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Diabetes mellitus, glucose abnormalities and acute coronary syndromes

Studies on prevalence, risk and impact of treatment

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Bevara det gamla – men känn till det nya
Kinesiskt ordspråk

CONTENTS

ABSTRACT

Background: Persons with diabetes mellitus and impaired glucose tolerance are at increased risk for cardiovascular disease.The prevalence of known diabetes among patients with acute myocardial infarction, about 20%, is expected to increase in the coming decades. Despite recent improvements in the overall management of cardiovascular disease, the mortality after myocardial infarction in patients with diabetes remains high.

Aims: This thesis analyses the relation between glucose abnormalities and acute coronary syndromes focus on

1. Risk factors and the importance of insulin based meticulous metabolic control in patients with diabetes and acute myocardial infarction
2. The actual prevalence of glucose abnormalities in patients with acute myocardial infarction
3. The use of evidenced based treatment in patients with diabetes and acute myocardial infarction
4. The effect of early revascularisation in patients with diabetes and with unstable coronary artery disease

Blood glucose as a risk factor: In the prospective randomised DIGAMI study including 620 patients with acute myocardial infarction, insulin-based intense metabolic care initiated by a 24 hours insulin-glucose infusion followed by at least three months of subcutaneous multidose insulin treatment, reduced the long-term mortality with almost 30%. The most important risk factors for long-term mortality were high age, previous heart failure, and the glucometabolic state at admission. Besides established risk factors poor metabolic control at admission indicated a worse prognosis, which was attenuated by intense insulin treatment. Plasma glucose was examined at admission in 197 patients with acute myocardial infarction without previously known diabetes mellitus. During two years of follow up 40% had a major cardiovascular event. Independent risk factors for such event were a high admission plasma glucose, previous heart failure and high age. Thus, even among non-diabetic patients with acute myocardial infarction a high glucose level at admission identifies patients with worse prognosis.

Glucose abnormalities and acute coronary syndromes: In 181 non-diabetic patients with acute myocardial infarction, who were examined with oral glucose tolerance tests during their initial hospitalisation, 31% fulfilled established criteria for diabetes mellitus while 35% had impaired glucose tolerance. These proportions were similar three months later, 25% and 40% respectively. Thus, previously undetected diabetes mellitus and pre-diabetes were surprisingly common.

Diabetes and acute coronary syndromes: In RIKS-HIA, (Swedish Register of Information and Knowledge about Swedish Care Units) the mean prevalence of diabetes was 20% among 25 632 persons below the age of 80 years who were hospitalised 1995-98 with an acute myocardial infarction. Diabetes was a strong independent predictor for mortality during the first year. Evidenced based treatment was similarly efficacious in patients with and without diabetes, however, significantly less utilised in the diabetic cohort. Thus, there are potentials to improve the prognosis of diabetic patients with myocardial infarction simply by better use of standard treatment. In the FRISC II trial, on the effect of early revascularisation in patients with unstable coronary artery disease, 299 (12%) of the patients had a previously diagnosed diabetes mellitus. The primary endpoint, death or a non-fatal reinfarction during one year of follow up was more prevalent among patients with diabetes. The relative improvement in prognosis induced by early revascularisation was similar in both groups. After adjustment for risk factors including number of diseased coronary arteries, diabetes remained as the strongest predictor for an unfavourable outcome. Thus, factors beyond the extent of coronary artery atherosclerosis seems to be of importance for the outcome in patients with diabetes mellitus and unstable coronary artery disease.

Conclusions: Diabetes and pre-diabetes are considerably more common among patients with acute myocardial infarction than previously expected. Diabetic patient still have a worse outcome following an acute coronary event. Meticulous insulin-based metabolic care and a proper use of existing evidence-based treatment and when suited, early revascularisation, will improve the prognosis. It can be assumed that improved awareness of the glucometabolic condition among patients with acute coronary events may open for new secondary preventive treatment strategies in this patient category.

Key words: diabetes, glucose tolerance, hyperglycemia, prognosis, risk, mortality, prevalence, myocardial infarction

List of Original Papers

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

I

Malmberg K, Norhammar A, Wedel H, Rydén L.
Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study.
Circulation 1999;99:2626-2632

II

Norhammar A M, Rydén L, Malmberg K.
Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients.
Diabetes Care 1999;22:1827-1831

III

Norhammar A, Tenerz Å, Nilsson G, Hamsten A, Efendic S, Rydén L, Malmberg K.
Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study.
Lancet 2002;359:2140-2144

IV

Norhammar A, Malmberg K, Rydén L, Tornvall P, Stenestrand U, Wallentin L, For the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA).
Under utilisation of evidence-based treatment partial explanation for the unfavourable prognosis in diabetic patients with acute myocardial infarction.
Eur Heart J 2003;24:838-844

V

Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Rydén L, Wallentin L.
Diabetes mellitus the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization.
In manuscript

List of Abbreviations

ACS	Acute coronary syndrome
ADA	American Diabetes Association
AMI	Acute myocardial infarction
CABG	Coronary artery bypass grafting
CCU	Coronary care unit
CI	Confidence interval
CK	Creatine kinase
CV	Coefficient of variation
DCCT	Diabetes Control and Complications trial
DIGAMI	Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction
FBG	Fasting blood glucose
ECG	Electrocardiography
FRISC II	Fragmin and Fast Revascularisation during InStability in Coronary artery disease II
GAMI	Glucose abnormalities in acute myocardial infarction study
GIK	Glucose-Insulin Potassium infusion
HbA1c	Glycosylated haemoglobin 1
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IVGT	Intravenous glucose tolerance test
MI	Myocardial infarction
NDDG	The National Diabetes Data Group
NS	Non significant
OGTT	Oral Glucose Tolerance Test
OR	Odds ratio
PCI	Percutaneous coronary intervention
PIGAMI	Prognostic importance of admission glucose in acute myocardial infarction study
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
RR	Relative risk
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study

INTRODUCTION

Myocardial infarction and acute coronary syndrome

Historical and epidemiological background

In1859 the Swedish physician J P Malmsten presented one of the earliest reports on myocardial infarction with his paper: " Fall av ruptura cordis". In fact the term "myocardial infarction" was first used in 1896 (1-2). At that time the diagnosis had to be based on autopsy and it was not until Willem Einthoven, in 1902, introduced the electrocardiogram (ECG) that myocardial infarction started to be recognised more frequently (3).

Cardiovascular disease is presently the most common cause of death in Sweden, amounting to 43,277 in the year 2000, which is about 50% of the total mortality (4). There has been a decline in mortality during the last 15 years, which in particular has been related to a decreasing mortality from ischemic heart disease. Still about one third of all deaths are caused by myocardial infarction (5).

There are several manifestations of acute coronary artery disease. The most common clinical presentations are an acute myocardial infarction (AMI), (which can be characterised as ST-elevation (previous Q-wave) or non-ST-elevation (previous non-Q-wave) myocardial infarction), unstable angina pectoris or sudden cardiac death. The recently introduced term acute coronary syndrome (ACS) covers myocardial infarction and unstable angina pectoris. The predominant cause is acute rupture of an atherosclerotic coronary plaque triggering thrombus formation. The subsequent development of the thrombus may make it sub-occlusive or completely occlusive, the background to various clinical manifestations of an acute coronary syndrome (6-7).

Age-adjusted in-hospital and long-term mortality after myocardial infarction has declined. As an example a Swedish hospital reported on a decrease of in-hospital mortality from 18 % in 1979 to 12 % in 1990 (8). Some explain this by a change in incidence (9) and others by improvements in coronary care (10). Mortality in connection to unstable coronary artery disease or non-Q-wave myocardial infarction has also decreased with an improvement in two-year mortality from 30% in 1988 to 19% in 1995, in a Swedish report (11). Established risk factors for unfavourable outcome after an acute myocardial infarction are high age, previous myocardial infarction (MI), heart failure and diabetes mellitus. Furthermore indicators of a large infarct size, anterior infarction, low blood pressure, pulmonary congestion and the extent of myocardial ischemia also carries negative prognostic information (12).

Risk factors for cardiovascular disease

There are several firmly established risk factors for cardiovascular disease such as family history, increasing age, smoking, high blood cholesterol, hypertension, overweight and physical inactivity (13). Independently of the presence or absence of other risk factors diabetes mellitus adds to the risk for cardiovascular morbidity and mortality by a factor of two to four (14-17). In fact blood glucose predicts increased cardiovascular morbidity and mortality even at levels below the threshold for established diabetes (18). Accordingly and for every level of the risk factors hypertension, high blood cholesterol and smoking, diabetic patients have higher risk for cardiovascular mortality compared to non-diabetic persons. This risk accumulates with increasing number of risk factors in a multiplicative way but the excess mortality in diabetes is not fully explained by an increasing number of risk factors (16). A Finnish case-control study reported that patients with type 2 diabetes but no prior myocardial infarctions have the same probability of death from coronary artery disease as non-diabetic persons with previous myocardial infarctions (19). A more recent Scottish case-control study on a different patient material, including only diet treated type 2 diabetes and persons who just experienced a myocardial infarction, could not confirm these data (20).

Diabetes Mellitus

Epidemiology

The two major types of diabetes, type 1 and type 2, have a prevalence in the Western society of about 3-5%. Type 2 diabetes, accounting for 80-90% of all cases, is by far the most common. The global prevalence of diabetes increases rapidly and in the next 25 years there is an expected increase of the prevalence from 4 to 5.5 %. This translates into a doubling of the number of people with diabetes mellitus from 150 to 300 million. The vast majority of this increase relates to type 2 diabetes. Attributed reasons are the ageing population combined with major lifestyle changes characterised by decreasing demands of physical activity and over consumption of food especially in the economies in transition (21).

Definition and diagnostic considerations

Diabetes mellitus is a metabolic disease, characterised by chronic hyperglycemia in association with microvascular damage of the kidneys, eyes and nerves (microvascular complications). These alterations, caused by defect insulin secretion and/or action, are specific for diabetes. The defect in insulin action does not only influence carbohydrate but also fat and protein metabolism.

The definition of diabetes has changed during the years. The National Diabetes Data Group (NDDG) published the first generally accepted classification of and diagnostic criteria for diabetes in 1979. They included the first definition of impaired glucose tolerance (22). In 1980 the WHO Expert Committee on Diabetes presented their definition (23). Slight modifications were introduced in 1985 to make them coincide more closely with the recommendations from the National Diabetes Data Group (24). The NDDG later modified their criteria to become identical with those from WHO. New knowledge warranted a subsequent re-examination of this issue and the American Diabetes Association (ADA) published their new recommendations in 1997 (25). Most recently new recommendations from WHO were issued in 1998 and finally in 1999 (26-27). The major change in the diagnostic criteria of diabetes mellitus is a lowering of the fasting blood glucose level above which diabetes mellitus is diagnosed (from 6.7 to 6.1 mmol/l). In contrast to WHO, ADA does not recommend the use of an Oral Glucose Tolerance test for diagnostic purpose.There are also new classifications of diabetes mellitus that are based on etiology instead of insulin requirement. Glucose levels for diabetes diagnosis is shown in Table 1. In the clinical setting, one test-result is enough if the patient have symptoms of

Table 1. Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia. From the WHO report in 1998 and 1999 (references 26-27).

	Glucose concentration (mmol/l (mg/dl))		
	Whole blood Venous	**Whole blood** Capillary	**Plasma** Venous
Diabetes Mellitus			
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
or			
2-hours post glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
or both			
Impaired Glucose Tolerance			
Fasting (if measured)	< 6.1 (< 110)	< 6.1 (< 110)	< 7.0 (< 126)
and			
2 hours post glucose load	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 7.8 (≥ 140) and < 11.1 (< 200)
Impaired Fasting Glycemia			
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
2 hours post glucose load, if measured	< 6.7 (<120)	< 7.8 (< 140)	< 7.8 (< 140)

hyperglycemia otherwise a new confirming analysis has to be obtained.
Determinations of concentrations of glucose depend on how the samples are taken and handled. The blood samples are often venous or capillary taken. Concentrations of glucose in plasma are about 11 % higher than whole blood glucose if the hematocrit is normal.

Classification

Type 1 and type 2 diabetes mellitus

Type 1 diabetes was previously named IDDM, insulin-dependent diabetes mellitus or juvenile onset diabetes. Type 2 diabetes was previously called NIDDM, non-insulin dependent diabetes mellitus or adult onset diabetes mellitus. Reasons for replacing IDDM and NIDDM to type 1 and type 2 respectively, was that type 1 diabetes can be seen at any age and that type 2 diabetes sometimes requires insulin treatment and has become more frequent among young persons.

Type 1 diabetes is a condition with an absolute insulin secretion deficiency due to autoimmune destruction of the pancreatic β-cells. It usually develops before adulthood but may also be seen among adults. It has a fast onset and administration of insulin is a prerequisite for survival. It is often possible to detect autoantibodies against islet cells (as GAD-antibodies against the enzyme glutamatic acid decarboxylase) or insulin. LADA, late autoimmune diabetes in adults, is a more slowly progressive form of type 1 diabetes that generally occurs in adults. In type 1 diabetes there is a strong genetic HLA association. The prevalence and incidence in the world varies and is among the highest in the Scandinavian countries.

Type 2 diabetes is characterised by a relative insulin deficiency caused by a diminished tissue response to insulin (insulin resistance) and/or insufficient insulin secretion. It is a slowly progressing disease in which compensatory high levels of insulin initially keeps the glucose levels normal. Type 2 diabetes becomes apparent when declining insulin secretion causes blood glucose to rise above the normal level. The disease often remains undiagnosed for several years since initial symptoms are none or mild. Thus type 2 diabetes is often preceded by several years of asymptomatic impaired glucose tolerance or postprandial hyperglycemia with normal fasting glucose levels, a condition which only can be discovered by an oral glucose tolerance test (OGTT). Diabetes specific complications and cardiovascular complications (macrovascular complications) do already start to develop during this period. This explains why the prevalence of cardiovascular disease has been reported as high as 40% at the time when the diagnosis of type 2 diabetes finally is established (28). There are probably several different mechanisms behind this disease and specific etiologies of type 2 diabetes is not known. A majority of these patients are obese or have increased abdominal fat and a positive family history for type 2 diabetes is frequent.

Impaired glucose tolerance

Impaired glucose tolerance (IGT) is a condition between normal glucose tolerance and diabetes mellitus and an OGTT is needed to establish this diagnosis. IGT is the strongest risk factor for future type 2 diabetes. The annual progression rate varies between 2-6% although rates >13 % has been described for instance in the Hoorn population. The rate is influenced by ethnicity, family history and age (29-32). IGT is even an independent risk factor for future cardiovascular morbidity and mortality (33-35). Glucose limits for the diagnosis of IGT are shown in Table 1.

Impaired fasting glucose

This condition was introduced by ADA in 1997 with the purpose to replace impaired glucose tolerance (25). The diagnosis impaired fasting glucose (IFG) does only need the recording of fasting blood glucose avoiding the inconvenience of OGTT. The term IGT has, however, not be abandoned in the WHO recommendations. IFG was instead grouped together with IGT into a new entity named impaired glucose regulation (27). IFG and IGT are probably different disease processes with different defects in insulin release and resistance. In similarity to IGT, IFG predicts future diabetes. The risk for future cardiovascular disease has not been shown to be as strong as for IGT and a definite association is not clearly established (35). The condition IFG is not yet introduced in the Swedish national guidelines for diabetes. Glucose limits for the diagnosis of IFG are shown in Table 1.

The metabolic syndrome

Type 2 diabetes is often part of the metabolic syndrome initially described by Reaven in 1988 under the name of syndrome X (36). This syndrome comprises a clustering of several cardiovascular risk factors including insulin resistance with or without diabetes or IGT, hypertension, (central) obesity, elevated levels of triglycerides and low HDL-cholesterol levels. An abnormal haemostatic function is often part of the syndrome and increases the propensity for thrombus formation. Alone each component conveys increased cardiovascular risk but as a combination they become much more powerful. The suggested WHO definition is (27): glucose intolerance or diabetes mellitus and/or insulin resistance together with two or more of the other components; 1. Impaired glucose regulation or diabetes. 2. Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below the lowest quartile of the background population). 3. Raised arterial pressure ≥ 140/90 mmHg. 4. Raised plasma triglycerides ≥ 1.7 mmol/l and/or low HDL-cholesterol< 0.9 mmol/l. 5. Central obesity (waist to hip ratio: males >0.90; females > 0.85) and /or a BMI >30 kg /m^2. 6. Microalbuminuria (urinary albumin excretion rate ≥ 20 μgram/l or albumin: creatinine ratio ≥ 30 mg/g).

Complications to diabetes mellitus

Microvascular

Diabetes mellitus is defined as a condition of chronic hyperglycemia that gives rise to typical microvascular complications only seen in this condition. These develop at levels of fasting glucose that are lower than originally believed explaining the development of new and more strict diagnostic criteria as described. The typical microvascular complications, retinopathy, nephropathy and neuropathy are only seen when blood glucose regularly exceeds a random or post-load value of 11 mmol/l or a fasting blood glucose of 6.1 mmol/l. Their development and progression are related to a poor metabolic control (25-27) and it is firmly established that intensive metabolic control reduces microvascular complications in patients both with type 1 (37-38) and type 2 (39-41) diabetes.

Macrovascular

Mortality in patients with diabetes mellitus has changed with the discovery of insulin from diabetic coma and, particularly for type 1 diabetes, microvascular complications to cardiovascular diseases, due to macrovascular complications. As much as 70% of the total mortality in diabetes mellitus has been reported to be of cardiovascular origin with coronary artery disease as the leading cause (17,42). Poor metabolic control is a major risk factor for future coronary heart disease in patients with type 2 diabetes (43-45) but whether intensive metabolic control may decrease cardiovascular morbidity and mortality has not been extensively studied although it has been shown in post myocardial infarction patients (46). An early study presented in 1970 and a pilot study from USA did not verify a mortality reduction following intensive insulin treatment (47-48). In contrast cardiovascular events decreased by 40% (p=0.08) in intense insulin treated patients with type 1 diabetes in the Diabetes Control and Complications Trial (37). Recently the UK Prospective Diabetes Study reported that intensive blood-glucose control in patients with type 2 diabetes by either oral antidiabetic drugs or insulin caused a substantial reduction of microvascular complications. Furthermore, there was a 16 % (p=0.052) reduction in myocardial infarctions (39). A recent systematic overview of intensive metabolic control in type 1 diabetes showed a significant reduction in macrovascular complications (49). Presently it may be concluded that accumulated evidence indicates, that improved metabolic care may reverse the impact of elevated blood glucose on cardiovascular mortality whether there is a causal relationship or not. An overview of interventions with intensive metabolic control on micro- and macrovascular complications is presented in Table 2 (37-41, 46-48, 50-54).

Monitoring metabolic control

During the past decades new monitoring techniques for blood glucose have improved patient management considerably. Until 1975 metabolic monitoring essentially was composed of determination of urine glucose and ketone bodies. Today self-monitoring of blood glucose is a cornerstone in the treatment of diabetes (55-56). Another major achievement is the intro-

Table 2. Overview of studies intervening with improved metabolic control in patients with type 1 and type 2 diabetes.

Study	Reference no	Diabetes type	Reduction in microvascular complication	Reduction in macrovascular complications	Numbers	Age (mean)	Follow-up years
Primary prevention							
UDPG, 1970	47	2	No	No Increased with tolbutamide	1023	53	8-13
Holman, 1983	51	1	Yes	X	74	42	2
Steno 1 type 1, (1985) 1991	52	1	Yes	X	34	34	8
Steno 2 type 1, (1986) 1991	52	1	Yes	X	36	18-50	5
Oslo, 1992	50	1	Yes	X	45	26	7
Stockholm study, 1993	38	1	Yes	X	102	31	7.5
DCCT, 1993	37	1	Yes 35-70% reduction	41% reduction p = 0.08	1441	27	6.5
Veteran affaires, pilot 1995	48	2	X	No	153	60	2.2
Kumamoto, 1995	40	2	Yes	X	110	50	6
UKPDS (33), 1998	39	2	Yes 25% reduction p = 0.0099	Myocardial infarction 16% reduction p = 0.052	3867	53	10
UKPDS (34), 1998 Metformin, obese	53	2	Yes		1704	53	10
Steno 2 type 2, 1999	41	2	Yes	X	160	55	3.8
Steno 2 type 2, 2003	54	2	Yes	Yes 53% reduction p = 0.008	160	55	7.8
Secondary prevention							
DIGAMI, 1995	46	1 and 2	X	Yes 29% reduction p = 0.027	620	68	1

X = Not reported

duction of glycosylated haemoglobin (HbA1c). HbA1c is a combination of haemoglobin and glucose, which slowly is formed by a non-enzymatic process. The rate of formation relates directly to the preceding blood glucose concentrations. Since erythrocytes are freely permeable to glucose the level of HbA1c mirrors the glycemic level during the previous 120 days, which is the lifetime of an erythrocyte. It is used in addition to day-to-day monitoring of blood glucose. HbA1c is the most validated marker of clinically important diabetic complications and the best expression of therapeutic efficacy (57). An advantages with HbA1c is the simplicity of sample handling. The disadvantages are a wide biologic variability and the use of different methods for the analysis. Thus methods used in the USA and in the DCCT and UKPDS studies results in approximately 1.1 % higher values than the commonly used Swedish techniques. This makes it somewhat difficult to compare results from major clinical trials and to implement them in Swedish practice. However, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) will develop a global standard for the measurement of HbA1c (58).

Diabetes mellitus and acute coronary syndromes

Prevalence and prognosis

The prevalence of known diabetes among persons with acute myocardial infarction and unstable angina pectoris varies between 10-24 % (59-

60, 65-68, 70, 72) and approximately 5 % have a previously undetected diabetes mellitus (73). Since the prevalence of diabetes mellitus in patients with myocardial infarction is high, and the prevalence of diabetes in the general population will increase rapidly over the nearest decades (21) management of the diabetic patients with acute coronary syndrome will have a substantial impact on future morbidity and mortality in patients with acute coronary syndromes and expenditures for health care.

Not only do patients with diabetes mellitus have an increased risk to develop cardiovascular disease, their prognosis is considerably worse than that of their non-diabetic counterparts if they get an acute coronary event (59-68). In the pre-thrombolytic era mortality was as high as 72% after five years of follow up (68) and their mortality has remained high even after the introduction of thrombolysis (64-67). Recent surveys and trials reveal that patients with diabetes mellitus have not benefited from improvements in coronary care to the same extent as patient without diabetes mellitus (69-71).

Treatment

Evidence based management of acute myocardial infarction combines pharmacological treatment with beta-blockers, aspirin, ACE-inhibitors and statins with reperfusion by means of thrombolysis or direct percutaneous interventions (PCI) (74-75). Since few trials specifically addressed diabetic patient populations, present knowledge on how to handle such patients is derived from retrospective subgroup analyses of various trials. These indicates that treatment benefits are comparable in diabetic and non-diabetic patients respectively (thrombolysis 76-77), (aspirin 78-79), (beta-blockers 80-83), (ACE-inhibitors 84-85), (statins 86-88). There are indications that treatment that may be effective in diabetic patients with myocardial infarction is withheld. Thrombolysis may be used as an example. Based on single case reports such therapy was discouraged due to worries for eye bleeding (89-90). However, the fear of eye-bleedings or cerebral haemorrhages has not been confirmed in a large-scale thrombolytic trial (91-92). Likewise, beta-blockade has been questioned due to concerns for deterioration of metabolic control and blunting of hypoglycaemic warning signs (93-94). Further analysis on the use of evidence-based treatment in diabetic patients is certainly of interest. The introduction of low molecular heparins (95) and early revascularisation (96-97) has considerably improved the care of patients with unstable coronary artery disease. There are indications that diabetic patients with multivessel-disease benefit from coronary artery by pass grafting (CABG) compared to percutaneuous coronary intervention (PCI) (98-99). PCI in diabetic patients is complicated by increased rate of restenosis and thrombosis compared to non-diabetic patients (100-102). The value of early revascularisation for handling diabetic patients has, however, not yet been specifically addressed.

Treatment modalities that may be of a particular value for diabetic patients with acute myocardial infarctions are those incorporating administration of insulin. Acute infusion of glucose-insulin-potassium (GIK) (103), glucose-insulin (46) or just insulin (104) has been tested in several settings with promising results. GIK treatment was initially proposed by Sodi-Pallares in 1963 as a tool to prevent ventricular tachyarrhythmias by promoting transportation of potassium into the myocardial cell (105). Later on it was used as an agent to provide myocardial metabolic support (103). A meta-analysis of nine trials comprising 1,932 patients, a majority non-diabetic, treated with GIK showed a 28% (OR 0.72; 95%CI: 0.57-0.90) reduction in hospital mortality (103). All these studies were, however, performed in the pre-thrombolytic era. An Argentinean pilot-study, using high-dose GIK infusion, indicated a beneficial effect in a subgroup of patients that concomitantly received reperfusion therapy (106). A recent study randomly assigning patients in need of intensive care to insulin-based tight glycemic control or to serve as controls had to be stopped prematurely due a dramatic decrease in mortality within the insulin group (104). The last three studies did, however, not especially address people with diabetes.

Reasons for the dismal prognosis

The most common specific mortality causes in person with diabetes mellitus after myocardial infarction are heart failure and fatal reinfarction (59, 65, 107-108). That is despite the lack of

evidence of more extensive infarctions among diabetic persons (59-60, 109).

Apart from withholding evidence based treatment as discussed above many factors may contribute to the unfavourable outcome such as a more severe and diffuse coronary artery disease, diabetic cardiomyopathy, disturbed autonomic balance and decreased fibrinolytic and platelet functions as extensively reviewed by Nesto and Jacoby (109). Other reasons are linked to the myocardial metabolism, which in diabetic patients is characterised by increased oxygen consuming free fatty acid utilisation, rather than glucose oxidation during periods of acute myocardial ischaemia (109).

As previously discussed impaired glucose control may operate in the long time run as well. In type 2 diabetes metabolic control measured as fasting blood glucose or HbA1c is a major risk factor of future coronary heart disease (43-45). Furthermore there is strong evidence that high blood glucose at admission is a powerful predictor for in hospital mortality following acute myocardial infarction both in patients with and in those without diabetes mellitus (110-113).

Hyperglycemia in acute myocardial infarction

It was Levine who in 1929 initially described elevated blood glucose during the acute phase of a myocardial infarction without any evidence for diabetes mellitus (114). Since then there has been a controversy on the meaning of carbohydrate intolerance seen in this setting as extensively reviewed by Opie and Stubbs in 1976 (115). Explanations varied from incipient diabetes, vascular degeneration of pancreas or precipitation of diabetes by the coronary event to a stress induced phenomenon (115-117). The possibility of incipient diabetes was first described by Goldberger (116) in 1945 and thereafter by Sowton (117) in 1962. Opie and Stubbs concluded that carbohydrate metabolism is temporarily disturbed in acute myocardial infarction and that the degree of hyperglycemia and failure to respond to insulin is related to the severity of the infarction. The probable explanation was considered to be stress induced secretion of catecholamines and glucagon (115). Subsequently the magnitude of the rise in plasma glucose was attributed to the degree of left ventricular failure (118) and raised concentrations of catecholamines and cortisol as a response to infarct extension and myocardial dysfunction (112).

The prevalence of diabetes and “borderline glucose tolerance” in patients with acute myocardial infarction has been addressed since long. Early work on this relation was hampered by the absence of a standardised glucose tolerance test and the lack of an exact definition of impaired glucose tolerance. The studies were small and the patient materials rather selected. The frequency of abnormal tests varied between 30-70% (115, 119). As already discussed the commonly used explanation to the findings was that it was an epi-phenomenon caused by transient stress. However, an admission blood glucose exceeding 10 mmol/l more likely indicates undiagnosed diabetes than just hyperglycemia provoked by the acute stress (120). Another study from 1975 showed that 80% of patients with fasting blood glucose above 6.7 mmol/l during the first 24 hours after an acute myocardial infarction had an abnormal glucose tolerance test several years thereafter (121).

In 1966 Walhberg, by applying intravenous glucose tolerance tests (IVGT), reported that approximately 60% of survivors of a myocardial infarction had abnormal IVGT tests and that an abnormal outcome was linked to an unfavourable long-term prognosis (119). These IVGT results were confirmed 1970 by Paasikivi (122) reporting that 29 % of patients with myocardial infarcts were diabetics while 28% had borderline test results. Paasikivi performed a placebo-controlled study with tolbutamid in survivors of an myocardial infarct. Although this treatment did not reduce total mortality it prolonged survival time and improved glucose tolerance (122). When the University Group Diabetes Program, UGDP-study in 1970 indicated harmful effects when tolbutamide and phenformin were used to reduce micro- and macrovascular complications in type 2 diabetes (47), the concept with improved glucose tolerance and control following myocardial infarction was not further tested until the DIGAMI-trial in 1995 (46). The exception is the GIK- trials, which, however, as already described focused on metabolic support during the acute event of an acute myocardial infarction.

There is a relationship between admission hyperglycemia and hospital mortality after myocardial infarction among patients with (110-111) as well as without previously established diabetes (112-113). This observation was recently confirmed in a systematic overview (123). The relation to long-term mortality is less well explored.

Glucose as a risk factor in non-diabetic persons

Summarising 15 longitudinal studies on asymptomatic hyperglycemia and coronary heart disease an international collaborative group in 1979 concluded that there was no consistent association between elevated glucose levels and future cardiovascular disease in non-diabetic persons (124). Subsequently results from some of these studies, including longer periods of follow-up, actually revealed a relationship between asymptomatic hyperglycemia and cardiovascular disease. In fact there are several longitudinal cohort studies indicating that mortality from cardiovascular disease is increased in patients with impaired glucose tolerance (33-35). This relation has been characterised as a threshold effect in some (15, 125-126) and a continuous, graded relationship in other studies (127-128). For example the recent 23-year follow up of the Paris Prospective study showed a progressive curvilinear relation with increasing glucose levels and future mortality still evident after adjusting for conventional risk factors (129). A curvilinear relationship was also apparent in a systematic overview quantifying the relationship between blood glucose and coronary artery disease starting at levels well below the present threshold for diabetes mellitus (18). This relation got further support from a recent Norwegian study verifying that increasing fasting blood glucose between 4.7 - 6.1 mmol/l could be related to future cardiovascular mortality following adjustments for other risk factors (130). A continuous relationship between increasing blood glucose and future cardiovascular risk has also been established for HbA1c (131).

In summary, not only persons with diabetes but also those with prediabetic conditions are at high risk for future cardiovascular morbidity and mortality. The true prevalence of diabetes among patients with acute myocardial infarction is not known but it may be assumed that it is higher than commonly believed. Elevated admission blood glucose is frequent but the exact reasons for and long-term prognostic impact of this finding needs to be further explored. Improved knowledge is also highly demanded as regards possibilities for the early detection of patients at risk due to undetected glucose abnormalities. This may open a possibility to introduce new preventive measures directed towards the metabolic aberration.

Aims of the Study

1. To study the effect of hyperglycemia and impact of metabolic control on long-term mortality in patients with acute myocardial infarction and diabetes mellitus.

2. To investigate the relationship between admission plasma glucose and long-term prognosis in patients with acute myocardial infarction without previously known diabetes mellitus.

3. To investigate the actual prevalence of glucose abnormalities in patients with acute myocardial infarction without previously diagnosed diabetes mellitus.

4. To investigate the actual prognosis and the use of evidence based treatment and its effect on prognosis in patients with diabetes mellitus and acute myocardial infarction.

5. To investigate the influence of an early invasive management strategy in diabetic patients with unstable coronary artery disease.

MATERIAL AND METHODS

Definitions

Acute coronary syndrome and myocardial infarction

Acute coronary syndrome is an entity describing an acute coronary event of either ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or unstable angina pectoris. In study V the term unstable coronary artery disease is used for the combination of unstable angina or non-ST-elevation myocardial infarction. The difference between these two conditions is that elevated levels of biochemical markers of myocardial injury are present only in non- ST-elevation myocardial infarction.

During the last years there has been a change in the definition of myocardial infarction. This relates to the introduction of more sensitive and specific methods to detect myocardial damage. Thus, there are different definitions of myocardial infarction in this thesis.

In study I and II the definition was based on WHO criteria from 1979 (132).
At least two of the following criteria had to be fulfilled.
1. Chest-pain lasting more than 15 minutes.
2. At least two serum enzyme values above the upper normal limit. Serum creatine kinase (S-CK) combined with serum creatine kinase isoenzyme B (S-CKB) 10-16 hours after the onset of symptoms or serum lactic dehydrogenase (S-LD), with a LD-isoenzyme pattern typical of myocardial infarction, 48-72 hours after onset of symptoms.
3. Development of new Q-waves in two or more standard ECG leads.

The diagnosis of possible AMI (study I) was used if typical chest pain was accompanied by only 1 S-CK or S-LD value above the normal range and/or new Q-waves in one ECG lead only. A reinfarction (study I and II) was defined as a new AMI (>72 hours after the index infarction).

Study III used the diagnostic criteria jointly recommended by the European Society of Cardiology and the American College of Cardiology (133-134). Acute myocardial infarction was diagnosed if two serum troponin T were >0.05 μg/l or CK-MB was >10 μg/l together with either typical symptoms or development of new Q-waves in at least two of twelve standard ECG-leads.

In study IV the criteria for the diagnosis of AMI were based on the World Health Organisation criteria from 1994 (135) with the double upper level of normal of an appropriate biochemical marker (mainly CK-MB) as the biochemical criterion. ECG was evaluated concerning the presence or development of Q-wave, ST-changes, T-wave inversions or bundle branch block. The main biochemical markers were CK-MB >100% above the hospitals reference level, total CK >3.3 μkat/l for men and >2.5 μkat/l for women and CK-B >0.2 μkat/l. During the years 1995-1998 mainly CK-MB mass ≥10 μg/l and Troponin T ≥ 0.1 μg/l were the discrimination limits for AMI.

In study V myocardial infarction was based on the presence of two of the conventional three criteria, i.e. typical chest pain, diagnostic ECG recording (mainly new Q-wave) or elevation of biochemical markers of myocardial damage. The decision levels for biochemical markers were i) CK-MB-mass above the decision level of the local hospital for myocardial infarction at one measurement or ii) catalytic activity of CK, CK-B, or CK-MB above the local decision level at two subsequent determinations or iii) above the double local decision level at one measurement. Myocardial infarction in relation to PCI was defined by i) CK-MB-mass 1.5 times above the local decision level for myocardial infarction at one measurement or ii) catalytic activity of CK, CK-B or CK-MB at one measurement three times above or iii) at two occasions 1.5 times above the local decision level. Only new Q-waves were used for the diagnosis of myocardial infarction in association with CABG.

Diabetes mellitus

Since the criteria of diabetes mellitus have changed over the years (see introduction) the five studies in this thesis have used different definitions.

Study I, II, IV and V used the definitions from 1979 (22). Diabetes was defined as previously known diabetes mellitus or prescription of anti-diabetic treatment (diet, oral drugs or insulin). In study I diabetes was also considered present if admission blood glucose >11 mmol/l in patients without previously known diabetes.

In study III diabetes mellitus and impaired glucose tolerance were defined according to the World Health Organization from 1999 (27) (shown in Table 1). Thus, patients were classified as having diabetes mellitus if fasting blood glucose (FBG) exceeded 6.0 mmol/l and/or the two-hours post load blood glucose (2-h BG) exceeded 11.0 mmol/l. Impaired glucose tolerance was defined as fasting blood glucose <6.1 mmol/l and 2-h BG ≥ 7.8 mmol/l - ≤11.0 mmol/l. Normal glucose tolerance was defined as FBG <6.1 mmol/l and 2-h BG <7.8 mmol/l.

Glucose abnormalities

The term glucose abnormalities is used in this thesis and considered as either diabetes (27) and/or impaired glucose tolerance (27) (see table 1).

Patients and study protocols

Study I to V consist of five different study populations recruited during different time periods between the years 1990 to 2000. An overview of the patient materials is given in Table 3.

Study I

Patients

Between January 1990 and December 1993 patients admitted to the CCUs of 19 Swedish hospitals were considered for the randomised trial of insulin-glucose infusion followed by subcutaneous insulin in diabetic patients with acute myocardial infarction (DIGAMI). Details on the study design and main results have been published elsewhere (46). Patients admitted due to suspect acute myocardial infarction within the preceding 24 hours were recruited if they had a previously known diabetes mellitus and blood glucose > 11 mmol/l or a blood glucose >11 mmol/l even without known diabetes mellitus. Exclusion criteria were: refusal to participation, inability due to serious concomitant disease, residence outside the catchment area, enrolment in other studies and previous enrolment in DIGAMI. Patient selection and details on the excluded patients is outlined in Figure 1. In all 1,240 patients fulfilled the inclusion criteria. Half of them were excluded, mostly because of

Table 3. Overview of essential details regarding studies I –V. Figures on non-diabetic versus diabetic patients are shown for studies IV and V.

					Previously known diseases %			
Study number	**Recruitment period**	**Study design**	**Patients no**	**Age years**	**Diabetes**	**MI**	**HT**	**Heart failure**
I								
DIGAMI	1990-1993	Prospective, randomised, controlled	620	68	87	38	48	22
II								
PIGAMI	1995	Retrospective with prospective follow up	197	68	0	18	24	15
III								
GAMI	1998-2000	Prospective	181	64	0	20	31	8
IV								
RIKS-HIA	1995-1998	Prospective register study	25 633	68 vs. 70	20	21 vs. 33	29 vs. 46	Not known
V								
FRISC II	1996-1998	Prospective, randomised, controlled	2 457	64 vs. 66	12	21 vs. 30	28 vs. 49	3 vs. 6

HT = Hypertension; MI = Myocardial infarction

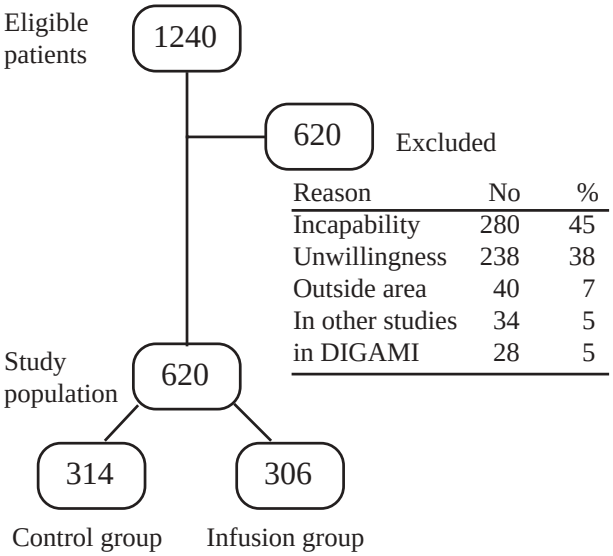

Fig 1. Patient selection in the DIGAMI study. Study I.

inability or unwillingness to participate, leaving 620 patients for randomisation, 314 to the control and 306 to the intensive insulin group respectively.

Protocol

This study was a multicenter randomised controlled study designed as shown in Figure 2. The randomised treatment was acute glucose-infusion for 24 hours followed by subcutaneous multidose insulin treatment for at least three months. The insulin-glucose protocol is presented in the appendix. Details on stratification and concomitant therapy have previously been described (46). The patients were seen at three and 12 months after randomisation. Information on the vital status of all patients on July 31, 1995 was obtained from each of the locally responsible investigators.

The primary endpoint in the main study was mortality after three months with mortality after one year as a secondary endpoint. The objectives in study I was to investigate long-term mortality after a mean follow-up time of 3.4 years (range 1.6-5.6).

Study II

Patients

Case records from all patients (n=300) admitted to the coronary care unit at the Karolinska Hospital during 1995 with the diagnosis acute myocardial infarction (International Classification of Diseases codes 410A, 410B, 410X) were reviewed. Patients with known diabetes mellitus, a second admission in 1995 and without an available plasma glucose recording at admission were excluded leaving 197 patients as the final study population (Figure 3).

Protocol

The design of study II was a prospective follow of the 197 retrospectively collected consecutive non-diabetic patients with acute myocardial infarction. Follow up lasted until June 1, 1997 thereby ranging from 1.5-2.5 years. Data was collected in two steps: 1) a retrospective review of hospital records, 2) a prospective telephone interview with all survivors. Information on hospitalisation for congestive heart failure, angina pectoris, nonfatal reinfarction, PCI and CABG were collected from hospital files. Information on mortality and causes of death was obtained from the official Swedish national death

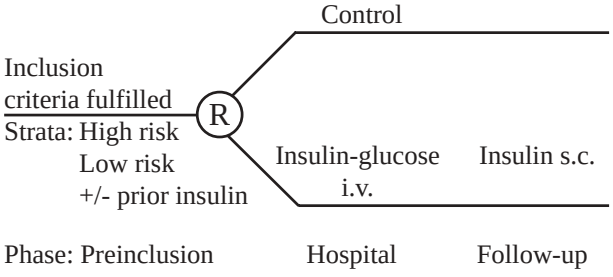

Fig 2. Schematic presentation of the DIGAMI study protocol. Study I.

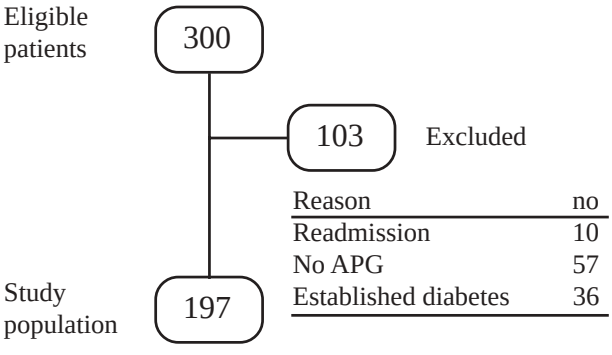

Fig 3. Patient selection in the PIGAMI study. Study II. APG = Admission plasma glucose.

certificates. For completeness of information death certificates were checked against available hospital records.

The primary endpoints were mortality, non-fatal reinfarction (>72 hours after the index infarct) and hospitalisation due to severe congestive heart failure. The presence of any of these events was used as a composite endpoint.

Study III

Patients

This study enrolled patients admitted to the coronary care units at the Karolinska and Västerås hospitals for acute myocardial infarction between November 1, 1998 and December 15, 2000. Eligible for inclusion were patients free from previously known diabetes and with a baseline capillary blood glucose <11.1 mmol/l. Patients older than 80 years and with a serum creatinine≥200 μmol/l were excluded as was those living outside the catchment area. The final study population consisted of 181 non-diabetic patients with acute myocardial infarction.

Protocol

This study was a prospective study including consecutive patients admitted to the coronary care units of Västerås and Karolinska hospitals. Blood glucose was analysed as soon as possible after hospital admission. During the hospital phase HbA1c was measured on the first morning following admission and capillary fasting blood glucose (FBG) daily until the day of hospital discharge. A standardised oral glucose tolerance test (OGTT) with 75 g of glucose in 200 ml of water was performed on day 4 or 5 prior to hospital discharge. HbA1c, fasting blood glucose and a new OGTT were obtained three months thereafter. The primary endpoint in this study was glucometabolic state during hospitalisation for an acute myocardial infarction and three months thereafter.

Study IV

Patients

The patient material in study IV was recruited from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA), described more in detail by Stenestrand (136). The register comprises all patients admitted to the coronary care units of participating hospitals. This number increased from 19 hospitals 1995 to 32 in 1996, 46 in 1997 and 58 in 1998. Data for study IV, which were collected 1995-1998, comprised 137,262 admissions at 58 CCU:s. Because of an increased risk of concomitant disease among elderly, patients >80 years were excluded. The final patient material consisted of 25,633 patients with a first acute myocardial infarction, out of whom 5,193 had a known diabetes mellitus.

Protocol

In RIKS-HIA information of clinical relevance for the care of patients with AMI is reported on special case record forms that include 100 easily obtained variables. Information on the performance on coronary procedures before and after hospital admission was obtained by matching patient data with the National Registers on coronary angiography, PCI and CABG. One-year mortality was obtained by merging the RIKS-HIA database with the National Cause of Death Register covering the vital status of all Swedish citizens for the years 1995 to 1999.

The primary end point in study IV was mortality while the use of established management routines including evidence based pharmacological treatment served as secondary endpoints.

Study V

Patients

The patient population in study V is based on FRISC II (Fragmin and Fast Revascularisation during InStability in Coronary artery disease) (137). This study recruited patients between June 17, 1996 and May 7, 1998, in 58 Scandinavian hospitals out of whom 6 of were interventional centres. Patients were eligible for inclusion if they had increasing symptoms of anginal chest pain or symptoms at rest warranting the suspicion of acute myocardial infarction since <48 hours. Myocardial ischemia had to be verified by ECG (ST-depression ≥ 0.1 mV or T-wave inversion ≥ 0.1 mV), or by elevation of biochemical markers. The exclusion criteria included raised risk of bleeding or anaemia, indication for or administered thrombolysis within the last 24 hours, angioplasty within the last six months or other severe diseases or anticipated problems of co-operation. Patients

with previous open-heart surgery, advanced age (>75 years) or other conditions that, according the physician in charge, made randomisation to revascularisation inappropriate were not eligible for randomisation and accordingly excluded from the trial. In all 2,457 patients were enrolled of which 299 (12%) had diabetes mellitus.

Protocol

The FRISC II trial consisted of two different studies including one pharmacological and one interventional part (137-138). Patients were randomised into a two by two- factorial design to an early non-invasive or invasive strategy and to three months of treatment with subcutaneous dalteparin or placebo. The 1,032 patients in the pharmacological part who were not randomised in the FRISC II invasive study were not included in study V.

The FRISC II invasive study compared a primarily non-invasive with an early invasive strategy in patients with unstable coronary artery diseases in a prospective open randomised controlled trial design. The direct invasive strategy required coronary angiography within a few days of enrolment, aiming for revascularisation within seven days from the start of open-label dalteparin or standard heparin. Revascularisation was recommended in all patients with ≥70% diameter obstruction in any artery supplying a significant proportion of the myocardium. Percutaneous coronary intervention (PCI) was recommended if there were one or two target lesions, while coronary artery bypass grafting (CABG) was to be preferred in patients with three-vessel or left main disease. The final decision on PCI or CABG were left to the discretion of the physician in charge.

The comparison of the invasive and non-invasive strategies was open and that of prolonged dalteparin treatment versus placebo double blind. Follow-up was performed in hospital, by telephone after two weeks, by outpatient visits after six weeks and three and six months and by telephone contacts after 12 months. The primary endpoint in this study was a composite endpoint of death or myocardial infarction after one year. Study V analysed the characteristics and outcome comparing diabetic with non-diabetic patients.

Laboratory procedures

Blood and plasma glucose

Glucose concentrations were in Study I obtained as venous blood glucose, in study II as venous plasma glucose and in study III as capillary blood glucose. Concentrations of glucose in plasma is about 11% higher than in whole blood (139). In study I the blood samples were analysed at the coronary care units by means of a reflectance meter (Reflolux II®, Boehringer Mannheim Scandinavia AB). Admission plasma glucose was analysed immediately via a commercially available colorimetric glucose oxidase method (Ektachem Clinical Chemistry Slide, Johnson & Johnson, Rochester, NY) at the departments of clinical chemistry of the hospital in study II. In study III blood glucose was analysed in capillary whole blood with HemoCue® (HemoCue® AB, Ängelholm, Sweden), which measures the total concentration of blood glucose independent on hematocrit. The coefficient of variation (CV) for HemoCue® is ≤ 3.5%.

Oral Glucose Tolerance Test

A standardised OGTT (22) with 75 g of glucose dissolved in 200 ml H_2O was administered after 12 hours overnight fast including restriction of smoking and physical activity. Glucose in capillary whole blood was analysed bedside by means of the HemoCue® procedure (as described above) before and after one and two hours following the ingestion of glucose.

HbA1c

In study I HbA1c was analysed locally using the standard method of the respective hospital.

The HbA1c specimens in study III were analysed at a core laboratory (Department of Laboratory Medicine, Malmö Allmänna Sjukhus, Sweden) by a high-performance liquid chromatographic technique (the Mono S method) on capillary blood applied on filter paper attached to a request card: HbA1c Via Post (Roche Diagnostics Scandinavian AB) (140).The upper normal limit of this method is 5.3% with a CV of <3% (140). The methods used for HbA1c analysis in the DCCT and UKPDS studies are approximately 1.1% higher compared to this method used in Sweden (141).

Troponin T

A third generation of Troponin T assays, with the lower limit of detection of 0.01μg/l, was used in study V (Elecsys, Roche Diagnostics). The upper reference level of healthy individuals is 0.01 μg/l. At this level the CV is high. The cut-off level was put at 0.03 μg/l to have a high sensitivity and a CV < 20%.

Statistical methods

In study I and V the statistical calculations were based on intention-to-treat analysis. Standard statistical methods were applied. Values are presented as mean ± standard deviations (SD) and/or 95% confidence intervals (CI). Analysis was performed using the Student's paired t-test (two-tailed), Wilcoxcon´s test, Fisher's exact test and the Chi-Square test. In study III analysis of variance or Chi-Square tests were used to assess differences between the three groups diabetes, impaired glucose tolerance and normal glucose tolerance. The Cox proportional hazard regression model was used to evaluate univariate relative risks and their CI in study I, IV and V. Graphs of the Kaplan-Meier estimate of the survival function were used in study I, II and V. Multivariate statistics was used in study I, II, IV and V according to the Cox proportional hazard regression model and a multiple logistic regression analysis was applied in study III, as well as in study IV and V. Receiver operator characteristic curves(ROC-curve) were constructed in study III with the relation between sensitivity of different cut-offs on the y-axis (true positive rate) and 1-specificity for the same cut-offs on the x-axis (false positive rate) (142). A two-tailed p-value <0.05 was accepted as statistically significant.

Ethical considerations

Study I, III and V were approved by the Ethics Committees in participating University Regions. Study II was approved by the Ethics Committee at Karolinska Hospital. The National Board of Health and Welfare and the Swedish Data Inspection Board had approved study IV. All patients in studies I, II, III and V (in study II also relatives) had given their informed consent to study participation. The patients in study IV had given their consent to be included in the RIKS-HIA database.

RESULTS

Admission hyperglycemia and metabolic control in relation to long-term outcome after myocardial infarction in diabetic patients (Study I)

Mortality

The long-term mortality is shown in Figure 4A (all patients) and in Figure 4B (stratum I, low cardiovascular risk and no previous insulin treatment). The mean follow-up time was 3.4 years (1.6-5.6). During long-term follow-up there were 240 deaths (39%), 138 (44%) in the control group and 102 (33 %) in the insulin group. The relative mortality reduction was 28% (95 % CI: 8 to 45%; p=0.011). The most apparent mortality reduction was seen in stratum 1 (patients without previous insulin and at low cardiovascular risk). The absolute mortality reduction in this group was 15%, from 44 (33%) among controls to 24 (18%) in the insulin group, which corresponds to a relative mortality reduction of 51% (95%CI: 19 to 70%; p=0.004).

Risk factors

Of glucometabolic state, presence of heart failure and treatment at during the hospital phase, the most powerful univariate predictors for an unfavourable outcome were high blood glucose at admission and onset of heart failure during the hospital phase. A high level of HbA1c at admission predicted long-term mortality in control patients but not in those given intensive insulin treatment. Looking at long-term mortality in different admission blood glucose tertiles there was a significant trend for increased mortality with increasing blood glucose levels (log-rank for trend p <0.001) among the control patients, a trend that was eliminated in the insulin group (Figure 5).

Independent predictors for long-term mortality (Figure 6) were old age, previous heart failure, diabetes duration, admission blood glucose and HbA1c at admission (borderline significant) while previous AMI, hypertension, smoking habits and gender did not add independent predictive value. Blood glucose and HbA1c at admission predicted long-term mortality in control patients, however, not in those given intensive insulin treatment.

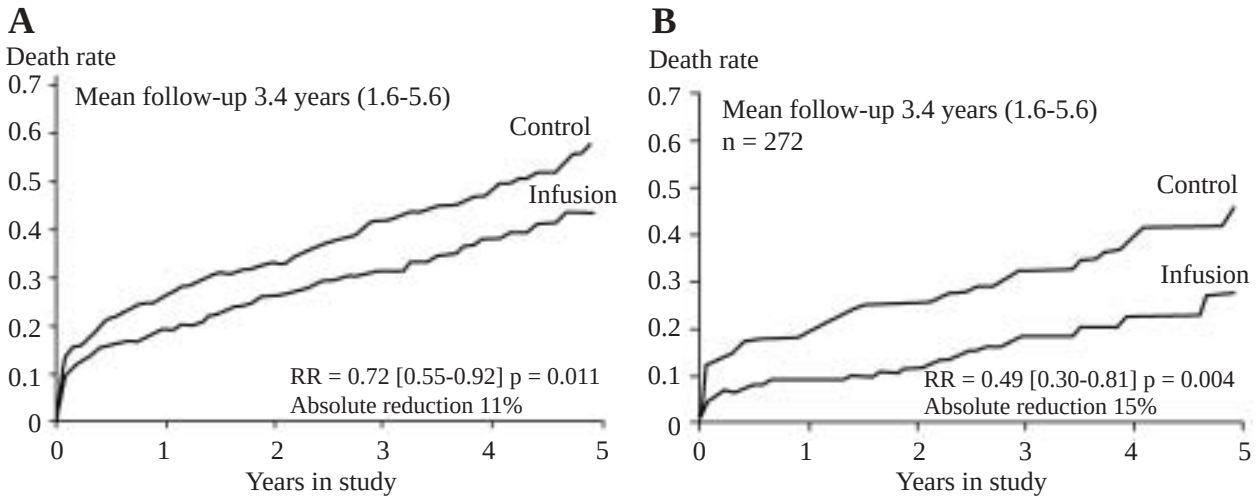

Fig 4 A+B. Study I. Kaplan-Meier curves for patients in the intense and in the control group. A: Long-term mortality among all patients. B: Long-term mortality in strata I.

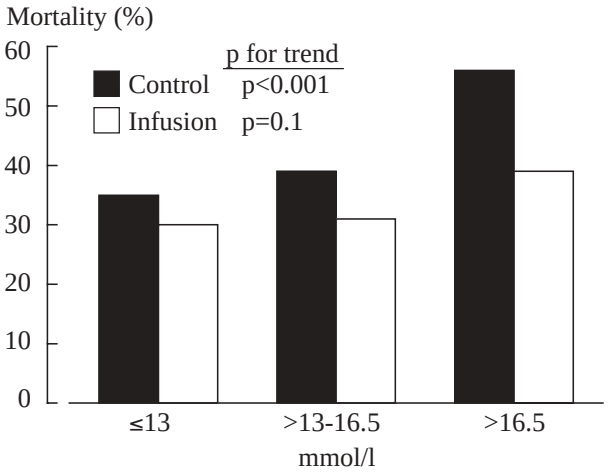

Fig 5. Long-term mortality by admission blood glucose tertiles within 2 treatment groups. Study I.

Admission hyperglycemia and long-term outcome after myocardial infarction in patients without diabetes (Study II)

Clinical data

Pertinent clinical characteristics of the 197 patients at the time of hospital admission are outlined in Table 3. The follow-up time was 1.5-2.5 years. The average time of follow-up was 1.5-2.5.

Morbidity and mortality

A total of 60 (30%) of the patients died, 30 during the initial hospitalisation and 30 during the remaining period of follow up. The causes for death were cardiovascular in all but two patients, in whom the specific cause remained unknown. Of the other end-points 20 patients developed congestive heart failure, 12 had a non-fatal reinfarction. The composite endpoint of at least one major cardiovascular event was reached by 79 of the patients.

Risk factors

Patients who died were characterised by high age, more frequent previous ischemic heart disease and congestive heart failure while smoking was less frequent than among those who survived. Admission plasma glucose was significantly higher in patients with any of the endpoints. The Kaplan-Meyer survival analysis revealed that patients with admission plasma glucose above the median level (7.4 mmol/l) had a significantly worse prognosis as regards mortality and the composite endpoint (Figure 7A + 7B). In the multivariate analysis (Figure 8) the only remaining predictors for mortality were high age and previously known congestive heart failure while admission plasma glucose was of borderline significance (relative risk 1.2; p=0.097). The only independent predictor for reinfarction was admission plasma glucose. Age together with admission plasma glucose predicted future congestive heart failure. Admission plasma glucose (p=0.0042), age (p=0.036) and previous congestive heart failure (p=0.0025) remained as the independent predictors of the composite cardiovascular endpoint.

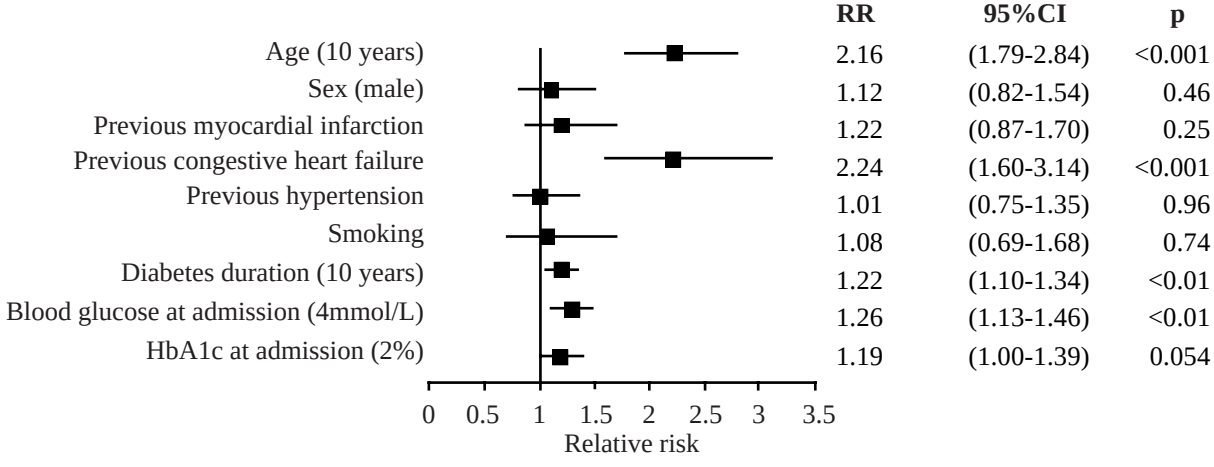

Fig 6. Independent predictors at baseline for long-term mortality. Study I.

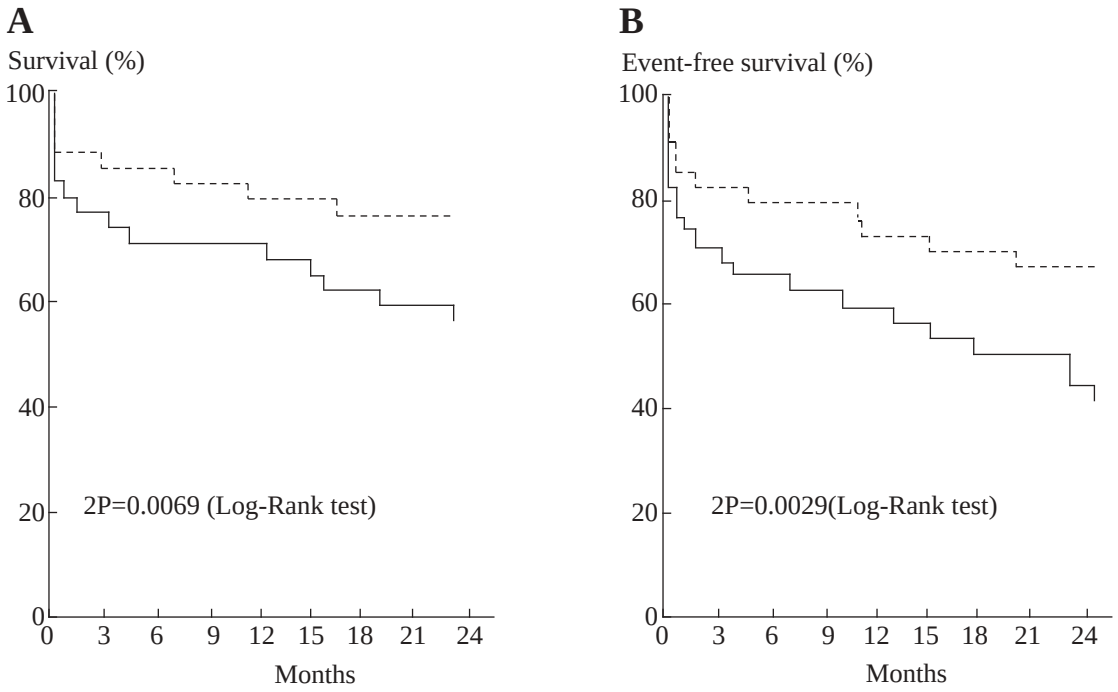

Fig 7 A + B. Kaplan-Meier curves for patients above and below the median admission plasma glucose level (7.4 mmol/l). Dashed lines indicates plasma glucose less than or equal to median. **A**: Time to fatal outcome, **B**: Time to major cardiovascular event. Study II.

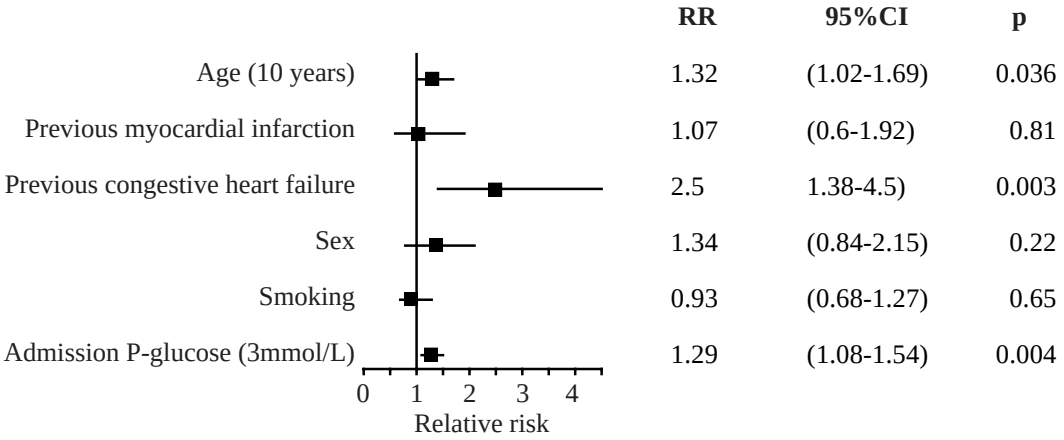

Fig 8. Independent predictors for cardiovascular event. Study II.

Previously unknown diabetes and impaired glucose tolerance in patients with acute myocardial infarction (Study III)

Clinical data

A total of 181 patients were included with a mean age of 63.5 ± 9.4 years (range 41-79) and out of whom 68% were males. An OGTT before hospital discharge was obtained in 164 and after three months in 144 of the patients respectively. The main reasons for not obtaining an OGTT after three months were death (n=6), concomitant diseases (n=17) and unwillingness (n=14). Patient characteristics including treatment are presented in Table 4. Characteristics in patients who could not perform OGTT at 3 months is shown in Table 5.

Table 4. Baseline characteristics of all individuals enrolled. Study III.

	Patients (n=181)
Age (mean (SD) (years)	63.5 (9.4)
Sex	
Men	123 (68%)
Women	58 (32%)
Previous disorders	
Myocardial infarction	36 (20%)
Angina pectoris	60 (33%)
Heart failure	14 (8%)
Hypertension	57 (31%)
Current smoker	
Yes	61 (34%)
No	120 (66%)
Hyperlipidemia (treated)	27 (15%)
Body Mass Index (mean, SD) (kg/m2)	26.6 (4.1)
HbA1c at admission (mean, SD) (%)	5.0 (0.6)
Blood glucose at admission (mean, SD) (mmol/l)	6.5 (1.4)
Treatment during the hospital stay and at discharge	
Thrombolysis	68 (38%)
Primary PCI	9 (5%)
Aspirin	160 (93%)
Beta-blocker	158 (92%)
ACE-inhibitors	25 (14%)
Lipid lowering agents	114 (66%)

Data are number (%) unless otherwise indicated**.**

Table 5. Baseline characteristics in patients with no glucose tolerance test at 3 months. Study III.

Baseline variables	**Not performed OGTT** (n=37)
Age (years)	64.6 ± 10
Male (%)	58
Previous MI	25%
Previous heart failure	11%
Previous HT	28%
Weight (kg)	76.5 ±14
HbA1c (%)	4.9 ± 0.5
Admission blood glucose (mmol/l)	6.5 ± 1.1
Fasting blood glucose day 4 (mmol/l)	5.57 ±1.2

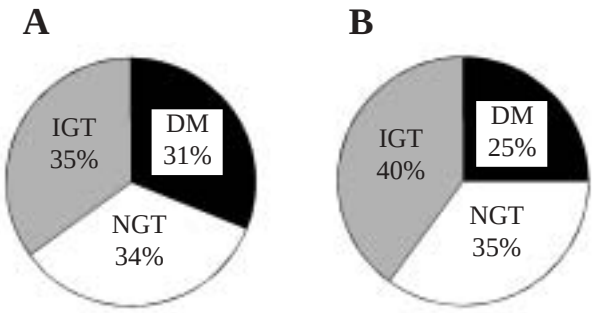

Fig 9. Proportions of patients with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM). **A**: at discharge, **B**: after 3 months. Study III.

Glucose tolerance

At discharge 66% of the patients had abnormal glucose tolerance and the corresponding proportion after 3 months was 65 % (Figure 9A +9B). In all 35% and 40% had IGT at discharge and after 3 months respectively. The corresponding proportions for newly detected diabetes were 31% and 25 %. If, as suggested by ADA 1997 (25), only fasting blood glucose had been applied to explore the glucometabolic state only 10% and 13 % of the total population would have had newly detected DM at discharge and at follow-up respectively. The pharmacological treatment in the different glucometabolic categories is shown Table 6 and Table 7.

Predictors of impaired glucose tolerance and diabetes at three months.

The multiple logistic regression analysis is adjusted for baseline dissimilarities, gender, age and smoking habits. Independent predictors of newly detected diabetes after three months were BMI (p=0.042) and HbA1c (p=0.031) at admission. When fasting blood glucose on day four was entered in the analysis this parameter (p= 0.002) was the only remaining independent predictor of diabetes. The only independent predictor of abnormal glucose tolerance (either IGT or DM) at three months was HbA1c (p=0.016). When fasting blood glucose on day four was included in the model both HbA1c (p=0.024) and fasting blood glucose (p=0.044) remained as independent predictors of abnormal glucose tolerance (Table 8).

Table 6. Medication at discharge in different groups of gluco-metabolic categories according to OGTT prior to hospital discharge Study III.

Medication at discharge	NGT at discharge	IGT at discharge	DM at discharge	p-value
Beta-blocker	93%	93%	90%	NS
Aspirin	95%	96%	88%	NS
ACE-inhibitor	16%	12%	18%	NS
Thiazides	6%	3.5%	7.8%	NS
Loop diuretics (furosemide)	9%	16%	31%	0.01
Steroides	1.8%	3.5%	2%	NS

Table 7. Medication at 3 months in different groups of glucose metabolism categories at OGTT at 3 months Study III.

Medication at 3 months	NGT at 3 months	IGT at 3 months	DM at 3 months	p-value
Beta-blocker	90%	93%	94%	NS
Aspirin	88%	91%	97%	NS
ACE-inhibitor	29%	34%	42%	NS
Diuretics	20%	26%	25%	NS
Antidiabetic drug	0%	0%	0%	NS
Diet	0%	0%	5%	0.06

Table 8. Multiple logistic regression analysis of independent predictors of diabetes mellitus and abnormal glucose tolerance at oral glucose tolerance test 3 months after discharge. Study III.

	Diabetes mellitus		Impaired glucose tolerance and diabetes mellitus	
Parameter	Odds ratio (95% CI)	p-value	Odds ratio (95%CI)	p-value
FBG day 4	2.97 (1.55-6.4)	0.002	1.90 (1.05-3.69)	0.044
HbA1c	1.73 (0.72-4.31)	0.220	2.58 (1.17-6.09)	0.024

Univariate risk factors with p-values <0.2 were considered in the model, including body-mass index, hypertension and fasting blood glucose (FBG) at day 4 and HbA1c. Odds ratios are given for increase of 1 mmol/l in blood glucose and 1% in HbA1c.

Prevalence, prognosis and evidenced based treatment in diabetic patients with acute myocardial infarction (Study IV)

Clinical data and mortality

A total of 5,193 of the 25,633 patients (20.3%) had a previously known diabetes. Diabetic patients were older (70 vs. 68 years), more often females (36 vs. 28%) and had more often a history of ischemic heart disease (33 vs. 21%). At admission the diabetic group were more often on treatment with aspirin, beta-blocker, ACE-inhibitors and statins.

One year mortality was higher in the diabetic group compared to those without this disease. The mortality rate among male patients without diabetes was 13.0 % compared to 22.3 % in those with diabetes (OR 1.92, 95% CI: 1.74-2.11; p<0.001) and among women the corresponding figures were 14.4 % and 26.1% (OR 2.10, 95% CI: 1.85-2.38; p<0.001). Survival curves are shown in Figure 10. The adjusted relative risk for mortality among diabetic patients during the first year of follow-up was 1.48 (95% CI:1.30-1.60; p<0.001) compared to patients without diabetes. The one-year mortality and OR in three different age groups are shown in Figure 11.

Evidence based treatment

After multiple adjustments for dissimilarities in baseline characteristics between the two groups patients with diabetes were significantly less likely to be treated with reperfusion therapy, heparins, statins or to be revascularised within 14 days from hospital discharge (Figure 12). As outlined in Figure 13 the mortality reducing effects of evidence-based treatment like reperfusion, heparins, aspirin, beta-blocker, lipid-lowering treatment and revascularisation were similar in diabetic and non-diabetic patients.

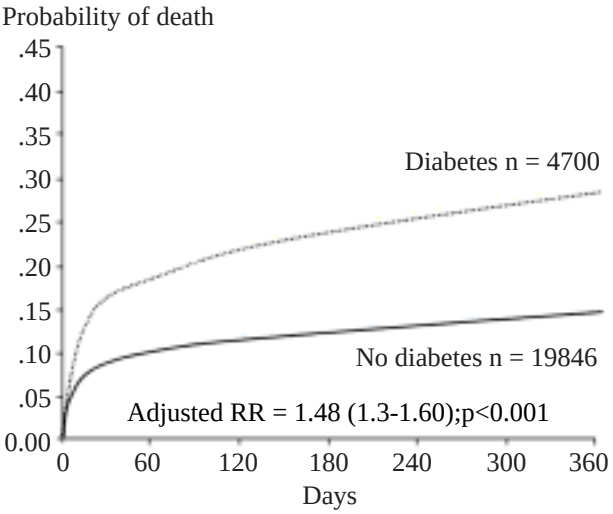

Fig 10. Kaplan-Meier curves showing cumulative mortality during 1-year follow-up in RIKS-HIA. Dotted line = patients with diabetes mellitus; solid line = patients without diabetes. Study IV.

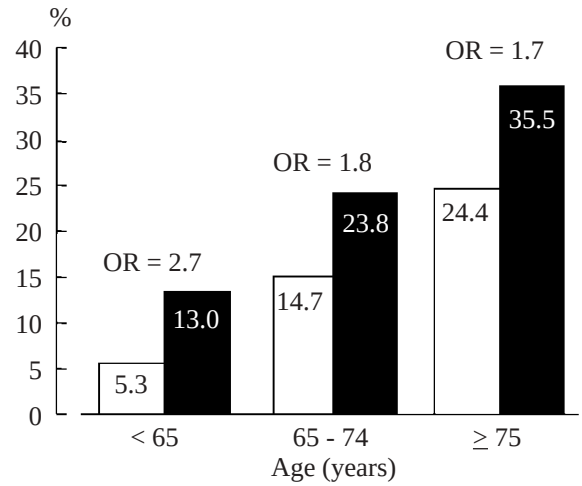

Fig 11. One-year mortality (%) in three different groups. Values above bars = OR; filled bars patients with diabetes mellitus; unfilled bars = patients without diabetes mellitus. Study IV.

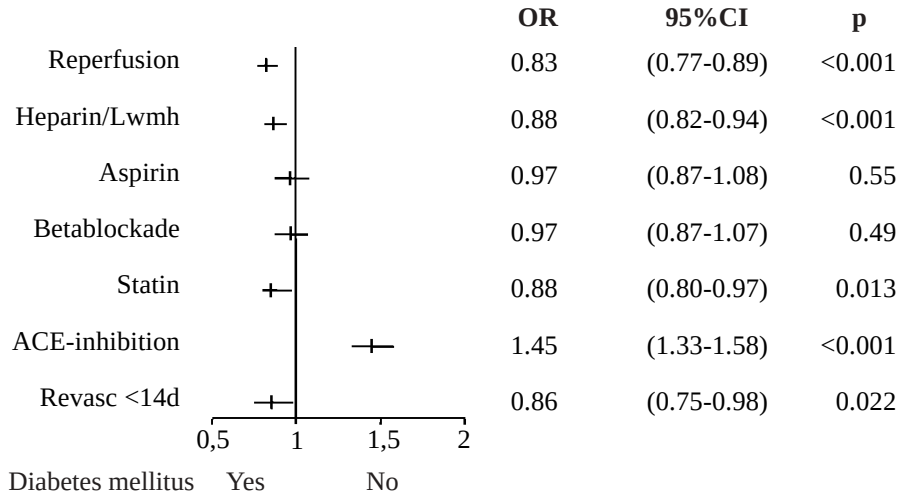

Figure 12. Adjusted difference in treatment between patients with and without diabetes mellitus. The values are OR and 95% CI. Study IV.

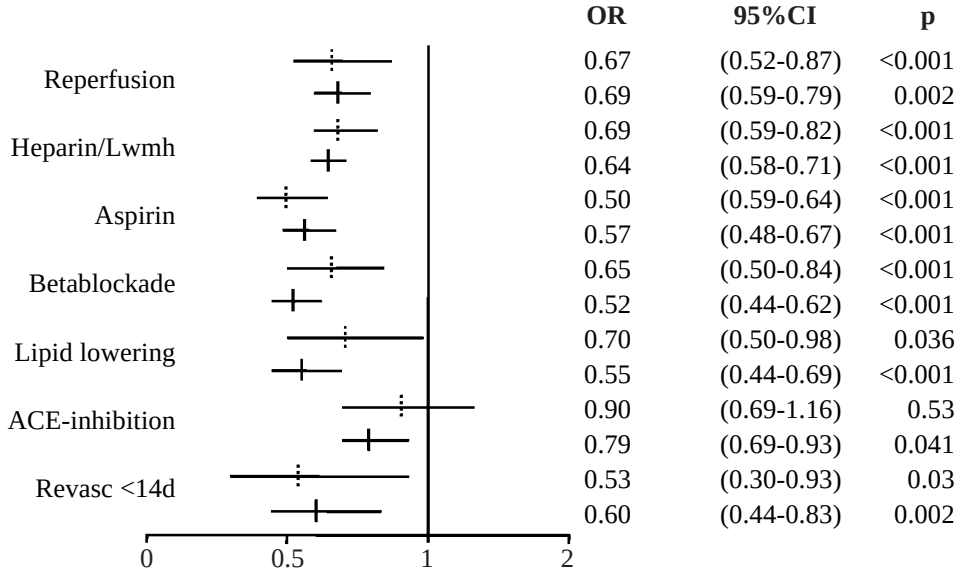

Fig 13. Multiple adjusted treatment effects on 1-year mortality in patients with diabetes (dotted line) and without diabetes (solid line). The values are OR and 95% CI. Study IV.

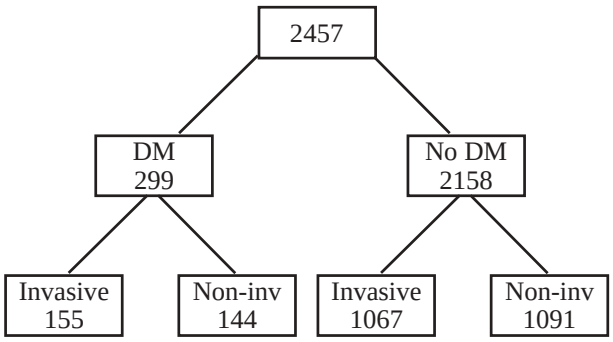

Fig 14. Schematic inclusion in the FRISC II trial. Study V.

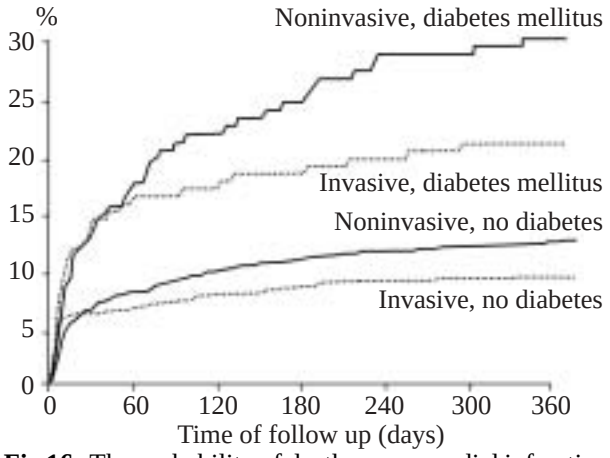

Fig 16. The probability of death or myocardial infarction over time. The FRISC II trial. Study V.

Early revascularisation in patients with diabetes mellitus and unstable coronary artery disease (Study V)

Clinical data

A total of 2,457 patients, 299 (12%) with and 2,158 (88%) without diabetes mellitus were randomly allocated to the invasive or non-invasive management strategy. The distribution of patients to the different strategies is shown in Figure 14. The diabetic group was at higher risk as revealed by a somewhat higher age (66 versus 64 years) and a higher prevalence of previous angina pectoris, myocardial infarction, heart failure and peripheral vascular disease. During hospitalisation the diabetic patients were more frequently treated with calcium channel blockers, ACE-inhibitors and diuretics. Moreover three-vessel disease was significantly more common in the diabetic group (42% vs. 31%; p<0.006).

Morbidity and mortality

Allocation to invasive management reduced the occurrence of the primary endpoint among non-diabetic patients from 12.0 % to 8.9% (invasive vs. non-invasive management, OR = 0.72; CI: 0.54-0.95; p=0.019). As could be expected the corresponding event rates were higher in the diabetic group with a reduction by the invasive strategy from 29.9% to 20.6% (invasive vs. non-invasive management OR = 0.61; CI: 0.36-1.04; p =0.066) (Figure 15). Kaplan-Meyer curves over time to event is shown in Figure 16. Diabetes mellitus was a strong and independent predictor of death or myocardial infarction (RR 2.61; CI: 1.88-3.60; p=0.0001) in the combined group of patients (invasive and non-invasive). To rule out the extent of coronary artery disease as possible confounder the distribution of coronary artery disease was introduced in a multivariate analysis on the patients in the invasive group. In this analysis diabetes mellitus still remained as an independent predictor of the combined endpoint (RR 2.40 RR 2.40; CI: 1.47-3.91; p=0.0001) and even more pronounced for mortality (RR 5.43; CI: 2.09-14.12; p=0.001.

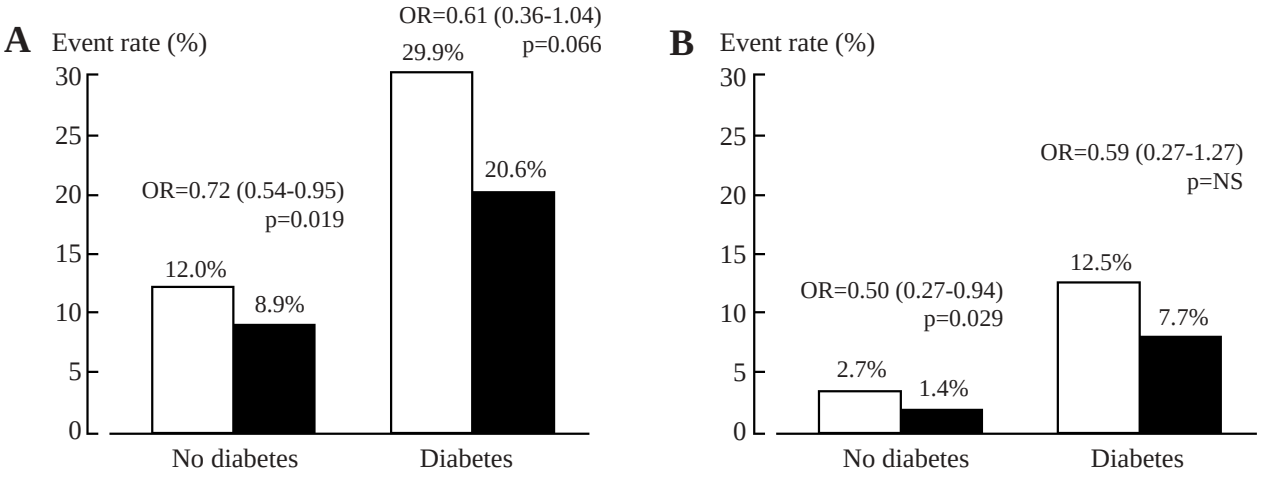

Fig 15. Crude one-year event rates as regards myocardial infarction and mortality in patients with and without diabetes mellitus subjected to an invasive (filled bars) and non-invasive (open bars) management strategy. The Frisc II trial. Study V.

General Discussion

Diabetes is common among patients with acute coronary syndromes and the morbidity and mortality after such event is high. Even conditions preceding diabetes are at increased risk for cardiovascular mortality. This thesis deals with risk factors for increased mortality, how to optimise and improve care and prognosis in patients with diabetes mellitus and acute coronary syndromes. It does also consider how to detect impaired glucose tolerance or previously unknown type 2 diabetes as soon as possible following an acute event. This may have major implications for future coronary care. Preventive measures directed towards the disturbed glucometabolic state instituted as early as possible, may perhaps be of particular importance considering that there is an expected dramatic increase of people with type 2 diabetes.

The prevalence of glucose abnormalities

The prevalence of diabetes in a modern population of patients with AMI remains high. In study IV it was 20.3%. In fact the prevalence of previously undiagnosed diabetes and glucose abnormalities preceding diabetes was unexpectedly high among patients with acute coronary syndromes, as shown in study III. The OGTT disclosed that 31% of the patients had diabetes and 35% IGT. To rule out the influence of acute stress, the OGTT was repeated after three months with almost consistent results, 25% had diabetes and 40% IGT. In total almost two-thirds of presumed "non-diabetic" patients with acute myocardial infarction turned out to have an abnormal glucose metabolism.

The prevalence of diabetes among patients with acute myocardial infarction has previously been reported to vary between 10-24% (59-60, 65-68, 72) while the prevalence of previously undetected diabetes was reported to be 5% (73). Corresponding proportions in patients with unstable coronary artery disease were reported to be 18-21% (70-71) and in a recent study on early revascularisation in unstable coronary artery disease 27% had diabetes (97). Access to the RIKS-HIA registry offered an opportunity to study the true prevalence of diabetes in an unselected AMI-population without the limitations that by necessity afflicts clinical trials with established inclusion and exclusion criteria. An age limit of 80 years was adopted in studies III and IV as a precaution to avoid too much influence of unrecorded co-morbidities. Since the prevalence of diabetes increases with age this limit may have introduced a possible underestimation of the actual prevalence. However, even at ages below 65 years 16% of male and 21% of female patients had diabetes in study IV. The information on diabetes was based on the case history but it is known that type 2 diabetes may be preceded by undiagnosed diabetes during several years and that glucose is a continuous risk factor for cardiovascular disease already below the internationally established diabetic threshold (18). This was the background for study III, which was planned to test the hypothesis that glucose abnormalities is much more common than what can be disclosed by using databases like the one in study IV. This was also the reason to exclude not only patients with already established diabetes but also those with an admission blood glucose >11 mmol/l.

To our knowledge study III is one of the first prospective investigations in a modern setting applying repeated OGTT tests in patients with myocardial infarction. Inclusion was consecutive when ongoing but did not by practical reasons comprise weekends and holidays. The study protocol included an OGTT prior to hospital discharge and recruitment had to be planned to allow this investigation, only available ordinary weekdays. During the days open for patient recruitment there were no losses. Two different catchments areas were covered by study III. One study centre was a county hospital serving a medium sized city and its rural surroundings while the second centre, a university hospital, recruited from a large city. Thus a potential

influence of environmental factors and life style habits were at least to some extent taken into account. Patients in study III were somewhat younger than those in study IV although the same upper age limit of 80 years was applied. In study III the elderly were excluded together with those with already known diabetes. Patients, who by various reasons (mortality, CABG, unwillingness) did not perform the OGTT after three months were somewhat older, more often females and a higher proportion had a history of heart failure and previous myocardial infarction. This group had a somewhat higher fasting blood glucose on the fourth hospital day (5.6 vs 5.3 mmol/l). Accordingly the prevalence of impaired glucose tolerance should have been higher in these patients. This together with the fact that diabetes increases with age implicate that prevalence data from study III if anything should represent an underestimation of the true prevalence of glucometabolic abnormalities.

Study III indicates that patients with glucometabolic disturbances are possible to identify already during the hospital stay. There was a strong correlation between the 2-hour blood glucose at the time for hospital discharge and three months thereafter indicating that acute glucose abnormalities must relate to other conditions than stress induced by the acute coronary event. This conclusion is further supported by the fact that the only independent predictors of an abnormal glucose tolerance after three months were admission HbA1c and fasting blood glucose at discharge. Identification of glucose abnormalities may therefore be reasonably well established by an HbA1c at admission, fasting blood glucose at the fourth hospital day or an OGTT before discharge.

Considering the unexpectedly high prevalence of glucose abnormalities among the patients in study III it would have been of interest to compare the results with those derived from a population based control group recruited from the catchments area. Preliminary findings in an age and sex matched control group specifically selected to balance the population in study III, shows that two thirds of the control persons have normal glucose tolerance tests (data on file). Moreover, when looking at already available populations the results remain striking. In a recent study in northern Sweden, excluding patients with known diabetes, 60- year old men had a prevalence of abnormal glucose tolerance of 10 % and 60-year old women of 13 % (143). Among 70- year old men from central Sweden, all of them survivors from a longitudinal population based study initiated in 1970, the highest prevalence of diabetes and IGT, 33%, was found among men with a low birth weight (<3.25 kg; 144). Following exclusion of subjects with a history of diabetes, myocardial infarction and fasting hyperglycemia the Rancho–Bernardo study, an American community-based study of Caucasian adults of European ancestry (mean age 70 years), reported that 16% of males and 11 % of females fulfilled criteria for the diagnosis of diabetes (145). Although these cohorts are not perfectly matched to our patients it is obvious that the prevalence of disturbed glucose metabolism in an ordinary population is far below that in study III.

In fact high prevalence of glucose disturbances during the acute phase of an acute myocardial infarction is not a completely new finding. Wahlberg (119) and Paasikivi (122) had already 1966 and 1970 noted such abnormalities. Evidence is in fact accumulating that the prevalence of glucose disturbances in patients with acute coronary syndromes indeed is high. In a case-control study in non-diabetics South Asians with acute myocardio infarction 64% had some glucose disturbances compared to 30% among controls when studied with fasting glucose or OGTT 10 days after the myocardial infarction (146). Moreover it seems that glucometabolic derangement is not specifically linked to acute coronary events but also is prevalent in other manifestations of coronary heart disease such as demand of coronary interventions and heart failure. Among patients without diabetes referred for coronary angiography after positive exercise test about 50% had abnormal glucose tolerance according to an OGTT (147). In RESOLVD, a heart failure trial, a total of 43% of the patients had disturbed glucose tolerance when fasting blood glucose was added to the case history, according to which 27 % had a previously known diabetes (148).

The oral glucose tolerance test

In study III categorisation of the glucometabolic state was based on OGTT. This test has two

major limitations. The test may be experienced as inconvenient in clinical practice and it has a rather low reproducibility. The within variability of the post-load glucose values have been described to be up to 25-35 % (149-151). The results in study III are based on a highly selected population with an already established cardiovascular event and with a high prevalence of glucose disturbances. The exact variability of the OGTT has not been studied in such population. Even if the reproducibility has some limitations there are indications that if one out of two tests are abnormal this is associated with an increased risk for future diabetes (152-153). A preliminary analysis indicates that a single diabetic OGTT test or fasting blood glucose, will unveil persons with a high cardiovascular risk-profile and questioned the need for a confirmatory diabetes test in a high-risk population (154).

An advantages with OGTT compared to fasting glucose values is that it will not fail to detect the majority of subjects who indeed have an IGT or previously undetected diabetes which often is the case for fasting glucose (35, 155-157). Furthermore the 2-hour post-load glucose level is a stronger predictor for cardiovascular mortality than fasting glucose (18, 35, 158-164).

Medical therapy and glucose tolerance

It may be argued that the OGTT in study III may have been influenced by ongoing pharmacological therapy. In particular studied in hypertensive patients, beta-blocker have been associated with adverse effects on glucose (165-167) and lipid metabolism (168-169). Beta-blocker has been claimed to increase the incidence of non-insulin dependent diabetes mellitus (166, 170-172) as to enhance insulin resistance (167) and delay insulin clearance by 20-25% (93, 173). There are, however, diverging opinions and there seems to be a difference between selective and non-selective beta-blockers. Recently 12 weeks treatment with the beta-1-selective-blocker metoprolol (100 mg/day) did not cause any alterations in glucose or insulin response to a standard oral glucose challenge in middle-aged men with modestly increased cardiovascular risk (169). When given to healthy, non-obese, middle-aged men, a daily dose of 100 mg metoprolol, did not alter the insulin-stimulated glucose uptake during clamps compared to placebo (174). In study III the vast majority (92%) of patients on beta-blockade were given a beta-1-selective blocker and there was no significant difference in such treatment between the three glucometabolic groups at hospital discharge or three months thereafter.

ACE-inhibitors have been associated with a reduced incidence of diabetes mellitus (85, 175). In a recent study on primary hypertension comparing the ACE-inhibitor trandolapril with the selective beta-1-blocker atenolol, glucose tolerance did not differ after 8 and 48 weeks (176). In study III there was no significant difference in the use of ACE inhibitors in the three different glucometabolic groups at hospital discharge or after three months.

Accordingly discrepancies in pharmacological treatment can not have influenced the outcome of study III to any important extent.

Concluding remarks

In conclusion the prevalence of diabetes, previously not known diabetes and glucose disturbances preceding diabetes is much higher than previously considered among patients with acute coronary syndrome. Such patients are possible to detect already during the initial hospitalisation for a coronary event. An abnormal test results after an OGTT implies increased risk for both future DM and diabetes specific complication and for future cardiovascular morbidity and mortality (33-35). It seems as a missed opportunity not to look for patients with such strong risk factor and the most optimal must be to identify them before another coronary event.

Prognosis

Studies I and IV clearly revealed that mortality is high in patients with diabetes and myocardial infarction. A similar pattern was seen in study V comprising diabetic patients with unstable coronary artery disease and non- ST-elevation infarction. Despite a management strategy including early revascularisation 21% had died or suffered a new coronary event within one year. Thus a consistent finding is that patients with diabetes had about twice the mortality and/or event rate as that among non-diabetic patients. Moreover patients with a high admission glucose but no previously known diabetes had a more

dismal long-term prognosis than those with lower glucose levels as shown in study II.

Mortality trends

The present disappointing results are in accordance with a report on mortality trends in the USA. It was reported that patients with diabetes have not experienced the same mortality reduction as that seen in non-diabetic subjects (69) due to considerable improvement in the management of coronary artery disease. Similar experiences were recently gained from the MONICA register in Sweden as regards the outcome after a myocardial infarction (177). Recent results from the MONICA register in Finland and Germany have shown a still high mortality rate for diabetic persons after myocardial infarction (178-179). Improved mortality trends has also been shown after unstable coronary artery disease (11), however, and in accordance with the outcome of study V, diabetic patients have a worse outcome (70-71).

The outcome for women with diabetes after acute myocardial infarction has been reported to be more serious than for men (63, 180). In the analysis of mortality trends from coronary heart disease in the USA, diabetic women experienced an increase in mortality (69). Following adjustments for baseline dissimilarities female sex did not remain as an independent predictor of long-term mortality in study I. This is in accordance with a recent meta-analysis showing no significant difference in mortality from coronary heart disease between diabetic women and diabetic men after adjusting for such risk factors as high age, cholesterol, hypertension and smoking (181). The present findings are also in accordance with Bueno et al who suggested that the previously reported increased mortality for women relates to risk factors rather than sex per se (182).

Prediction of mortality

A high admission blood glucose was an independent predictor of long-term mortality in study I as demonstrated by a significant trend for increased mortality with increasing glucose levels in the control group. Interestingly this trend was eliminated in the intensively treated insulin group. High admission glucose was an independent predictor of worse long-term outcome even in study II, which in contrast to study I only recruited patients without previously known diabetes. Taking the results of study III into account it is, however, obvious that many of the patients in study II in fact had glucometabolic abnormalities, some of them unrecognised diabetes. Studies I and II are the first to report on an independent relation between admission hyperglycemia and long-term prognosis following a myocardial infarction. It extends and underlines previous reports on a relation between elevated blood glucose and hospital mortality after myocardial infarction (110-113, 123, 183). Admission hyperglycemia has also been shown to relate to the short-term outcome in non-diabetic patients following stroke, CABG and admission to general wards (184-187) as well as to long-term mortality after stroke (188).

As already discussed admission hyperglycemia in acute myocardial infarction was originally experienced as a transient phenomenon induced by acute stress increasing the levels of cortisol and cathecholamines (110, 115, 118). It has also been linked to the extent of myocardial damage (110-113, 118). In study I there were no differences in controls and intensively insulin treated patients as regards the release of enzymatic indicators of myocardial damage. In correspondence there was no difference in enzyme levels between survivors and those who died in study II. Moreover HbA1c was the most powerful predictor of a high admission glucose in study I. This indicates that blood glucose at admission is not only a marker of acute stress but that it rather reflects the prevailing glucometabolic state. A reasonable explanation for admission hyperglycemia would then be that stress evoked by for example an acute myocardial infarction unmasks patients with a glucometabolic disturbance. This assumption gain support from a study by Fajans (189) who noted that disturbed carbohydrate metabolism in healthy individuals with a family history of diabetes could be unmasked by a standardised single-dose of cortisone. Patients with a positive test subsequently developed diabetes eight times more often than those with a normal test. The proposed mechanism was that pre-diabetic persons have an impaired secretion of insulin following the cor-

tisone glucose tolerance test (189-190). Similar results were obtained in a more recent study (191).

Reasons for increased mortality

Autonomic dysfunction is a feature of potential importance, leaving the diabetic persons with a sympathetic drive that is partly unopposed by parasympathetic influence. This causes heart rate to increase which is unfavourable in the setting of an acute coronary event. It also decreases the pain perception, which may delay the time between onset of symptoms and medical help. This aspect was not further studied within the concept of this thesis.

Three vessel disease is more frequent in patients with than in those without diabetes and in addition the coronary lesions are often more widely distributed and diffuse in the diabetic patient (64). Study V offered a unique opportunity to further explore the importance of diabetes mellitus as a risk factor controlling not only for generally available risk factors but also for the extent of coronary artery disease. In the multivariate analysis within the invasive group, including the number of vessels diseased, diabetes remained a strong independent predictor of the combined endpoint mortality and/or reinfarction after 12 months and of mortality while for example ST-depression and age did not. Moreover diabetes was a better marker for worse outcome than the release of troponin T elevation. It may be claimed that the classification of coronary artery disease as 1, 2 or 3-vessel disease is to simplistic for the prognostic purposes. When, however, a coronary arterial score index was constructed including a more detailed analysis of the distribution of the disease beyond the number of vessels engaged the outcome remained the same (data on file).

Turning to more metabolically oriented factors elevated levels of blood glucose are associated with increased platelet reactivity, impaired fibrinolysis, endothelial dysfunction, disturbed lipid metabolism, reduced myocardial flow reserve, increased levels of cytokines, increased oxidative stress and prolonged QTc intervals (192-200). Some of these mechanisms are closely interrelated and several of them may cause myocardial damage to increase. It is reasonable to assume that such negative influence is not an on-off phenomenon at a defined glucose level but that it is continuously increasing with the magnitude of glucometabolic disturbance. Many of these perturbations improve with normalisation of blood glucose or with insulin treatment. Insulin treatment, and often accompanied improved glucose levels, has resulted in a less atherogenic lipoprotein profile, reduced the thromboxane A2 production, decreased plasminogen activator inhibitor-1, fibrinogen and C-reactive protein. It also improves blood flow response to acetylcholine in type 2 diabetes (192, 201-206). Inflammatory markers are reduced in obese, non-diabetic humans infused with insulin (207). Thus there are reasons to believe that hyperglycemia per se is related to vascular dysfunction and the atherosclerotic process and that improved glucose levels are beneficial. This may be in particular be true for insulin treatment.

Concluding remarks

In summary persons with diabetes continue to have an unfavourable prognosis after an acute myocardial infarction. This is also true for non-diabetic patients with elevated levels of glucose at admission.

Treatment

Evidence based treatment

Three months mortality in the control-arm of study I (the DIGAMI-trial) was lower, 16% than the 35% that had been predicted based on available reports (59, 60). One rather likely explanation would have been the application of a very detailed protocol for prescriptions besides the glucometabolic control to which the participants were assigned randomly. This raised suspicions of under treatment of diabetic patients with acute myocardial infarction and was part of the background to study IV.

The RIKS-HIA registry offered excellent opportunities to further analyse the use of evidence-based treatment and to compare the efficacy of such therapy comparing myocardial infarction patients with and without diabetes. Following statistical adjustment for confounding factors, for example age, gender and previous diseases, study IV revealed that several well established treatment modalities were equally

effective in patients with and without diabetes, however, less often offered to those with diabetes. The representativeness of the RIKS-HIA database is strengthened by the inclusion of patients with myocardial infarction representing a vast majority of the Swedish population recruited from hospitals with different levels of care. In study I, including only diabetic persons, thrombolysis and the administration of beta-blocker were associated with improved prognosis. Study V (the FRISC II trial) further underline that patients with diabetes have similar proportionate event reduction from early revascularisation as patients without diabetes.

The observations in study IV are unfortunately not unique. Several investigators have, although looking at the problem from a usually more restricted angle and in selected populations, reported on similar experiences with a less well advanced use of evidence-based treatment in patients with diabetes, in particular as regards thrombolysis and revascularisation (67, 71, 179, 208). The most apparent reason for this underutilisation is perhaps a common belief that diabetic patients are more vulnerable and have more co-morbidity, making the use of various treatments more complex and less effective. Such factors were, however, considered in study IV, which still revealed therapeutic benefits among patients with diabetes. Another reason may be lack of typical symptoms in diabetic patients with coronary ischemia, a consequence of autonomic neuropathy (209). The prevalence of silent ischemia has been reported to be 10-20% in diabetic compared to 1-4 % in non diabetic populations respectively (210). Accordingly silent infarctions or infarctions with atypical symptoms are more common in diabetic patients delaying hospital admission time as well as time to diagnosis thereby reducing the opportunity to administer adequate treatment. Finally fear for side effects in diabetic patients has to be taken into account. Although claimed to be a problem in early case reports (89-90), bleeding complications after thrombolysis, ocular or cerebral, has not been confirmed to be more prevalent in diabetic populations when thoroughly investigated (71, 92).

Beta-blockers may reduce early warning-signs of hypoglycaemia. However, the choice of beta-blocker seems to be of importance. Although prolonged hypoglycaemia has been reported for non-selective beta-blockers it has not been confirmed for beta-1-selective compounds (94). Thus, metoprolol, did not prolong the duration of hypoglycaemia and the warning signs were unaltered except for increased sweating (93). Beta-blocker reduces mortality and the risk for reinfarctions (80-82, 211) and they also improve the prognosis in heart failure (212-214) in diabetic patients. In addition micro and macrovascular complications are reduced in patients with hypertension (215). Beneficial effects have consistently been reported for different beta-blockers apart from pindolol, which exerts intrinsic sympatomimetic effects (216).The explanation for the beneficial effect of beta-blockers in diabetic patients with acute myocardial infarction is presumably multifactorial. Experimentally propranolol reduces myocardial oxygen consumption by reducing energy production via free fatty acids, promoting glucose utilisation (217). This may be important in patients with diabetes, who have increased levels of circulating free fatty acids (218-222). Furthermore, and as has been discussed, heart rate is elevated in diabetic patients with acute myocardial infarction (209, 223). Mortality reduction of beta-blocker treatment relates to heart rate reduction and is most pronounced in patients with high initial heart rates (224-227). An interesting observation from study I was that beta-blockade was of value for control patients but did not induce added and significant reduction of mortality in the intensively treated insulin group. This indicates that at least part of the beneficial mechanism of action for insulin and beta-blockade in the diabetic patient with acute myocardial infarction may be along a similar pathway. Common to both treatment modalities is a reduction of free fatty acids and thereby beta-oxidation and a concomitantly promotion of glucose utilisation in the ischemic and non-ischemic myocardial tissue.

Patients, who received ACE-inhibitors in study I had a worse outcome and in study IV ACE-inhibitors did not exert any beneficial effect of significance in the diabetic cohort. The choice to start ACE-inhibitors was according to the discretion of the attending physician and it is likely that such treatment mainly was administered to high risk patients with clinical signs of heart failure. Such selection bias was difficult to ac-

count for even in the multivariate analysis. Supportive for this assumption is that studies I and IV were performed before the results of the HOPE study was known and ACE-inhibitors were started by prophylactic reasons (85). Analysis of ACE-inhibitor trials in heart failure do not support a particularly pronounced effect in the diabetic subgroups (228-229) apart from GISSI-III. In this post myocardial infarction trial early institution of lisinopril was followed by a reduced mortality in patients with diabetes, however, not among those free from this disease (230).

Early revascualrisation

In study V (the FRISC 2 trial) patients with unstable coronary artery disease were randomised to an early (<7 days) revascularisation management strategy or to a non-invasive strategy. The present analysis focused on patients with diabetes and the main finding was a significantly higher mortality and more frequent non-fatal reinfarctions among such patients than in those without diabetes. This was apparent both in the early revascularisation and the non-invasive study arm. The relative benefit of an early revascularisation was of the same magnitude in diabetic and non-diabetic patients. Since the diabetic patients are at a substantially higher risk the absolute reduction of events was considerably more pronounced among patients with diabetes. The numbers to avoid one combined endpoint (NNT) was 32 for non diabetic persons compared to 11 for diabetic persons. The corresponding number to save one life was 78 in non diabetic and 21 in diabetic persons.

The proportion of patients with known diabetes in study V was 12 %. This is lower than the 20 % that could have been expected from study IV and from previous reports on patients with unstable coronary artery disease (70). The most likely reason is a selection bias in study V. This assumption gets further support by the low prevalence of heart failure, 6 % compared to 22% in study I and by a lower prevalence of previous interventions than usually seen in persons with diabetes and acute myocardial infarction. Thus there may very well have been a hesitancy to expose diabetic patients with acute coronary syndromes to early coronary interventions and thereby to recruit them for the FRISC trial. Such reluctance was also noted in study IV, in which myocardial infarction patients with diabetes were offered revascularisation within the nearest 14 days after hospital discharge significantly less often. In the light of such selection bias, reasonably avoiding more complex patients, the present data if anything may underestimate the true risk for diabetic patients with acute coronary syndromes. It is obvious that study V confirms previous reports on the dismal prognosis for this patient category (70) and that it underlines that non-ST-elevation infarctions and unstable angina pectoris are major events for these persons.

The choice of coronary intervention, PCI or CABG, was left to the discretion of the attending physician. Study V does therefore not to give an answer to which procedure to prefer in patients with compared to those without diabetes. The diabetic patients had more often 3-vessel disease. Accordingly they were somewhat more often subjected to CABG than to PCI. Several subgroup analysis from different trials and registries indicate that diabetic patients with multi-vessel-disease benefit more from CABG compared to PCI (98-99).

Early revascularisation was beneficial for the patients in study V. Still this may not be used as direct evidence for benefits even in an older and/or sicker population of diabetic patients. Study IV does, however, contribute indirect support for such assumption. Among unselected patients with diabetes, up to the age of 80, those who were revascularised within 14 days following hospital discharge had a better one year survival than those who were not. It is therefore reasonable to believe that the outcome of study V can be extended to a broader group of diabetic patients.

In summary, non-ST-elevation myocardial infarctions and unstable angina pectoris are major events for patients with diabetes mellitus. A management strategy based on early coronary angiography and if possible an early coronary intervention is as beneficial for these patients as for their non-diabetic counterparts.

Metabolic support

The prognosis for patients with diabetes and myocardial infarction should improve by a more frequent prescription of established therapy. It is still unlikely that lack of evidence-based therapy is the only, not even the most important,

explanation for the increased mortality among such patients. Thus interventions directed towards the unfavourable effects of glucose abnormalities must be given priority besides proper patient management according to established routines.

Studies on diabetes specific treatment strategies are sparse. Study I is still the only randomised trial testing the concept of myocardial metabolic support and control during and following an acute myocardial infarction. After an average of 3.4 years of follow up the overall mortality had decreased from 44% in the group managed according to traditional routine to 33% in patients exposed to insulin based intensive metabolic control. The study design did not permit any conclusion on which of the treatment phases, the initial 24 hours of insulin-glucose infusion or the long-term multi-dose insulin administration aiming at tight continued metabolic control, that is most important. This important question is now studied in the ongoing DIGAMI 2 trial. Evidence does, however, exist supporting the influence of both acute and long-term treatment.

Enhanced adrenergic activity, triggered by stress due to acute myocardial ischemia, increases the release of free fatty acids and directs myocardial metabolism towards beta-oxidation rather than glucose utilisation (231). This is even more apparent in the diabetic myocardium, which already under normal conditions is proportionately more dependent on fatty acids for energy supply (232). Glucose is, however, a more favourable substrate in the ischemic situation. It consumes less oxygen for the same production of ATP, it may be metabolised anaerobically and glucose derived ATP accumulates in the cytosol, close to the cell-membrane ion pumps and seems of particular of value for their function (233). Infusion of insulin and the administration of beta-blocker reduce the blood concentration of free fatty acids (231). Infusing glucose together with insulin add to the beneficial effects by promoting myocardial glucose uptake thereby improving the balance between free fatty acid oxidation and glycolysis.

Glucose-insulin infusions supplemented with potassium (GIK) were used in the management of myocardial infarction patients, with and without diabetes, in the early days of coronary care units. At that time the intention was to prevent ventricular tachyarrhythmia by promoting myocardial potassium uptake through insulin-glucose administration (105). The patient materials in these studies were too small to disclose any mortality impact. However, a meta-analysis based on these studies, and a recent pilot study with GIK indicate benefit (103, 106). In contradiction a Polish study, using low-dose-GIK in non-diabetic patients with myocardial infarction, could not confirm such mortality benefits (234). A study using insulin infusion alone aiming at a rapid normalisation (4.5-6.1 mmol/l) of blood glucose levels, did recently demonstrate decreased mortality in patients in intensive care. In this trial 62% of the patients had cardiac surgery and only 13% had diabetes (104). Continuous insulin infusion given postoperatively following open heart surgery, aiming at blood glucose levels of 8-11 mmol/l in patients with diabetes reduced the incidence of sternal infections (235). Except for the last study, these studies did not address patients with diabetes in particular, which, however, was the objective in study I (DIGAMI). Glucose and insulin may, as has been seen in experimental and clinical studies, be of value for the protection against myocardial reperfusion injury (106, 236-239). This may be the explanation that thrombolysis improved survival particularly in the insulin-glucose infused group in study I.

Improved metabolic control reduces microvascular and to some extent also macro vascular complications in type 1 and type 2 diabetes (37, 39, 53). This gives support to the value of long-term treatment in study I. Interestingly the most pronounced mortality reduction was seen in patients belonging to stratum 1 i.e. those without any previous use of insulin and at low cardiovascular risk. These were also the patients in whom the reduction of HbA1c after one year of follow up was most apparent.The glucometabolic state at admission was an independent predictor for poor outcome in the control group but this relation was eliminated in the intensively insulin treated group. Accordingly strict insulin based treatment seems to reduce the adverse effect of an initially poor metabolic control. This supports the assumption that glycemic control is of fundamental importance for secondary prevention in diabetic patients, including those that

has been called "non-insulin dependent" and also newly detected diabetes. An alternate explanation would be adverse effects of oral antidiabetic drugs. As already discussed it is, however, more likely that insulin has advantages adding to the value of glycemic control as such.

Future directions

Diabetes and impaired glucose tolerance are common in patients with acute coronary syndromes. Accounting for the increasing prevalence of type 2 diabetes they will become even more common in the future. Patients with glucose abnormalities are possible to detect already during the initial hospitalisation. It would, however, be even more ideal to find them before an acute coronary event. Lifestyle modification based on weight loss and increased physical activity delay the risk for future diabetes in overweight persons with IGT (240-242). Improved insulin sensitivity and reduced stress on the pancreatic beta-cells by acarbose (243) and metformin (242) prevent the onset of diabetes in obese persons with IGT, while troglitazone has shown similar effects in young Hispanic women with gestational diabetes (244). Improved metabolic control reduces microvascular complications in persons with diabetes (37, 39). In addition evidence start to accumulate that lowering blood glucose might reduce macrovascular complications in persons with established diabetes, at least following myocardial infarction (37, 39, 46, 53, study I). No studies have so far analysed the benefit of improved metabolic control on macrovascular complications in subjects with pre-diabetes. However, such studies are running or in the planning phase. It would be of great interest with future studies on the value of optimal myocardial metabolic control prior to and following coronary interventions in particular in the setting of acute interventions.

Besides new studies efforts must be put in implementing already available and documented treatment in patients with acute coronary syndromes or myocardial infarctions and diabetes. Success will depend on education, establishment of guidelines for patient management and local rules for their implementation. These guidelines should also deal with early detection of glucose abnormalities. It may very well be advocated that screening with oral glucose tolerance tests should be a routine in the coronary care unit to be considered of the same importance as for example routine screening for dyslipidemia.

CONCLUSIONS

1. Long-term outcome in diabetic patients with myocardial infarction is predicted by age, previous heart failure and the glucometabolic state at hospital admission. Intensive insulin-based treatment seems to attenuate the harmful effect of a high admission blood glucose.

2. High admission plasma glucose is an independent predictor of long-term outcome even in non-diabetic patients with myocardial infarction.

3. The prevalence of glucose abnormalities in patients with myocardial infarction but no previously known diabetes is surprisingly high. Furthermore, it is possible to identify patients with glucose abnormalities already during the initial hospitalisation.

4. Diabetes mellitus is still a major independent predictor of 1-year mortality following an acute myocardial infarction. This may partly be explained by less use of conventional evidence based treatment.

5. An early invasive strategy improves the prognosis in patients with diabetes and unstable coronary syndromes to a similar extent as in patients without diabetes. However, diabetes is still a major predictor for worse outcome even after consideration of the numbers of coronary arteries involved. Thus, diabetes specific metabolic alterations may be of considerable importance for the outcome in diabetic patients with unstable coronary artery disease.

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APPENDIX

Protocol of insulin-glucose infusion used in the DIGAMI-trial study I.

Infusion: 500 ml 5 % glucose with 80 IU of soluble insulin (approximately 1 IU/6 ml).

Start with 30 ml per hour. Check blood glucose after 1 hour. Adjust infusion rate according to the protocol and aim for a blood glucose level of 7-10 mmol/L. Blood glucose should be checked after 1 hour if infusion rate has been changed, otherwise every 2 hours. If the initial fall in blood glucose exceeds 30% the infusion rate should be left unchanged if blood glucose is higher than 11 mmol/L and reduced by 6 ml/h if blood glucose is within the targeted range 7-10.9 mmol/L.

If blood glucose is stable ≤ 10.9 mmol/L after 10 p.m., reduce infusion rate by 50% during night.

B-glucose > 15 mmol/L:	Give 8 IU of insulin as an i.v. bolus injektion and increase infusion rate by 6 ml/h
11-14.9 mmol/L:	Increase infusion rate by 3 ml/h.
7-10.9 mmol/L:	Leave infusion rate unchanged.
4-6.9 mmol/L:	Decrease infusion rate by 6 ml/hour.
<4 mmol/L:	Stop infusion for 15 minutes. Then test B-glucose and continue testing every 15 minutes until B-glucose ≥7 mmol/L. In the presence of symtoms of hypoglycaemia administer 20 ml 30% glucose i.v. The infusion is restarted with an infusion rate decreased by 6 ml/h when B-glucose ≥7 mmol/L.