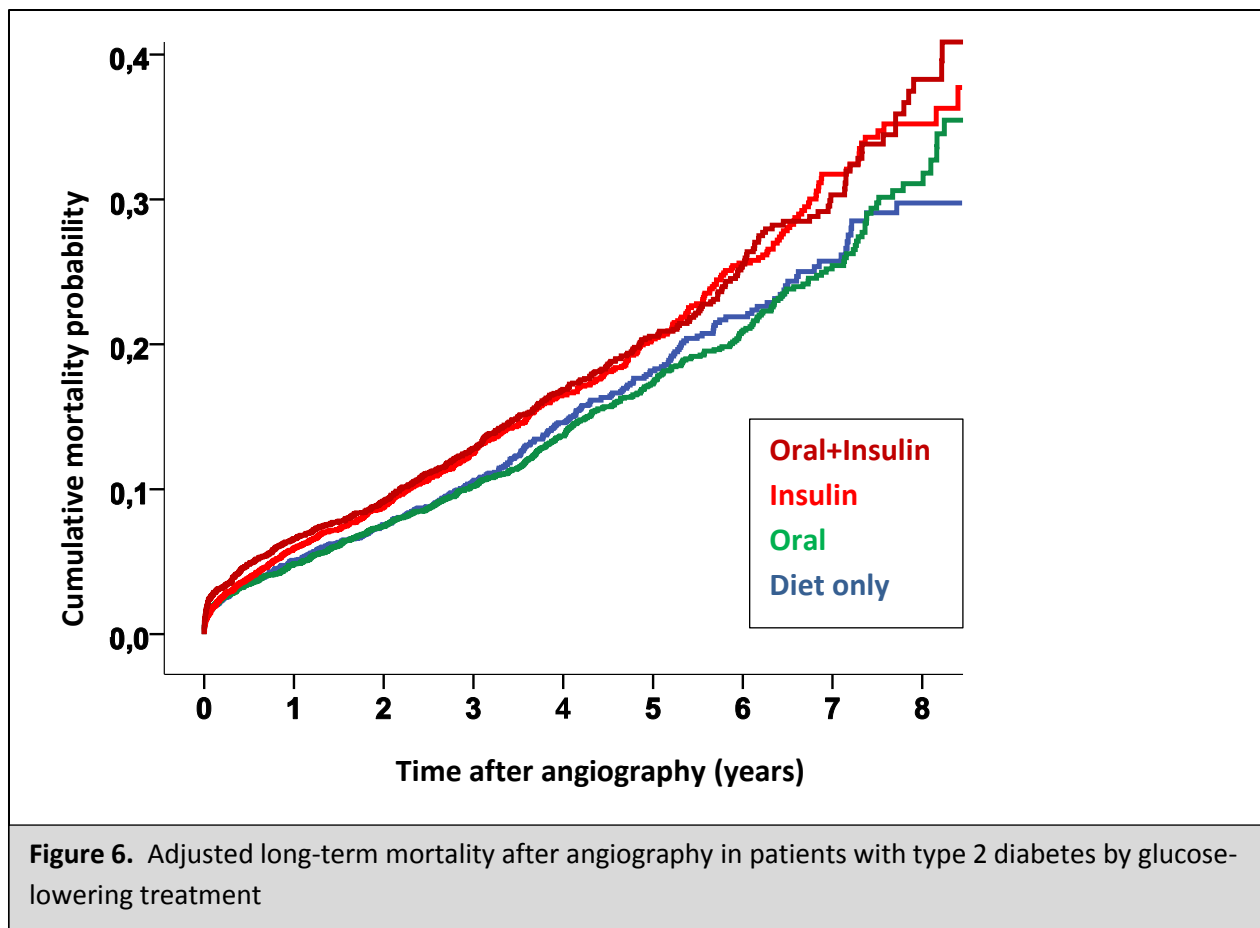
Characteristics and risk factors	No treatment n = 2428	Oral treatment n = 5051	Insulin+oral treatment n = 2803	Insulin treatment n = 2233	p-value
Baseline characteristics					
Age, years (mean, SD)	69.0 (9.8)	68.0 (9.6)	68.1 (8.3)	69.2 (8.8)	<0.0001
Male (%)	65.0	68.4	64.1	65.1	0.0001
BMI (kg/m$^{2)}$)	28.2 (5.2)	28.6 (4.5)	30.3 (4.9)	28.6 (7.8)	<0.0001
Weight (kg)	82.9 (15.5)	84.7 (15.6)	90.3 (15.6)	83.8 (16.1)	<0.0001
Previous disease (%)					
Hypertension (treated)	68.1	73.0	78.4	73.4	< 0.0001
Hyperlipidaemia (treated)	59.2	66.1	73.7	69.1	< 0.0001
CABG	10.7	10.5	13.7	15.3	< 0.0001
PCI	15.1	14.6	16.0	17.8	0.02
Myocardial infarction	30.9	30.0	35.3	40.2	< 0.0001
Heart failure (hospitalised)	12.9	11.6	16.4	23.9	< 0.0001
Stroke (hospitalised)	9.5	8.2	11.0	11.4	<0.0001
Renal insufficiency (hospitalised)	1.6	0.8	2.1	7.3	<0.0001
Smoker (current)	11.7	12.5	10.7	9.6	0.002
Peripheral artery disease (hospitalised)	5.4	4.3	6.7	11.1	< 0.0001
Dialysis	0.4	0.2	0.3	2.5	<0.0001
Amputation (hospitalised)	1.0	0.9	1.3	2.2	0.0001
Hospitalised for cancer	3.2	2.8	2.5	4.1	0.009
Diabetes related variables					
HbA1c %	6.5 (2.2)	7.1 (2.4)	7.8 (2.5)	7.7 (2.6)	<0.0001
HbA1c mmol/l	47.5 (0.5)	54.1 (2,7)	61.7 (3.8)	60.7 (4.9)	<0.0001
Diabetes duration, years	5.6 (5.8)	8.6 (6.1)	13.6 (6.6)	15.0 (8.3)	<0.0001

Creatinine (µmol/l)	87.8 (34.6)	84.9 (28.1)	88.7 (37.1)	107.4 (81.9)	<0.0001
Systolic blood pressure (mmHg)	142 (18)	142 (18)	141 (18)	142 (19)	0.498
Diastolic blood pressure (mmHg)	77 (10)	77 (10)	76 (10)	75 (10)	<0.0001
Pulse pressure (mmHg)	64 (17)	65 (16)	65 (16)	67 (17)	0.002
HDL (mg/dl)	1.28 (0.40)	1.24 (0.36)	1.20 (0.37)	1.32(0.46)	<0.0001
Triglycerides (mg/dl)	1.78 (1.02)	2.02 (1.21)	2.13 (1.41)	1.88 (1.36)	<0.0001
Total cholesterol (mg/dl)	4.99 (1.03)	4.93 (1.04)	4.74 (1.02)	4.87 (1.07)	<0.0001
Low physical activity level %	13.8	14.2	22.1	22.3	< 0.0001
High physical activity level %	35.5	27.4	22.8	28.2	< 0.0001
Retinopathy %	13.0	24.3	50.3	53.9	<0.0001
Only angiography (no PCI) %	56.7	57.1	59.0	59.2	0.142
Angiography findings %					
Normal	22.1	20.6	18.7	17.5	
One-vessel disease	23.6	23.8	21.8	19.6	Overall
Two-vessel disease	20.9	19.8	20.0	20.8	p < 0.0001
Three-vessel disease	21.7	26.2	27.8	29.9	
Left main stem disease	11.7	9.5	11.4	12.0	
Angiography decision %					
No coronary intervention	35.1	34.7	34.7	36.0	
CABG	17.7	19.2	19.9	19.0	Overall
PCI	47.2	46.1	45.4	45.0	p < 0.001
Indication %					
Stable angina	28.2	31.0	31.9	26.6	Overall
NSTE-ACS	44.7	43.6	43.8	46.8	p= 0.475
STEMI	10.6	10.0	8.5	10.3	
Fragile patient days (mean, SD)	6.8 (18.3)	5.7 (13.0)	7.6 (16.1)	11.9 (31.3)	p<0.0001

Table 4. Baseline characteristics of 12,515 patients with type 2 diabetes undergoing coronary angiography

Diabetes treatment	Unadjusted HR	95% CI	Adjusted HR	95% CI
Diet	1		1	
Oral	0.92	0.82-1.04	0.97	0.86-1.10
Oral+insulin	1.27	1.12-1.43	1.22	1.06-1.40
Insulin	1.62	1.44-1.83	1.17	1.02-1.35

Table 5. Unadjusted and adjusted hazard ratios for mortality by glucose-lowering treatment

After adjustment for baseline differences, treatment with insulin only (HR 1.17; CI 1.02 to 1.35; $p<0.01$) and insulin in combination with oral glucose-lowering treatment (HR 1.22; CI 1.06 to 1.40; $p<0.005$) remained independent predictors of long-term mortality (Figure 6 and Table 5).

Conclusion

Treatment with insulin in type 2 diabetic patients undergoing coronary angiography predicts long-term mortality risk even after adjustment for comorbidities. Whether or not this association is causal remains to be clarified.

GENERAL DISCUSSION

Hyperglycaemia as a predictor of AGR and outcome in patients with ACS

Why is hyperglycaemia so prevalent in the acute phase of ACS?
Admission hyperglycaemia is common in patients with ACS [47-49]. In *Study I,* 33% of the patients without previously known diabetes had admission plasma glucose of ≥7.0 mmol and in *Study II,* the prevalence of plasma glucose of >9.4 mmol/l was 65% among diabetics and 13% among non-diabetics. There are two main reasons for this high prevalence of hyperglycaemia in these patients.

First, acute-phase hyperglycaemia in ACS may be the result of a transient stress response mediated through the release of cortisol, adrenaline and noradrenaline [93]. In patients with AMI, this catecholamine response is acute and restricted to the first few days. The magnitude of the catecholamine activation correlates with the extent of myocardial damage and left ventricular dysfunction [94, 95].

Second, patients with hyperglycaemia at admission may have abnormal glucose regulation and remain hyperglycaemic after the acute phase. For example, diabetes is common in patients with ACS and hyperglycaemia is more prevalent in patients with diabetes than in patients without [47, 48]. A substantial proportion of ACS patients have undiagnosed diabetes and while untreated they tend to have hyperglycaemia by definition [19, 36, 96]. A large proportion of ACS patients have IGT and their non-fasting glucose levels are subsequently higher than normal.

To summarise, the reason for the high prevalence of admission hyperglycaemia in patients with ACS is probably a combination of a normal stress response due to the myocardial injury and the high prevalence of AGR in this population.

Can we predict future disturbances in glucose regulation after ACS?
Limited data are available to support the usefulness of admission glycaemia in predicting future disturbances in glucose regulation. On the other hand the relationship between fasting glycaemia and the risk of diabetes is a continuum with a graded risk at glycaemic levels well within the normal range [97, 98]. In the Mauritius study the five-year incidence of diabetes was approximately 15% for an FPG of 5.5.-5.7 mmol/l compared with 30% for an FPG 6.1-6.9 mmol/l [99]. A meta-analysis from the McMaster group showed that people with IFG had an approximately five-fold increase in the risk of progressing to diabetes compared with people with normal glucose regulation [34].

The risk of progression to diabetes is similar for IGT and IFG [34]. An OGTT is probably the best tool available to identify patients with AGR. Even though the test has fairly low reproducibility, patients identified as having diabetes will usually still have AGR when the test is repeated [27, 28, 34].

There are studies that suggest that HbA1c can be used as a predictor of future diabetes [100-103]. As with glucose measurements the relationship between HbA1c and the risk diabetes is curvilinear, i.e. the risk of diabetes rises disproportionately with rising HbA1c. The incidence of diabetes in people with HbA1c above the normal range but below the diagnostic cut-off point for diabetes (6.0 to <6.5%) is more than ten times the risk for those with lower levels [100-102]. HbA1c values at admission in patients with AMI have been shown to predict AGR at three months [96, 104].

Our results from *Study I* show that admission hyperglycaemia defined as plasma glucose of ≥7.0 mmol/l at admission in patients with ACS is associated with high prevalence (42%) of glycometabolic disturbance (defined as fasting plasma glucose of ≥6.1 mmol/l) 2½ years later. It is plausible that in some of the patients the admission hyperglycaemia was a reflection of undiagnosed diabetes. However, studies have shown that admission hyperglycaemia in non-diabetic patients with AMI does not necessarily represent undiagnosed abnormal glucose regulation. In only approximately 50% of non-diabetic patients with admission glucose levels in the diabetic range or ≥11.0 mmol/l can the diabetes diagnosis be confirmed with an OGTT [105-107].

In *Study I,* we found that HbA1c of ≥5.5% was an even stronger predictor of future glycometabolic abnormalities than admission glucose of ≥7.0 mmol/l. There are two main reasons for this. First, in this study HbA1c was measured using the Mono-S method and the normal reference range was 3.9-5.3% and 3.6-5.0% for those ≥50 years and <50 years respectively. As a result, values of ≥5.5% must be regarded as abnormally high. In fact, the corresponding HbA1c measured with the NGSP (DCCT) method would be approximately 6.5% [32], which is the cut-off point for the new ADA diagnostic criteria for diabetes [7] . Second, HbA1c reflects mean glycaemia for the previous two to three months. High levels of HbA1c in patients with ACS are therefore likely to be a sign of underlying glycometabolic disturbance. It is reasonable to assume that the prevalence of undiagnosed diabetes in the group with HbA1c of ≥5.5% should be higher than in the group with admission plasma glucose of ≥7.0 mmol/l.

According to our results the combination of high admission glucose and high HbA1c was the strongest predictor of future glycometabolic abnormalities. In all probability, a large percentage of these patients already had abnormal glucose regulation at admission.

Risk scores based on risk factors for diabetes can be used to identify patients running a high risk of developing diabetes [108]. However, because of the high prevalence of disturbances in glucose regulation among patients with established coronary heart disease, using risk scores to detect patients running a high risk of developing diabetes may be more appropriate for the general population [109].

Should evaluation of glucose regulation be performed in patients with ACS? Why, how and when?
Patients with ACS present an opportunity for targeted screening for AGR and the initiation of treatment when indicated. The optimal timing and the preferred test for evaluating the glucose

regulation in these patients are unclear. In the setting of ACS none of the above mentioned tests for the evaluation of glucose regulation is perfect. Admission hyperglycaemia is a poor indicator of undiagnosed diabetes, as it lacks both sensitivity and specificity [46, 105, 106]. Fasting glucose measurements during hospitalisation are a better test for detecting diabetes than admission glucose. However, fasting hyperglycaemia during the first few days after admission may be a reflection of an adrenergic stress response rather than undiagnosed diabetes and it is unable to reliably identify undiagnosed diabetes in patients with ACS [46, 105, 106].

Using only FPG as a diagnostic tool will fail to diagnose more than 50% of people with diabetes detected by an OGTT [17, 18]. An OGTT is probably the most appropriate method for the clinical assessment of glucose regulation in patients with coronary heart disease [18]. With an OGTT both those with undiagnosed diabetes and those at the highest risk (i.e. IFG and IGT) of future diabetes can be identified. Because of stress hyperglycaemia, an OGTT is probably not to be recommended before day 4 after an ACS [104, 110] and the majority of patients will therefore be discharged before the optimal timing for the test. The most suitable time for an OGTT is therefore probably at the follow-up visit at the outpatient clinic. The main arguments for not using the OGTT in clinical practice is that FPG is more convenient for patients, less costly and less time consuming [111]. Further, the OGTT has relatively poor reproducibility [27, 28].

An alternative way to identify those running a high risk of diabetes may be the combination of HbA1c and fasting glucose measured under stable circumstances [102, 112]. Compared with the OGTT both tests suffer from a lack of sensitivity [31]. As yet, there is no universal consensus on the cut-off point for the optimal HbA1c but in recently published guidelines from the ADA patients with HbA1c of 5.7-6.4% should be regarded as running an increased risk of diabetes [113]. Combining FPG and HbA1c with BMI may be an even more effective way of identifying patients running a high risk of future diabetes [114].

If we were to screen ACS patients for disturbances in glucose regulation, what clinical impact would it have?
The reason for evaluating glucose regulation in non-diabetics with ACS is to identify those with previously unknown diabetes and prediabetes. Because the majority of the patients with ACS have AGR detectable by an OGTT, a screening of this kind, if performed routinely would definitely have a major clinical impact. First, it would enable more early diagnosis and treatment of otherwise undetected diabetes. Second, it would lead to the detection of a large group of patients with prediabetes. This group, which accounts for at least a quarter of all ACS patients, includes patients with both IGT and IFG [19, 36]. However, there is no consensus on how or if these patients should be treated. There is extensive evidence from randomised controlled studies that lifestyle and pharmacological interventions in patients with IGT can prevent or delay progression to diabetes [115-122]. Currently, only limited data indicate that interventions are able to prevent the progression of IFG to diabetes [122]. Further, there are no data available from randomised trials showing that such interventions are able to reduce mortality or the incidence of cardiovascular disease in patients with

prediabetes. In a report from a 10-year follow up of the Finnish Diabetes Prevention Study (DPS) that randomised patients with IGT to intensive lifestyle intervention or general health behaviour, there was no significant difference in the rate of mortality or cardiovascular morbidity between the groups. However, compared with a cohort of individuals with IGT from the general population, the mortality rate was lower in the DPS study group [123].

How should we follow up patients with prediabetes?

According to recently published guidelines from the ADA, patients with IGT, IFG or HbA1c of 5.7-6.4% should be regarded as running a high risk of diabetes [113]. These patients should be referred to a lifestyle programme with goals of a 5-10% weight loss (when appropriate) and physical activity of at least 150 min/week. Further, metformin may be considered in those who run a very high risk of developing diabetes (i.e. those with risk factors for diabetes and/or those with more severe or progressive hyperglycaemia). Annual monitoring for diabetes is recommended. Apart from lifestyle modification in patients with IGT, the evidence level for these recommendations is low (i.e. expert consensus).

Implementing a preventive lifestyle programme for 25% of all ACS patients is obviously resource demanding. A cost-benefit analysis could be useful for local health care providers as a guide in the decision making for a programme of this kind.

What is the relative importance of admission hyperglycaemia as a predictor of poor prognosis in non-diabetic patients with ACS?

Admission hyperglycaemia in patients with ACS has been shown to be a strong predictor of both short-term and long-term morbidity and mortality [47-54]. Foo et al. found that admission glycaemia stratified patients with ACS syndromes according to their risk of in-hospital heart failure and cardiac mortality. There was no glycaemic threshold for the adverse outcome and the prognostic impact of hyperglycaemia was unaffected by diabetic status and did not differ significantly between patients with myocardial infarction and those with unstable angina [51].

In *Study II,* elevated admission glucose was associated with a higher risk of short-term mortality and similar long-term mortality in patients without diabetes as compared with patients with diabetes. This is in line with other studies showing that hyperglycaemia in patients with AMI who do not have previously known diabetes is associated with a poorer short-term outcome compared with patients with established diabetes [48, 49, 53].

Admission hyperglycaemia is therefore a strong predictor of poor prognosis after ACS and the predictive value of admission hyperglycaemia for short-term outcome appears to be higher in patients without diabetes.

What is the reason for the high short-term mortality rate in non-diabetic patients with hyperglycaemia?

In *Study II,* the short-term mortality rate among non-diabetic patients with hyperglycaemia (plasma glucose of >9.4 mmol/l) was extremely high or 20%. The corresponding mortality rate for those with plasma glucose of ≤9.4 mmol/l was 3.5%. For comparison data from the

Euro Heart Survey showed that the 30 day mortality rate in patients with ACS was 5-6% [124].

The question of whether hyperglycaemia is a marker of disease severity or a direct mediator of adverse outcome has been the subject of discussion. Higher comorbidity may thus be one of the explanations for the high mortality rate in patients with hyperglycaemia. In *Study II,* the hyperglycaemic non-diabetics had higher CK-MB levels, as a marker of greater myocardial injury, and a higher prevalence of heart failure and pre-hospital or in-hospital cardiac arrest. Hyperglycaemia in these patients may therefore be a marker of stress response due to more extensive myocardial damage or the cardiac arrest. However, after adjustment for potential confounders, hyperglycaemia still remained a predictor of both short-term and long-term mortality. Other studies have also shown that after adjustment for co-morbidities hyperglycaemia remains a strong predictor of short-term mortality in patients with ACS [48, 49, 51]. However, the possibility of residual confounding by unmeasured factors cannot be eliminated.

There is evidence supporting the hypothesis that hyperglycaemia can have a direct detrimental effect on the ischemic heart. Hyperglycaemia has been shown to be associated with both endothelial and platelet dysfunction [125-127]. Oxidative stress is activated by hyperglycaemia and in particular acute fluctuations in glucose levels [128]. Acute hyperglycaemia can also disturb cardiac repolarisation and induce QTc prolongation [129]. Further, animal studies have shown that acute hyperglycaemia reduces coronary collateral blood flow, abolishes ischemic preconditioning and promotes apoptosis [130-132].

Another possible explanation is that the non-diabetic group may have included some patients with true diabetes who have been neither diagnosed nor adequately treated for diabetes (and concurrent cardiovascular risk factors) and thus may have had a higher mortality risk. Studies have shown that 20-30% of ACS patients without a previous history of diabetes, have diabetes disclosed by an OGTT [19, 36].

What is the reason for the high long-term mortality in diabetic patients with admission hyperglycaemia?
Even if hyperglycaemic patients without diabetes had the highest short-term mortality in *Study II*, the long-term prognosis did not differ between hyperglycaemic patients with and without diabetes. Ishihara et al. demonstrated that non-diabetic patients with admission hyperglycaemia had a three-year mortality rate similar to that of patients with established diabetes [48]. It is possible that admission hyperglycaemia in patients with diabetes reflects generally poor glycaemic control and may therefore be associated with a higher mortality rate in the long run. In our study there was a weak trend towards increased early mortality in the diabetic patients with hyperglycaemia. However, it appears not unlikely that poor glycaemic control affects both the short-term and long-term outcome in diabetic patients with ACS.

Glycaemia and cardiac arrest

What can explain the poor prognosis associated with diabetes after cardiac arrest?
In *Study III*, the patients with diabetes had a higher prevalence of previously known heart failure, myocardial infarction, stroke and renal disease than patients without diabetes. Both the degree of heart failure and a previous history of ischemic heart disease are negative prognostic factors among high-risk patients after acute myocardial infarction [133]. Higher comorbidity may therefore be one possible reason for the poorer outcome. However, diabetes remained an independent predictor of mortality after adjustment for dissimilarities in comorbidity. This indicates that other undefined factors might contribute to the poor outcome. For example, hyperglycaemia is associated with adverse outcome in post-resuscitation care [134-136]. Endothelial and platelet dysfunction [125-127], increased oxidative stress [128], metabolic abnormalities in the diabetic heart [137] and more extensive coronary artery disease [138] are some of the factors associated with hyperglycaemia and diabetes that may impact survival after cardiac arrest. Furthermore, diabetic microvascular disease leads to autonomic neuropathy which may affect electrical stability with reduced heart rate variability, increased QT dispersion and prolonged QT interval [139-141].

For these reasons, factors like macro- and microvascular disease, autonomic dysfunction and metabolic abnormalities may all contribute both to the high prevalence of cardiac arrest and to the poor prognosis after cardiac arrest in patients with diabetes.

Should the treatment during and after cardiac arrest differ between diabetic and non-diabetic patients?
In *Study III*, patients with and without diabetes received similar treatment with the exception that diabetic patients were more frequently given anti-arrhythmic drugs. There is nothing in our results to indicate that treatment routines for cardiac arrest and post-resuscitation care should be different for diabetics than non-diabetics.

To our knowledge, no convincing data are available to indicate that treatment during and after cardiac arrest should differ between patients with diabetes and patients without diabetes. According to guidelines, patients with diabetes should generally be treated in the same manner as those without [67]. Furthermore, hyperglycaemia in the acute phase should be treated, regardless of prior diabetes history [142].

Is any evidence available to support the hypothesis that the rapid normalisation of blood glucose improves the prognosis in patients who survive the acute phase of cardiac arrest?
Hyperglycaemia is common after cardiac arrest. A recent report from the US National Registry of Cardiopulmonary Resuscitation found that, while the hospital survival of diabetic patients was not much affected by the level of glycaemia, there was a U-shaped relationship between blood glucose level and hospital survival in patients without diabetes [136]. A similar U-shaped relationship between blood glucose and outcome after cardiac arrest has previously been noted [143, 144].

Limited data are available on the effect of glucose control on outcome after cardiac arrest. To date only one randomised study has assessed the impact of strict glucose control on outcome after cardiac arrest [145]. In this study strict glucose control (blood glucose target of 4-6 mmol/l) was compared with moderate glucose control (6-8 mmol/l) in 90 patients suffering an out-of-hospital cardiac arrest who were treated with therapeutic hypothermia. The study revealed no difference in 30-day mortality.

The effect of tight glucose control on outcome has been tested in other clinical settings. In 2001, van den Berghe et al. published a randomised controlled trial of critically ill surgical patients showing that tight glucose control reduced in-hospital mortality by 34% [146]. However, this survival benefit could not be confirmed in subsequent randomised trials [147]. The largest study by far on this topic is the NICE-SUGAR study, a multicentre randomised controlled trial comparing intensive glucose control (target blood glucose 4.5-6.0 mmol/l) and conventional control (target blood glucose ≤10 mmol/l) in 6,104 patients expected to require treatment in the intensive care unit on ≥3 consecutive days [148]. The primary endpoint, death from any cause within 90 days, occurred in 27.5% of the intensive control group and in 24.9% of the conventional control group (OR for intensive control, 1.14; 95% CI, 1.02 to 1.28; p=0.02). Strict glucose control in critically ill patients is therefore probably harmful and should be avoided.

Even though the benefit or harm of aiming for strict normoglycaemia may depend on the clinical setting, it is now generally accepted, based on the available data, that the maintenance of near normoglycaemia is beneficial for critically ill patients. In patients with ACS, three randomized trials have studied the impact of intensive glucose control on mortality, i.e. DIGAMI 1, DIGAMI 2 and HI-5 [149-151]. However, DIGAMI 1 is the only trial to have achieved a significantly reduced glucose level in the intensive control arm compared with the control arm. Further, DIGAMI 1 is the only randomised trial that has demonstrated survival benefit associated with tight glucose control in patients with AMI [149].

To summarise, there is limited evidence to support strict glucose control in post-resuscitation patients. However, the frequent monitoring of blood glucose and the treatment of hyperglycaemia is recommended [142]. Even though the optimal level of glucose control remains to be defined, a blood glucose target of ≤10 mmol/l has been suggested, based on the available data [152].

Is it possible that warning symptoms of cardiac arrest are less distinct in patients with diabetes?
Most cases of cardiac arrest are preceded by warning symptoms such as angina pectoris, dyspnea, nausea and dizziness [153]. It has been claimed that patients with diabetes more frequently have silent myocardial ischemia and even a higher prevalence of asymptomatic myocardial infarction [154, 155]. It is therefore possible that warning symptoms, e.g. angina pectoris may be less distinct in patients with diabetes than in those without. We are however, not aware of any studies that give a direct answer to this question.

Abnormal glucose regulation after CABG

What is the prevalence of abnormal glucose regulation in patients treated with CABG?
Our analysis showed that in patients treated with CABG, approximately 40% had diabetes and two-thirds had AGR. Similar findings have previously been reported in patients undergoing CABG [156, 157]. These prevalence figures are in agreement with the results of two large surveys that have shown that approximately three-quarters of patients with CAD (both stable and unstable) have AGR [19, 36]. Our results thus confirm that the majority of patients with CAD have AGR.

Does the severity of abnormalities in glucose regulation impact the long-term prognosis after CABG?
The prognostic impact of diabetes in patients treated with CABG is fairly well documented and diabetes has been associated with an almost doubling of the mortality risk after CABG [158]. Prediabetes has been associated with a poorer outcome in patients with stable CAD [159] but the relationship between prediabetes and outcome after CABG has not been studied in detail. In *Study IV,* there was a successive increase in mortality and non-fatal cardiovascular events from normoglycaemia through prediabetes to diabetes (adjusted HR 1.40; 95% CI, 1.01 to 1.96; *p*=0.045). Our results thus indicate that not only diabetes but also prediabetes have an impact on the long-term outcome after CABG. However, because of the small sample size we did not perform a separate comparison between the groups with normoglycaemia and prediabetes.

What is the optimal treatment for prediabetes after CABG?
Several randomised controlled trials have shown that in patients with IGT the progression to type 2 diabetes can be prevented or at least delayed by lifestyle interventions [115-117, 120] and/or drug treatment with metformin [116, 117, 120], acarbose [118] and rosiglitazon [122]. Two of these studies, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program study, showed that a lifestyle modification programme with the goals of at least a 5-7% weight loss and at least 20-30 minutes of physical activity per day reduced the three-year relative risk of diabetes by 58% [116, 117]. In these studies the estimated cumulative incidence of diabetes after 3 years was 20-30% in the control groups. Two studies of lifestyle intervention have shown a sustained reduction in the incidence of diabetes which remained after the individual lifestyle counselling was stopped [160, 161]. Even if lifestyle intervention may reduce the rate of progression to type 2 diabetes, its impact on prognosis is still unclear. An analysis of 10-year follow-up data from the Finnish Diabetes Prevention Study did not reveal any significant difference in the rates of mortality and cardiovascular events between the intensive lifestyle intervention group and the control group [123]. The ADA guidelines recommend that patients with IGT should be referred to a lifestyle programme with goals of a 5-10% weight loss and physical activity of at least 150 min/week. Further, metformin may be considered in those who run a very high risk of developing diabetes [113]. Accordingly, the evidence available to date indicates that the optimal treatment for all patients with prediabetes, including CABG patients, is probably lifestyle counselling with the goals of a weight loss of at least 5% and moderate physical activity of at least 150 min/week.

Should an OGTT be a routine test after CABG?

The OGTT is currently the best test available for identifying patients with previously unknown diabetes and IGT. The ESC guidelines recommend that an OGTT should be performed on all patients without diabetes but with established CVD [109] . The prevalence of prediabetes and previously unknown diabetes in patients undergoing CABG is at least as high as in the general CAD population. For this reason, an OGTT should be a routine test according to the guidelines. However, performing OGTT on this large patient group and offering lifestyle intervention to all those identified as having prediabetes is resource demanding. In an era of economic constraints, the resources may be better allocated elsewhere.

Glucose-lowering strategies in patients with CAD

What is the optimal level of glycaemic control in diabetic patients with CAD?

The use of glucose-lowering treatment in order to maintain glycaemic levels as close to normal as possible has been shown to have beneficial effect on diabetes-specific microvascular complications in patients with both type 1 [73, 74] and type 2 diabetes [75, 76]. In patients with type 1 diabetes, intensive glycaemic control has been shown to have beneficial effects on macrovascular (i.e. cardiovascular) complications as well [77] and intensive glucose-lowering treatment in patients with newly diagnosed type 2 diabetes has been shown to improve cardiovascular outcome and survival [78]. However, randomised controlled trials have failed to confirm the beneficial effect of intensive glycaemic control in patients with established type 2 diabetes and high cardiovascular risk [162-164]. On the contrary, it has been speculated that strict glycaemic control might even be harmful. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was designed to determine whether intensive glycaemic control (i.e. HbA1c <6.0%) would reduce the rate of mortality and cardiovascular events, as compared with standard therapy (i.e. HbA1c 7.0-7.9%). The study did not reveal any statistically significant difference in the primary outcome which was a composite of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. However, the rate of death from cardiovascular causes was higher in the intensive therapy group (2.6% vs. 1.8%; HR, 1.35; 95% CI, 1.04 to 1.76; *p*=0.02) [163]. The prevalence of cardiovascular disease at baseline in the above-mentioned studies was 35-40%.

The optimal HbA1c level in the group of diabetic patients with CAD is unknown. In the DIGAMI trial, patients with diabetes and AMI were randomised to conventional treatment or intense insulin treatment including an insulin-glucose infusion during the first 24 hours followed by subcutaneous insulin for ≥ 3 months. The one-year mortality was reduced by 30% in the intensively treated group [165]. The study was unable to answer the question of whether the beneficial effects were related to the acute insulin-glucose infusion or to the long-term insulin treatment. In order to clarify this question the DIGAMI 2 trial was conducted. In this study of patients with AMI and type 2 diabetes, strict glycaemic control with long-term insulin treatment was compared with standard glucose control with and without an insulin-

glucose infusion for the first 24 hours. The treatment goal for the insulin group was a fasting blood glucose level of 5-7 mmol/L and a non-fasting level of < 10 mmol/L. Compared with standard treatment, insulin-based treatment did not reduce mortality and morbidity. One important limitation of the trial was that long-term glycaemic levels did not differ between the treatment groups [166]. According to a consensus statement from the ADA and the EASD, the goal is to achieve and maintain HbA1c levels of <7% in patients with type 2 diabetes [81]. To date there is no strong evidence to indicate that glycaemic control strategies should differ between patients with CAD and those without.

What is the optimal glucose-lowering treatment in patients with CAD?
In addition to uncertainty regarding the optimal glycaemic control, the preferred glucose-lowering therapy in patients with CAD remains to be clarified. The results of *Study V* showed that in patients with type 2 diabetes undergoing coronary angiography, treatment with insulin alone (adjusted HR 1.17; CI 1.02 to 1.35; $p<0.01$) and insulin in combination with oral glucose-lowering treatment (adjusted HR 1.22; CI 1.06 to 1.40; $p<0.005$) was an independent predictor of long-term mortality. These findings are in agreement with retrospective analyses of epidemiological data that have raised concerns about the possibly harmful effects of insulin treatment in patients with CAD [40, 89, 90, 167]. To date however, no randomised controlled trial testing different glucose-lowering regimens in patients with CAD have convincingly demonstrated that insulin-based therapy is inferior to non-insulin-based therapy. The BARI 2 trial randomised 2,368 patients with type 2 diabetes and CAD to either prompt revascularisation or intensive medical therapy alone; and to either insulin-provision or insulin-sensitisation therapy. Insulin-provision and insulin-sensitisation had similar five-year mortality rates, 12.1% and 11.8% respectively ($p=0.89$). Even the rates of major cardiovascular events did not differ significantly among the groups [6]. However, these data are somewhat difficult to interpret in terms of the safety of insulin treatment as almost 30% of the patients in the insulin-sensitisation arm were treated with insulin as compared to 60% of the patients in the insulin-provision arm.

The mainstay of the treatment of newly diagnosed diabetes is lifestyle intervention and metformin. If treatment with lifestyle and metformin is not enough to achieve the glycaemic goals, the addition of insulin or sulfonylurea is the preferred recommendation [81]. According to current evidence patients with CAD should generally receive the same glucose-lowering treatment as patients without CAD. Caution when using thiazolidinediones is recommended, as they may increase the risk of cardiovascular complications [85, 86].

What are the explanations of a poorer outcome in patients treated with insulin?
It is unclear whether the insulin may directly contribute to the poorer prognosis or whether the treatment is just a marker of more advanced diabetes. Several potentially harmful effects of insulin have been identified. In a number of studies, hypoglycaemia has been associated with a poorer outcome in patients with myocardial infarction [62, 168-170]. However, iatrogenic hypoglycaemia in patients who are given insulin has not been shown to predict a poor prognosis in this patient population [171, 172]. Other possible negative effects of insulin include endothelial dysfunction [173], platelet dysfunction [174] and sympathetic activation

[175]. Moreover, cohort studies have suggested that exogenous insulin may exacerbate the already increased risk of cancer in patients with diabetes [176, 177].

It is important to recognise that the evidence, including our results, suggesting that there may be an association between insulin treatment and a poor outcome in patients with CAD is derived from observational data [40, 89, 90, 167]. Limitations of observational studies include the fact that the study groups may not be comparable, either because of differences in measured characteristics at baseline (i.e. an overt bias) or because they may differ in ways that have not been measured (i.e. a hidden bias) [178]. We are therefore unable to exclude the possibility that our findings may be a result of a study bias. The most intuitive explanation for the association between insulin and a poor prognosis may be the fact that the patients with the longest diabetes duration and the most advanced disease are usually those treated with insulin. In that case, the treatment groups may not be comparable because of an overt bias. One of the strengths of our study was that, by merging two registries, one focusing on diabetes variables and the other on cardiovascular variables, it was possible to perform extensive adjustments for dissimilarities between treatment groups and thereby limit the effects of potential confounders on the results. Despite a careful attempt to account for all known potentially confounding variables, it is possible that unidentified confounders may have influenced the results. In an observational study like this, a hidden bias cannot be excluded.

Future perspectives

The present thesis shows that abnormalities in glucose regulation are associated with a poor prognosis in various manifestations of coronary heart disease. Even though diabetes is the most serious form of glucose dysregulation, stress hyperglycaemia and prediabetes also appear to predict unfavourable outcome. The best way to prevent diabetes complications, e.g. CAD, is to prevent the development of diabetes. This can be done in two ways: population-based primary prevention and prevention in high-risk individuals. The most effective tool available for identifying high- risk individuals is the OGTT. This test has limitations and a more reliable and convenient test would be desirable. Identifying high-risk patients is obviously a waste of time and resources if appropriate preventive measures cannot be offered. So clarifying how to prevent diabetes cost-effectively in high-risk patients is important.

The early diagnosis of diabetes is mandatory in order to prevent complications in patients who have already developed the disease. The early detection of diabetes requires the screening of high-risk patients. For this purpose the OGTT is considered by many to be the golden standard, but the drawbacks of the test are a barrier to widespread use. Improved tools for the detection of diabetes would therefore enable earlier treatment and hopefully prevent diabetes complications.

The recommended glucose-lowering treatment in patients with diabetes is usually not affected by concurrent cardiovascular disease. However, some glucose-lowering agents have been associated with an increased risk of cardiovascular events. The optimal glucose-lowering strategy in patients with diabetes and concomitant cardiovascular disease is yet to be defined.

CONCLUSIONS

1. Non-diabetic patients with ACS and elevated admission plasma glucose should be regarded as running a high risk of developing glycometabolic disturbance.

2. Admission plasma glucose is a strong predictor of mortality after ACS, both in patients with and without known diabetes. Hyperglycaemic patients without known diabetes have a higher short-term mortality risk than hyperglycaemic patients with known diabetes.

3. Diabetes is a strong independent predictor of mortality after in-hospital cardiac arrest.

4. Given the high prevalence of AGR and its prognostic impact after CABG, we assume that systematic screening for AGR in patients undergoing CABG is reasonable in order to identify these high risk individuals.

5. Treatment with insulin in type 2 diabetic patients undergoing coronary angiography predicts long-term mortality risk even after adjustment for comorbidities. Whether or not this association is causal remains to be clarified.

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