Glucose Regulation and Coronary Artery Disease

Studies on prevalence, recognition and prognostic implications

by

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Stockholm 2005
Nothing can ever happen twice.
In consequence, the sorry fact is
that we arrive here improvised
and leave without the chance to practice.

Nic dwa razy się nie zdarza
i nie zdarzy. Z tej przyczyny
zrodziliśmy się bez wprawy
i pomrzemy bez rutyny.

Wisława Szymborska
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Study I-IV
Coronary artery disease and diabetes mellitus type 2 represent chronic diseases of substantial and growing prevalence. Their coincidence is common, markedly enhancing mortality and morbidity. The risk for cardiovascular disease increases along a spectrum of blood glucose concentrations from levels regarded as normal. Therefore, strategies for the early detection of glucometabolic disturbances in patients with coronary artery disease are needed to better understand the impact on prognosis and improve treatment.

Aims
This thesis addresses glucose regulation in patients with coronary artery disease with the following specific aims
1. To study glucose tolerance in patients with myocardial infarction and population-based controls
2. To assess the prevalence of glucose regulation categories in patients with acute and stable coronary artery disease
3. To compare the different diagnostic modalities for recognising abnormal glucose regulation
4. To investigate whether the glucometabolic state detected early after myocardial infarction relates to long-term prognosis

Glucose tolerance in patients and population-based controls
In a prospective study 181 patients without diabetes admitted for acute myocardial infarction were matched for age and gender with control individuals without cardiovascular disease recruited from the population registry. A standard 75-g oral glucose tolerance test revealed that 35% of 185 controls compared with 67% of 168 patients at hospital discharge and 66% of 145 three months later had abnormal glucose tolerance. Compared to controls dyslipidaemia and hypertension was more common among patients, who were further characterised by higher glycaemia, insulin resistance, triglycerides, fibrinogen, and proinsulin levels.

The prevalence of glucose regulation categories
A total of 4 961 patients referred to a cardiologist due to coronary artery disease were recruited in 110 centres across Europe (acute admissions n=2 107; elective consultations n=2 854). Diabetes was already known in 1 524 patients. From 3 437 of the remaining subjects, fasting glycaemia was available in 2 679 while 1 920 underwent an oral glucose tolerance test. Newly detected diabetes was recognised in 22 and 14% of patients with acute and elective manifestation of coronary artery disease. Impaired glucose tolerance was found in 32% of each group and impaired fasting glucose in further 4 and 5%. Thus, more than half of patients without already known diabetes had abnormal glucose regulation.

Recognition of patients with abnormal glucose regulation
Glucometabolic status was assessed by means of fasting and 2-hour post load glycaemia in 1 867 patients with confirmed diagnosis of coronary artery disease without previously known diabetes or impaired glucose regulation. Among 591 patients with impaired glucose tolerance, 84% had fasting plasma glucose < 6.1 and 65% < 5.6 mmol/L. Out of 319 patients with newly detected diabetes 45% had fasting glycaemia < 6.1 and 29% < 5.6 mmol/L. If the glucometabolic state was classified by fasting glycaemia only, abnormal glucose regulation would have remained undetected in 48% (478) patients. The best algorithm to estimate abnormal glucose regulation was obtained by a neural network statistical model including fasting glucose, age and HDL-cholesterol. The model enabled a reduction of the number of glucose tolerance tests inevitable for appropriate classification by 25%.

Glucose tolerance as prognostic factor
During follow-up (median 34 months) of 168 patients with acute myocardial infarction, who had glucose tolerance assessed before hospital discharge, 31 experienced at least one major cardiovascular event (cardiovascular death, non-fatal stroke, recurrent myocardial infarction or severe heart failure). The probability of remaining free from cardiovascular events was significantly lower in patients with abnormal than those with normal glucose tolerance (p=0.002). Abnormal glucose tolerance (hazard ratio 4.18, 95% CI 1.26-13.84, p=0.019) and prior myocardial infarction (hazard ratio 3.38, 95% CI 1.62-7.04, p=0.001) were the strongest predictors of future events.

Conclusions
Abnormal glucose tolerance is almost twice as common among patients with a myocardial infarction as in population-based controls. Normal glucose regulation is less common than abnormal among patients with coronary artery disease. Abnormal glucose tolerance is a strong risk factor for future cardiovascular events after an acute myocardial infarction. An oral glucose tolerance test should therefore be a part of the evaluation of total risk in all patients with coronary artery disease. Since glucose disturbances are common and easy to detect they may be suitable targets for novel secondary preventive efforts.

Key words
Glucose metabolism, coronary artery disease, classification, prevalence, prognosis, risk, oral glucose tolerance test, diabetes mellitus
LIST OF ORIGINAL PAPERS

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

I
Abnormal glucose tolerance - a common risk factor in patients with acute myocardial infarction in comparison with population-based controls.

II
on behalf of the Euro Heart Survey Investigators
The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart.

III
on behalf of the Euro Heart Survey Investigators
Identifying abnormal glucose regulation in patients with coronary artery disease. A report from the Euro Heart Survey on diabetes and the heart.
Manuscript.

IV
Newly detected abnormal glucose tolerance - important predictor of long term outcomes after myocardial infarction.
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-Converting Enzyme</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>ARB</td>
<td>Angiotensin-II Receptor Blocker</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Tri Phosphate</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (weight/height^2; kg/m^2)</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft surgery</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DAG</td>
<td>Diacylglycerol</td>
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<tr>
<td>DECODE</td>
<td>Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>EUROASPIRE</td>
<td>European Action on Secondary Prevention through Intervention to Reduce Events</td>
</tr>
<tr>
<td>FPG</td>
<td>Fasting Plasma Glucose</td>
</tr>
<tr>
<td>GAMII</td>
<td>Glucose tolerance in patients with Acute Myocardial Infarction study</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycosylated Haemoglobin A1c</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High-Density Lipoprotein cholesterol</td>
</tr>
<tr>
<td>HOMA</td>
<td>Homeostasis Model Assessment</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>High sensitivity C-Reactive Protein</td>
</tr>
<tr>
<td>IFG</td>
<td>Impaired Fasting Glucose</td>
</tr>
<tr>
<td>IGT</td>
<td>Impaired Glucose Tolerance</td>
</tr>
<tr>
<td>IGR</td>
<td>Impaired Glucose Regulation</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>NADH</td>
<td>Nicotinamide Adenine Dinucleotide H+</td>
</tr>
<tr>
<td>NGT</td>
<td>Normal Glucose Tolerance</td>
</tr>
<tr>
<td>NGR</td>
<td>Normal Glucose Regulation</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health And Nutrition Examination Survey</td>
</tr>
<tr>
<td>OGGT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>PAI-I</td>
<td>Plasminogen Activator Inhibitor type-1</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>PKC</td>
<td>Protein Kinase C</td>
</tr>
<tr>
<td>RIKS-HIA</td>
<td>Register of Information and Knowledge about Swedish Heart Intensive care Admissions</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</table>
INTRODUCTION

Glucose regulation

Historical perspective

The earliest known record related to diabetes is by a physician Hesy-Radaates, who mentioned a disease associated with polyuria in the 3rd Dynasty Egyptian papyrus dating back to about 1552 B.C. Although known for a long time, it was not until the 16th century, when Paracelsus first recognised diabetes as a general and serious disorder. Glucose regulation became a subject of scientific investigation since the early 19th century when the chemical methods to assess presence of glucose in the urine were developed. Paul Langerhans described in his dissertation in 1869 the two types of pancreatic cells and a first report on experimental diabetes caused by pancreatic removal came 20 years later by Oscar Minkowski (1, 2). The next step was extraction of pancreatic hormone and a series of tests in dogs performed by Frederick G. Banting in collaboration with John Macleod. Insulin was applied for treatment of the first patient in January 1922 and has been saving lifes ever since (3). In the appreciation of the discovery of insulin Frederick Banting and John Macleod received the Nobel Prize in 1923.

Classification criteria

The criteria for diagnosis of diabetes, except from the well established clinical symptoms, were first unified following the reports from the National Diabetes Data Group in 1979 (4) and the World Health Organisation in 1980 (WHO; 5). The classification criteria have subsequently been updated to follow the expanding knowledge on the aetiology of the disease and the predictive value of blood glucose for disease specific complications. Glucose regulation is classified in different stages ranging from normoglycaemia to diabetes. Table 1 summarises the categories according to the most recent recommendations by the WHO in 1999 (6) and the American Diabetes Association (ADA) in 1997 and 2004 (7, 8). The WHO criteria are based on an oral glucose tolerance test with measurements of fasting and two hours post load glycaemia, while a fasting glucose is favoured by the ADA recommendations.

Diabetes mellitus

Definitions and manifestations

Diabetes mellitus is a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or a combination of both (6). Long-standing diabetes is associated with development of specific microvascular complications with a substantial risk of progressing to long-term organ damage including retinopathy, nephropathy and neuropathy that may include autonomic dysfunction. These complications, once developed, may progress to blindness, end-stage renal failure, foot ulcers, amputation, Charcot-joints and impairment of sexual function. Patients with diabetes are also likely to develop macrovascular complications including cardiovascular, cerebrovascular and peripheral artery disease. The diagnostic criteria for diabetes mellitus were originally set at blood glucose concentrations associated with an increased risk for developing microvascular complications specific for diabetes (9, 10).

Classification of diabetes includes both aetiological types and different stages of hyperglycaemia as suggested by Kuzuya and Matsuda (11). Four main aetiological processes potentially resulting in the onset of diabetes have been identified as type 1, type 2, other specific types and gestational diabetes (6).

Diabetes type 1 is characterised by deficiency of insulin due to an autoimmune process that
The natural history of absolute or relative insulin deficiency progressing from normoglycaemia to diabetes as outlined in Figure 1 (6, 12-14). The intermediate stages of disturbed glucose metabolism include impaired fasting glucose and impaired glucose tolerance, which have different characteristics and physiological determinants (14-17). Impaired fasting glucose denotes failure to maintain appropriate basal insulin secretion and to control hepatic glucose production, while impaired glucose tolerance is associated with peripheral insulin resistance and inadequate capacity of insulin production/secretion to the postprandial demands. Glucose homeostasis is a dynamic state affected by various not only metabolic factors and individual subjects may move from one category to another in either direction (Figure 1; 6, 18, 19).

**Table 1.** Criteria for glucometabolic classification according to WHO (6) and ADA (8).

<table>
<thead>
<tr>
<th>Glucometabolic category</th>
<th>Source</th>
<th>Classification criteria (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Glucose Regulation (NGR)</td>
<td>WHO</td>
<td>FPG &lt; 6.1 and 2-h PG &lt; 7.8</td>
</tr>
<tr>
<td>Normal Fasting Glucose</td>
<td>ADA 1997</td>
<td>FPG &lt; 6.1</td>
</tr>
<tr>
<td></td>
<td>ADA 2004</td>
<td>FPG &lt; 5.6</td>
</tr>
<tr>
<td>Impaired Fasting Glucose (IFG)</td>
<td>WHO</td>
<td>FPG ≥ 6.1 and &lt; 7.0 and 2-h PG &lt; 7.8</td>
</tr>
<tr>
<td></td>
<td>ADA 1997</td>
<td>FPG ≥ 6.1 and FPG &lt; 7.0</td>
</tr>
<tr>
<td></td>
<td>ADA 2004</td>
<td>FPG ≥ 5.6 and FPG &lt; 7.0</td>
</tr>
<tr>
<td>Normal Glucose Tolerance (NGT)</td>
<td>WHO</td>
<td>FPG &lt; 7.0 and 2-h PG &lt; 7.8</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance (IGT)</td>
<td>WHO</td>
<td>FPG &lt; 7.0 and 2-h PG ≥ 7.8 and &lt; 11.1</td>
</tr>
<tr>
<td>Impaired Glucose Regulation (IGR)</td>
<td>WHO</td>
<td>IFG or IGT</td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)</td>
<td>WHO</td>
<td>FPG ≥ 7.0 or 2-h PG ≥ 11.1</td>
</tr>
<tr>
<td></td>
<td>ADA 1997</td>
<td>FPG ≥ 7.0</td>
</tr>
<tr>
<td></td>
<td>ADA 2004</td>
<td>FPG ≥ 7.0</td>
</tr>
<tr>
<td>Abnormal Glucose Regulation</td>
<td>IFG or IGT or DM (IGR or DM)</td>
<td></td>
</tr>
</tbody>
</table>

Values represent venous plasma glucose concentrations; FPG fasting plasma glucose, 2-h PG two hours post load plasma glucose.
increasing overweight are predominant features of the ageing population of the developed countries. The rapid economical transition encountered in the developing countries results in substantial lifestyle changes with reduction of physical activity and increased availability of energy-dense food resulting in a growing prevalence of obesity. These demographic and economic changes favour clustering of classical cardiovascular risk factors and promote development of type 2 diabetes already at young age. The number of diabetic individuals, accounted for 151 millions in the year 2000, is expected to double reaching 300 millions in the year 2025 (21). The recent assessments for the population of the United States of America based on a survey in 2000 indicated a further increase of diabetes up to 7.2% in 2050 (22). The highest incidence of type 2 diabetes is to be seen in citizens of the developed countries above the age of 65 years, while the majority of affected individuals in the countries with developing economies will belong to the middle-aged population between 40 and 65 years (23).

Diabetes burden

Worldwide diabetes mellitus is a leading cause of blindness and end stage renal disease resulting from microvascular complications. Moreover, it is a major cause of premature atherosclerosis and macrovascular disease contributing to 75% of all deaths. As was first demonstrated by the Framingham study in 1979, patients with diabetes have a two-to-fourfold increased risk of developing angina pectoris and myocardial infarction with the highest increment of risk among young individuals before 45 years of age (24). A meta-analysis of 27 prospective studies conducted from 1966 onwards revealed that diabetes was associated with an annual mortality of 2.9% (95% CI: 2.8, 3.0) (25). Considering the high mortality and morbidity type 2 diabetes deserves being coined “a cardiovascular disease associated with hyperglycaemia” (23, 26). Moreover diabetes has a heavy impact on health care expenses in particular attributable to cardiovascular disease (26). The per capita medical expenditures for individuals with diabetes were more than five times higher than for their non-diabetic counterparts, reaching 29 billion euros in eight European countries in 1999 and 132 billion dollars in USA in 2002 (27, 28). The recent data from the CODE-2 (Cost of Diabetes in Europe - type II) study evaluating 7,000 patients from eight European countries found that only 28% of patients with type 2 diabetes were free from any complications, while 28% had micro- and 33% macro-vascular disease. The medical expenditures increased 1.7, 2.0 and 3.5 fold in relation to the presence of micro-, macro- and combined complications, as compared to subjects with a diagnosis of type 2 diabetes only (29).

The metabolic syndrome

The term metabolic syndrome identifies a cluster of metabolic features including central (abdominal) obesity combined with elevated blood pressure or triglycerides, low high-density lipoprotein (HDL) cholesterol, insulin resistance and/or abnormal glucose regulation. The association of these factors was first described by Avogaro and Crepaldi in 1967 subsequently to be redefined (6, 30, 31). The metabolic syndrome is related to a high risk of developing diabetes mellitus as well as macrovascular disease (6, 30-32). It is accompanied by a prothrombotic and proinflammatory state, microalbuminuria and hyperuricaemia. Type 2 diabetes is often associated with a range of cardiovascular risk factors including hypertension, dyslipidaemia, abdominal obesity as well as an enhanced procoagulatory and impaired fibrinolytic activity (6, 23, 24, 26). These metabolic features are also common in subjects with lesser stages of abnormal glucose regulation that often precede development of overt diabetes (Table 1, Figure 1; 12-18).

Coronary artery disease

Definition, pathogenesis and manifestations

Ischemic heart disease, denominates a condition with insufficient supply of blood carrying oxygen and energy substrates for the demands driven by the actual work load of the heart muscle. The most common reason is atherosclerosis in the coronary arteries. It occurs when the coronary arteries cannot adapt to the increased work of the heart by increasing the blood flow due to
impaired capacity for vasodilatation resulting from endothelial dysfunction in combination with narrowing of the vessel lumen by atherosclerotic lesions (33). Development of coronary artery disease is attributed to several pathogenetic processes initiated by endothelial damage followed by an inflammatory reaction involving macrophages, T-lymphocytes and chemokines (34). Expansion of atherosclerotic plaques progresses with accumulation of lipids and infiltration of cells. Even if the space occupying effect is important, the stability of the cap isolating the highly thrombogenic core of the lesion from the blood stream and platelets is crucial (35-37). If the fibrous cap overlying the atherosclerotic plaque becomes undermined, it may eventually fissure or rupture triggering aggregation of platelets and coagulation cascade within the coronary artery lumen resulting in a sudden narrowing or total occlusion corresponding to an acute coronary event/myocardial infarction (33-37). Clinically coronary artery disease is a multifaceted entity with manifestations ranging from asymptomatic disease via stable angina pectoris to acute coronary syndromes including unstable angina, myocardial infarction with (STEMI) or without (NSTEMI) ST-segment elevations and sudden cardiac death (38-39).

Epidemiology
The contribution of cardiovascular disease to the total population mortality was less than 10% until the beginning of the 20th century. The dramatic socio-economic transition including urbanisation, increased food supplies, less demand on physical activity for transportation and work combined with advances in the treatment of infectious diseases in young age groups, resulted in rapidly growing prevalence of degenerative diseases (40-41). Within half of the century coronary artery disease became the leading cause of morbidity and mortality (42). According to the WHO mortality database from the year 2002, the cardiovascular mortality varies across European countries from below 3 to 9 per 1000 inhabitants. Although progress in the diagnosis, treatment and prevention of cardiovascular disease have resulted in a substantial mortality reduction the total number of affected individuals is still increasing due to improved survival and an increasing overall longevity in the population (42-44).

Risk factors for coronary artery disease
The risk to develop coronary artery disease is influenced by multiple factors of which age, blood pressure, smoking, central obesity, dyslipidaemia, abnormal glucose regulation, physical inactivity and psycho-social deprivation are the most apparent (45-53). More recently recognised factors are insulin resistance, impaired fibrinolytic and enhanced procoagulatory activity and an increased inflammatory activity as reflected by an elevated C-reactive protein (54-57). Many of

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![Image](image.png)

**Figure 1.** Stages in the natural history of type 2 diabetes.
these factors are interrelated with each other and present in clusters (31, 57-60). The recently published INTERHEART study revealed that as much as 90% of the risk for an acute myocardial infarction can be attributed to modifiable risk factors, with the greatest impact of smoking and lipoprotein profile abnormalities followed by abdominal obesity, hypertension, diabetes, psychosocial factors, lack of regular physical activity and dietary habits (61).

**Coronary artery disease and hyperglycaemia**

**Concomitance**
The first report on a high incidence of glucosuria in patients with myocardial infarction was published by Levine in 1922 (62). This observation was confirmed in several other reports and received various interpretations (63-67). An original hypothesis was formulated by Cruickshank, who suggested that vascular degeneration was a common link to glucosuria and coronary disease, while Levine speculated on a causal relationship between high glucose levels and coronary thrombosis (63, 64).

The close interrelation between diabetes, hyperglycaemia and cardiovascular disease is undisputable and confirmed in various populations (68-74). Presence of diabetes is associated with a markedly increased risk for coronary artery disease and cardiovascular death. In the Multiple Risk Factor Intervention Trial participants with diabetes had a relative risk of 3.0 for coronary vascular death and 3.2 for development of coronary heart disease comparing with subjects without diabetes (70). A history of diabetes is found in 18% to 20% of patients with established diagnosis of coronary artery disease, as recently shown in the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) and the RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive care Admissions) studies (75-76). The presence of heart failure in an elderly Italian population predicted the subsequent development of diabetes mellitus (77). An unexpectedly high prevalence of abnormal blood glucose metabolism was reported in patients admitted to a coronary care unit due to acute myocardial infarction by the Swedish GAMI (Glucose Tolerance in patients with Acute Myocardial Infarction) study (78). Among patients without known diabetes and without overt hyperglycaemia at admission, diabetes was diagnosed in 25%, impaired glucose tolerance in 40% while only 35% had normal glucose tolerance three months after the coronary event (78).

Hyperglycaemia below the border for diabetes was suggested to indicate increased risk for atherosclerotic disease already in 1976 (79). Macrovascular complications increase along various stages of hyperglycaemia, already in the prediabetic state (16, 80-85). Data from the prospective Whitehall study revealed that the risk for cardiovascular disease was almost doubled in subjects with impaired compared with those with normal glucose tolerance (82). During 23-years of follow-up in the Honolulu Heart Program there was, independent of other risk factors, a dose-response relation between glucose intolerance at baseline and the incidence of coronary artery disease, cardiovascular and all cause mortality (83). The highest, more than three-fold absolute risk of death was found among subjects with known diabetes. During similar periods of follow up in three land mark studies, the Whitehall, the Paris Prospective and the Helsinki Policemen, men in the highest quintile of a two hour post load glucose concentration had an almost 2-fold higher risk of death, 1.6 from all causes and 1.8 from cardiovascular causes (85).

Accumulated evidence support a continuous relationship between glycaemia and cardiovascular disease progression starting already at blood glucose values regarded as normal. The relation between the level of glycaemia and the incidence of vascular complications related to diabetes has been outlined by Laakso et al (86; Figure 2). A systematic overview of 20 prospective studies following more than 95 000 patients for 12 years indicates that there is a positive relationship between glucose levels and cardiovascular events apparent already at glucose levels well below the diabetic threshold (87). The relative risk for cardiovascular mortality was 1.33 at a fasting blood glucose of 6.1 compared to 4.2
mmol/L (110 and 75 mg/dl), and 1.58 at a two-hours post load glucose levels of 7.8 versus 6.1 mmol/L (110 versus 140 mg/dl), respectively (87).

Common denominators
A large population-based autopsy study revealed a considerably higher atherosclerotic burden, including more advanced multivessel coronary artery disease, in subjects with known diabetes than in those without diabetes (88). This association between cardiovascular disease and hyperglycaemia may as already emphasised, be attributed to an accumulation of cardiovascular risk factors in patients with impaired glucose homeostasis, often in cluster as in the metabolic syndrome (89-90). It may, however, also relate to pathogenetic mechanisms directly or indirectly triggered by intermittent or constant hyperglycaemia inducing cardiovascular damage already before the onset of overt diabetes (91). Although such mechanisms have been discussed for some time they are still not fully understood (90-94).

Predictors of cardiovascular disease and dysglycaemia were studied in two population-based cohorts, the Rancho Bernardo and the San Antonio studies, recruiting people that were normoglycaemic at baseline. In both studies the elevated blood pressure and elevated triglycerides indicated increased risk for subsequent development of impaired glucose tolerance or diabetes in the long follow-up (95, 96). Considering the tight interrelation between diabetes and cardiovascular disease a "common soil" hypothesis was proposed by Stern, who suggested that these two degenerative diseases shared genetic and environmental antecedents (97). Shortly thereafter insulin resistance and hyperinsulinemia were proposed as such pathogenetic pathway (98, 99). Further evidence on this cross-talk emerged recently with the observations that hyperglycaemia, a well known predictor of diabetes, was identified as a continuous risk factor for subsequent cardiovascular events (87, 93-96).

This line of reasoning gained recently support from the report from the Health Professionals Study revealing that cigarette smoking increased the risk of developing type 2 diabetes by 1.94 times within six years of follow up (100). This effect was confirmed by a large prospective cohort study showing a dose-response relationship for this association (101). Furthermore, a synergistic interaction between smoking and insulin levels was reported to increase the risk of myocardial infarction (102). Another link in the search for a common denominator between dysglycaemia and vascular injury engages coagulation homeostasis. Already well recognised in the processes behind coronary artery disease haemostatic factors, among them

![Figure 2](image.png)

**Figure 2.** Development of insulin resistance, impaired insulin secretion, fasting glucose, and microvascular and macrovascular complications, in pre-diabetes and frank diabetes. *Reproduced by permission from ref. 86.*
factor VII, were recently found to predict type 2 diabetes (57, 103). In this context it is of interest that inflammatory markers, involved in the evolution and progression of atherosclerotic lesions, may indicate the development of type 2 diabetes (54, 104, 105). The relation between abdominal obesity and macrovascular and glucometabolic complications has been known since long. More recently the accumulation of visceral fat was claimed responsible for the classical relation between age and deterioration of glucose homeostasis (106, 107). This fits with the accumulated knowledge that lifestyle related factors, physical exercise and dietary habits including moderate alcohol consumption, decrease not only cardiovascular risk but also the incidence of diabetes (108). It is apparent that coronary artery disease and dysglycaemic conditions share a number of risk factors strongly supporting the hypothesis that these conditions have common pathogenetic mechanisms.

**Linking atherosclerosis and glucose homeostasis**

Glucose and free fatty acids are energy substrates that penetrate endothelial and myocardial cells along their concentration gradients. The break

![Image](image_url)
down of glucose starts with non-oxidative glycolysis generating nicotinamide adenine dinucleotide H+ (NADH) and pyruvate that transform to diacylglycerol (DAG), which enters the protein kinase C (PKC) pathway on its way to mitochondria. Further oxidation in Kreb’s tricarboxylic acid cycle produces energy rich phosphates in the form of adenosine triphosphate (ATP). Free fatty acids undergo beta-oxidation in mitochondria subsequently entering the Kreb’s cycle for ATP production (23).

Hyperglycaemia may induce cell damage via several processes including activation of PKC, predominantly the beta and delta isoforms, the polyol or aldose reductase pathway flux, enhancement of the hexosamine pathway flux and formation of advanced glycation end-products via non-enzymatic protein glycation (109, 110). During hyperglycaemic periods intracellular glucose overload causes disarrangement of the regulatory enzymes initiating a cytoplasmatic accumulation of DAG and activation of PKC (23, 109-110). Activation of PKC contributes to enzymatic uncoupling resulting in an uncontrolled overproduction of superoxide within the mitochondrial electron-transport chain (111). This has multiple functional and pathogenetic consequences as summarised in Figure 3 (109, 110, 112). Excessive superoxide generation at the mitochondrial level is a key element in the oxidative stress hypothesis, brought forward by Ceriello as a modern update of the common-soil hypothesis (97, 112). An over production of free oxygen radicals is useful in describing the mechanisms of insulin resistance and helps to explain the pathways through which exposure for various established risk factors for cardiovascular disease or diabetes leads to similar molecular consequences (91, 109, 112). According to this hypothesis a superfluous glucose or a free fatty acid supply causes PKC activation triggering a multiplicity of effects leading to functional impairment and tissue damage characteristic for vascular injury seen in diabetes and atherosclerosis. This may range from endothelial dysfunction during post prandial hyperglycaemic conditions to the induction of inflammatory cytokines and beta-cell apoptosis (113-117). In experimental studies a normalisation of the mitochondrial oxidative chain enzymes attenuated three of the four pathways for hyperglycaemic damage and selective inhibition of the PKC beta 2 isoform attenuated the increase of vascular cell adhesion molecule-1 (118, 119).

The oxidative stress - "common soil" hypothesis comprises mechanisms involved in endothelial dysfunction, the haemostatic homeostasis and platelet function, inflammatory processes, oxidised lipoproteins, insulin resistance and deterioration of the pancreatic beta-cell function, all elements that are recognised in the pathogenesis of atherosclerosis and diabetes (34, 109, 112, 120, 121). Furthermore it may explain why the pharmacological inhibitors of the renin-angiotensin system, administered for the treatment of cardiovascular disease, result in a substantially decreased incidence of diabetes (122-124). The crucial role of oxidative stress may also explain the reduction of cardiovascular events achieved by statins, which seems to offer enhanced benefits for patients with diabetes (125).

Unresolved issues

Considering that hyperglycaemia constitutes an independent predictor for cardiovascular mortality, a combination of elevated glycaemia and coronary artery disease can be expected to amplify the risk. The analysis of prospective cohort studies between 1966 and 1999, including 75 000 patients revealed that the adjusted relative risk for coronary death in patients with diabetes was indeed increased accounting for 1.9 in men and 2.6 in women (126). Moreover, despite successive and considerable improvements in the treatment of cardiovascular diseases there is a major disparity in benefits experienced by diabetic subjects compared with their non-diabetic counterparts. In an analysis of time trends in coronary artery disease mortality in two USA cohorts collected in 1971-1975 and 1982-1984 and followed on average for nine years, there was a clear contrast between the substantial decline in age-adjusted heart disease mortality in non-diabetic men (-36%) and women (-27%) as opposed to the very modest decline among diabetic men (-13%) and an actual increase in diabetic women (+23%; 127).
In fact, the in-hospital mortality among diabetic patients with acute coronary syndromes is still almost twice as high as in non-diabetic subjects and a substantially diminished life expectancy is observed during long-term follow up (75, 76, 128-131).

There are indeed indications that even the presence of hyperglycaemia recorded at admission for an acute coronary event, or in the fasting state some hours thereafter constitutes an independent risk factor for long-term prognosis including mortality (132-134).

An increased attention has to be devoted to patients with glucometabolic perturbations occurring in association with coronary artery disease. This additional concern should include patients with “hidden” glucometabolic disturbances, contemplating that glucose seems to be a continuous risk factor with prognostic implications apparent well below present targets for the diagnosis of diabetes (87, 134).

The GAMI trial (78) indicated that glucose abnormalities are common unveiling a high proportion of previously unknown hyperglycaemic conditions among patients admitted for an acute myocardial infarction. The high proportion of newly detected diabetes and impaired glucose tolerance in patients enrolled in the GAMI study raises questions regarding the actual prevalence of glucose abnormalities in the population the patients originate from. The observations made in the GAMI study, comprising somewhat less than 200 patients from two Swedish hospitals, need confirmation in a broader population of patients with various manifestations of coronary artery disease. Moreover, it is important to establish the actual risk attributable to newly detected impairment of glucose homeostasis in the light of the pathogenic mechanisms relating the atherosclerotic process to hyperglycaemia.
AIMS

The overall objective was to study glucose regulation in patients with coronary artery disease with the following specific aims:

1. To study glucose tolerance in patients with myocardial infarction and population based controls.

2. To assess the prevalence of glucose regulation categories in patients with acute and stable coronary artery disease.

3. To compare the different diagnostic modalities for recognising abnormal glucose regulation.

4. To investigate whether the glucometabolic state detected early after myocardial infarction relates to long-term prognosis.
MATERIAL AND METHODS

Definitions

**Coronary Artery Disease (CAD)** was defined, in studies II and III, as newly or previously diagnosed based on clinical information supported by at least one objective evidence. This included previous myocardial infarction revealed by a resting ECG, myocardial ischemia revealed by abnormal stress tests by means of exercise ECG, echocardiography, scintigraphy or magnetic resonance imaging, a coronary angiogram with more than 50% stenosis of lumen diameters in any major coronary artery or a previously documented cardiovascular event (hospitalisation for acute coronary syndrome, previous myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)) (38, 39).

**Acute myocardial infarction (MI)** was in all studies defined according to the joint recommendations by ESC and ACC (38) with markers of myocardial ischemia exceeding the upper reference limit at two occasions (troponin T > 0.05 g/l or CK-MB > 10 µg/l) in the presence of typical symptoms (chest pain > 15 min; pulmonary oedema in the absence of valvular heart disease, cardiogenic shock, ventricular tachycardia or ventricular fibrillation) or new Q-waves in at least two of the twelve standard ECG leads or ECG indicating acute ischemia (ST segment elevation, ST-depression or T-wave inversion).

**Previously known diabetes mellitus** was recognised if this diagnosis had been established before patient enrolment (study II only) and classified into four main etiological types, as diabetes type 1, type 2, gestational or other specific types (6).

**Glucometabolic status in patients without previously known diabetes** was classified into different categories according to diagnostic criteria issued by the World Health Organisation (6) and the American Diabetes Association (7, 8) as presented in Table 1.

Following the WHO recommendations, a standardised oral glucose tolerance test (OGTT; 75 g glucose in 200-250 ml water) was considered as “golden” standard for the assessment of glucose metabolism in all studies, unless the presence of overt hyperglycaemia (6).

**Heart failure** was recognised as recommended by European Society of Cardiology guidelines (6) based on clinical evidence with symptoms of heart failure (at rest or during exercise) in combination with objective evidence of cardiac dysfunction and in case of doubts supported by response to treatment directed towards heart failure.

**Hypertension** was accepted as present if treated prior to enrolment.

**Obesity** was recognised if body mass index (weight/height$^2$) BMI ≥ 30 kg/m$^2$.

**Dyslipidaemia** was applied as a term (studies I and IV) in the presence of HDL-cholesterol < 0.9 mmol/L in men and < 1.0 in women and/or triglycerides ≥ 1.7 mmol/L (6).

**Hyperlipidaemia** was recognised (studies II and III) in case of a lipid profile exceeding the reference limits recommended in the European Guidelines for Cardiovascular Disease Prevention (total cholesterol ≥ 5.0 mmol/L, HDL-cholesterol ≤ 1.0 mmol/L in men, or ≤ 1.1 mmol/L in women, triglycerides ≥ 2.0 mmol/L) or ongoing lipid-lowering treatment (52).

(To convert values from SI units to conventional units: 1 mmol/L cholesterol = 38.61 mg/dL, 1 mmol/L triglycerides = 88.5 mg/dL)

**Subjects and study protocols**

Studies included in the thesis are based on two different populations recruited in the GAMI study (Glucose tolerance in patients with Acute Myocardial Infarction; studies I and IV) and the Euro Heart Survey on diabetes and the heart (studies II and III), as summarised in Table 2.
Table 2. Summary of design, recruitment time and inclusion criteria in studies I-IV.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Time frame</th>
<th>N</th>
<th>Inclusion criteria</th>
<th>Age (years)</th>
<th>CAD type (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>GAMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>Prospective</td>
<td>1998 - 2000</td>
<td>181</td>
<td>No previously known diabetes</td>
<td>63</td>
<td>AMI (100), prior MI (20)</td>
</tr>
<tr>
<td>Controls</td>
<td>Population-based</td>
<td>2001 - 2002</td>
<td>185</td>
<td>AMI, &lt; 80 y, adm BG &lt; 11.1 mmol/L, C &lt; 200 μmol/L</td>
<td>63</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>EHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective survey</td>
<td>2003 - 2004</td>
<td>&gt; 18 years referred for CAD</td>
<td>4 961</td>
<td>66</td>
<td>AMI (27), UA (21), prior MI (44)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>EHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective survey</td>
<td>see above</td>
<td>Without known diabetes, IGT or IFG or specific treatment</td>
<td>3 362</td>
<td>65</td>
<td>AMI (28), UA (22), prior MI (43)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>GAMI</td>
<td></td>
<td></td>
<td>Patients with glucometabolic status classified before discharge</td>
<td>63</td>
<td>AMI (100)</td>
</tr>
</tbody>
</table>

Age median (years); y years; AMI - acute myocardial infarction; Adm BG - admission capillary blood glucose; C - serum creatinine at enrolment; CAD - coronary artery disease; CVD - cardiovascular disease; DM - known diabetes mellitus; IGT - impaired glucose tolerance; IFG - impaired fasting glucose; prior MI - myocardial infarction before recruitment; UA - unstable angina.

Figure 6. The Euro Heart Survey on diabetes and the heart. Red dots represent 110 participating centres from 25 ESC member countries, marked with blue colour.
The GAMI population. Studies I and IV

The GAMI population consists of patients (n=181) and population based control individuals (n=185). Patients with acute myocardial infarction and without known diabetes were prospectively enrolled when admitted to the coronary care units at the Karolinska and Västerås Hospitals in Sweden. Inclusion criteria comprised admission capillary blood glucose < 11.1 mmol/L, serum creatinine < 200 µmol/L, age ≤ 80 years. Patients were included if they were admitted on common working days and living within the catchment areas of the two hospitals. A total of 181 patients (125 men, 56 women, median age 63; Q1-Q3 57-71; years) were enrolled from November 1998 until December 2000 (Figure 4). Age and gender matched control subjects, without cardiovascular artery disease apart from mild hypertension, were prospectively recruited from the population registry between January 2001 and July 2002 (n=185; 127 men, 58 women; median age 64, Q1-Q3: 58-72 years; Figure 5).

Euro Heart Survey on diabetes and the heart, Studies II and III

Consecutive patients, above the age of 18 years, were screened for a diagnosis of coronary artery disease when admitted to hospital cardiology wards or visiting outpatient clinics in multiple participating centres across Europe. Enrolment of patients was initiated on February 10, 2003 and continued until January 16, 2004 with starting time varying between countries and

---

**Figure 4.** The GAMI study - Patients flow chart.

**Figure 5.** The GAMI study- recruiting control subjects
centres. The total survey cohort comprised 4,961 patients with confirmed coronary artery disease who were recruited within 2 to 12 weeks at 110 centres from 25 European Society of Cardiology member countries (Figure 6). Patients were enrolled either in a course of Acute admissions or Elective consultations based on the presentation at enrolment as outlined in Figure 7. Study III was limited to the 3,362 patients without previously known diabetes (n=1,524), impaired glucose tolerance, impaired fasting glucose or those receiving glucose lowering medication (n=75), as detailed in Figure 8.

Study protocols

Study I Metabolic characteristics were compared between patients and controls by means of various biochemical measures assessed in the early phase after acute myocardial infarction, before hospital discharge and three months thereafter in patients and at the enrolment visit of control subjects. The lipid profile included total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), triglycerides, apolipoprotein B and lipoprotein (a) Lp(a) measured after 12 hours fasting on the first morning following admission for patients and at the enrolment of control subjects. Plasma concentrations of plasma fibrinogen, high sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor type 1 (PAI-1) activity and cortisol were determined for the patients before hospital discharge (day 4-7) and three months thereafter and at the enrolment of control subjects. Plasma insulin and intact proinsulin were quantified in blood sampled fasting at the first morning following admission of patients and during OGTT testing (at 0 and 120 minutes) performed at enrolment of controls and before hospital discharge (n=168).

Laboratory measurements

Glucose measurements

In studies I and IV glucose concentration was measured in whole capillary blood immediately after sampling by means of a HemoCue® portable photometer (HemoCue® AB, Ängelholm, Sweden). This equipment, which is based on a glucose dehydrogenase reaction, has a coefficient of variation \( \leq 3.5\% \) (135). In studies II and III glycaemia was analysed according to local routines, if possible in venous plasma, but otherwise in venous whole blood or capillary whole blood. Glucose concentrations derived from different types of samples were converted to venous plasma glucose, expressed in mmol/L, before final data analysis. Conversion factors were those established by the European Diabetes Epidemiology Group and implemented in the analysis of DECODE study (136):

\[
\text{plasma glucose} = 0.558 + 1.119 \times \text{capillary whole blood glucose (mmol/L)}
\]

\[
\text{plasma glucose} = 0.102 + 1.066 \times \text{venous whole blood glucose (mmol/L)}
\]

(To convert values from SI units to conventional units 1 mmol/L = 18 mg/dL)

Oral glucose tolerance test (OGTT)

The OGTT was performed in a stable, fasting condition in patients before hospital discharge (studies I and IV) and three months thereafter...
Glucose regulation and coronary artery disease

(Figure 4) and at the enrolment of control subjects. In studies II and III OGTT was conducted within two months following the index consultation. Glucose metabolism was then categorised into three glucose tolerance categories (studies I and IV; Table 3) or several classes of glucose regulation (studies II and III; Table 1).

Table 3. Criteria for glucometabolic classification according to WHO (6) based on capillary whole blood measurements. Studies I and IV.

<table>
<thead>
<tr>
<th>Glucose tolerance</th>
<th>Classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (NGT)</td>
<td>FBG &lt; 6.1 and 2-h BG &lt; 7.8</td>
</tr>
<tr>
<td>Impaired (IGT)</td>
<td>FBG &lt; 6.1 and 2-h BG ≥ 7.8 and &lt; 11.1</td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td>FBG ≥ 6.1 or 2-h BG ≥ 11.1</td>
</tr>
</tbody>
</table>

Glycosylated haemoglobin A1c (HbA1c) was analysed in all studies by high-performance liquid chromatography on whole blood applied on filter paper (Boehringer Mannheim Scandinavian AB, Bromma, Sweden (137) in a Swedish core laboratory, at the Department of Laboratory Medicine, Malmö Allmänna Sjukhus (studies I and IV) or at the Department of Clinical Chemistry, Karolinska University Hospital, Solna (studies II and III). The upper normal limits and the coefficients of variation (CV) were 5.3% with CV <3% (studies I and IV) and 5.2% with CV of 2.2 and 2.6% for HbA1c at the levels 4.5 and 9.2% (studies II and III). The results obtained with this method can be compared and recalculated to the IFCC standard:

Swedish-HbA1c = 0.989 • IFCC-HbA1c + 0.88%; r²=0.996 (138).

Lipid profile

Total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were measured in the fasting state within 24 hours.
following admission by standard methods. HDL-cholesterol was quantified enzymatically by means of Genzyme liquid N-geneous HDL-cholesterol Assay on a Mitachi 911 instrument (Boehringer Mannheim, Mannheim, Germany) in studies I and IV and according to the local laboratory practice in studies II and III.

Other biochemical parameters
In studies I and IV plasma insulin and intact proinsulin were quantified with commercially available immunoassays (DAKO Ltd, Cambridgeshire, the UK). Plasma fibrinogen was determined by a functional assay using the IL Test Fibrinogen C kit (Instrumentation Laboratory Spa, Milan, Italy) and high-sensitivity C-reactive protein (hs-CRP) was determined by an ultra sensitive latex-enhanced immunoassay (BN II instrument, Dade Boehringer, Marburg GmbH, Germany).

Insulin resistance was estimated in studies I and IV at a fasting steady state by homeostasis model assessment (HOMA), calculated according to a following formula:

\[
IR = \frac{\text{Insulin} (\text{pmol/L}) \times \text{Fasting blood glucose} (\text{mmol/L}) \times 1.13 (\text{correction for plasma glucose})/22.5 \times 6 (\text{recalculation pmol to mU})}{22.5 \times 6 (\text{recalculation pmol to mU})}
\]

Plasma proinsulin and proinsulin-insulin ratio (Proins/Ins ratio) were considered as indicators of β-cell dysfunction (140).

**Statistical methods**
Continuous variables are summarised as medians with lower and upper quartiles and categorical variable as counts and proportions (%). Formal statistical comparisons were not applied in the descriptive study II. In study I the differences in the metabolic features between patients and controls were tested by means of the Wilcoxon Mann-Whitney rank sum test with corresponding 95% confidence intervals (CI) for the continuous variables. For the categorical variables logistic regression was used to estimate odds ratios with 95% CI. The profiles of selected variables with respect to glucose tolerance categories were analysed by a non-parametric test for interactions based on aligned ranks. Depending on the result of this test either a stratified Wilcoxon rank sum test or a Wilcoxon Mann-Whitney rank sum test within each glucose tolerance category was performed (141, 142).

In study III, the degree of coherence between the outcomes of OGTT and the ADA criteria was assessed by Cohan’s κ, the chance corrected proportional agreement (143). Attempts to predict glucometabolic classification based on OGTT were performed by applying a single hidden layer neural network and ordinal logistic regression (144, 145).

![Figure 8](image-url)

**Figure 8.** The Euro Heart Survey on Diabetes and the Heart. Study III.

# Diabetes was diagnosed after consultation/ at discharge in 84 patients who did not undergo OGTT but had an overt hyperglycaemia at enrolment in form of random plasma glucose ≥ 11.1 (n= 13) or fasting plasma glucose ≥ 7.0 mmol/L (n= 71).
In study IV the differences of baseline characteristics between patients grouped by glucose tolerance status were compared by Chi square test, two-tailed Fisher’s exact test or Wilcoxon Mann-Whitney rank-sum test, as appropriate. Kaplan-Meier curves were computed for the composite endpoint of major cardiovascular events and Gehan’s generalised Wilcoxon rank sum test was used to compare patients with normal and abnormal glucose tolerance. Cox proportional hazard regression was used to find risk factors for the composite endpoint. A simple Cox regression was used to identify the candidate predictors of cardiovascular events (p < 0.2; 146, 147). A best subset Cox regression was then run using the candidate predictors. The Akaike’s information criterion and a manual elimination of risk factors based on medical considerations were used to obtain a parsimonious model with good predictive capability. The final model included only predictors with a significant contribution (p<0.05; 148, 149).

In all analysis a two sided p value below 0.05 was considered significant, except when testing for interactions in which case a two sided p value below 0.10 was considered significant, since tests for interactions usually have low power (study I). When searching for candidate predictors of an outcome (studies III and IV) those with a p value below 0.20 were considered.

**Ethical considerations**

All studies complied with the Declaration of Helsinki. The protocol for studies I and IV (GAMI) was approved the Ethics Committee of the Karolinska Institute and all subjects enrolled gave their written informed consent. The protocol for the Euro Heart Survey on Diabetes and the Heart (studies II and III) was approved by the Ethics Committee of the Karolinska Institute. National Co-ordinators ascertained that requirements for ethical approval were adhered to in each participating country. Based on local routines the patients were recruited following oral or written informed consent.
RESULTS

Glucose tolerance in patients and population-based controls. Study I.

The prevalence of abnormal glucose tolerance was approximately twice as common among patients, irrespectively whether assessed before hospital discharge (number/all classified) 113/168 (67%) or after three months 95/145 (66%), as in controls 65/185 (35%) (p <0.001). Abnormal glucose tolerance in the control population was associated with hypertension (p= 0.006) and the use of beta-blockers (p= 0.011), while obesity and female gender were of borderline significance within the patient cohort. The distribution on different classes of glucose tolerance is outlined in Figure 9.

Metabolic differences between patients and controls

Dyslipidaemia (70% vs. 29%; OR= 5.72; CI: 1.91 – 3.00), smoking (34% vs. 11%; OR= 4.00; CI: 2.31 – 6.93), treated hypertension (32% vs. 18%; OR= 2.04; CI: 1.25 - 3.32) and hyperlipidaemia (15% vs. 8%; OR= 2.14; 1.108 - 4.23) were more common in patients while the presence of obesity (18% vs. 24%) and microalbuminuria (11% vs. 5%) did not differ significantly from controls. The metabolic differences between patients and controls were more pronounced than differences in conventional risk factors.

A multiple logistic regression model including age, gender, family history of diabetes, obesity (BMI ≥ 30 kg/m²), lipid parameters, HbA1c and hsCRP (at enrolment) and blood glucose, proinsulin, free fatty acids, fibrinogen (measured in patients before discharge; day 5) was built to identify significant parameters taking into account the history of treated hypertension or hyperlipidaemia, smoking status and medication (beta blockade, ACE inhibitors, diuretics and statins). All elements that contributed significantly, thereby allowing to distinguish patients from controls, are presented in Table 4. The best subset model enabled correct classification of 92% controls and 86% patients.

Three months after the index admission patients had significantly higher HbA1c, plasma proinsulin and fibrinogen (p < 0.001 for each) even following adjustment for glucose tolerance (Table 5; Figure 10 a, b, d). Insulin resistance assessed by HOMA did, however, not distinguish patients from controls (p= 0.143; Figure 10 c). The majority of the biochemical features were characteristic for patients irrespectively whether assessed before hospital discharge or

![Figure 9. The GAMI study - classification of glucose tolerance. Studies I and IV. Normal glucose tolerance , Impaired glucose tolerance , Diabetes .](image-url)
Table 4. Metabolic parameters that enable discern patients from control subjects. Study I. Data present a best subset model with a group (patient or control) as dependent variable and the significant predictors that enabled correct classification of 92% controls and 86% patients.

<table>
<thead>
<tr>
<th>Metabolic and clinical parameters</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.58</td>
<td>(2.17, 5.90)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>3.50</td>
<td>(1.07, 11.37)</td>
<td>0.038</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3.28</td>
<td>(1.42, 7.61)</td>
<td>0.006</td>
</tr>
<tr>
<td>Beta blockade</td>
<td>3.27</td>
<td>(1.38, 7.72)</td>
<td>0.007</td>
</tr>
<tr>
<td>HbA1c (%) at enrolment</td>
<td>1.98</td>
<td>(1.08, 3.61)</td>
<td>0.026</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.88</td>
<td>(1.22, 2.91)</td>
<td>0.005</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>1.15</td>
<td>(1.08, 1.23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Proinsulin (pmol/L)</td>
<td>1.10</td>
<td>(1.02, 1.19)</td>
<td>0.021</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>0.59</td>
<td>(0.40, 0.86)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Table 5. Metabolic parameters compared between patients and controls with respect to glucose tolerance. Patients classified by an OGTT three months after the index myocardial infarction. Study I.

<table>
<thead>
<tr>
<th>Metabolic parameters</th>
<th>Normal</th>
<th>IGT</th>
<th>Diabetes</th>
<th>Patients</th>
<th>Controls</th>
<th>Profiles</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>50</td>
<td>120</td>
<td>59</td>
<td>45</td>
<td>36</td>
<td>20</td>
<td>p</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.8</td>
<td>4.5</td>
<td>4.9</td>
<td>4.7</td>
<td>5.3</td>
<td>5.1</td>
<td>0.521</td>
</tr>
<tr>
<td>Insulin baseline (pmol/L)</td>
<td>47</td>
<td>45</td>
<td>51</td>
<td>48</td>
<td>71</td>
<td>71</td>
<td>0.224</td>
</tr>
<tr>
<td>Proinsulin baseline (pmol/L)</td>
<td>5.5</td>
<td>2.2</td>
<td>5.2</td>
<td>2.7</td>
<td>8.4</td>
<td>5.5</td>
<td>0.170</td>
</tr>
<tr>
<td>Proins/Ins ratio baseline (%)</td>
<td>11</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>12</td>
<td>8</td>
<td>0.426</td>
</tr>
<tr>
<td>Insulin resistance (HOMA)</td>
<td>1.9</td>
<td>1.8</td>
<td>2.2</td>
<td>2.2</td>
<td>3.4</td>
<td>3.3</td>
<td>0.130</td>
</tr>
<tr>
<td>PAI-1 (IU/ml)</td>
<td>8.3</td>
<td>7.2</td>
<td>9.5</td>
<td>9.2</td>
<td>12.0</td>
<td>7.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.9</td>
<td>3.8</td>
<td>3.9</td>
<td>3.7</td>
<td>4.0</td>
<td>3.7</td>
<td>0.758</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>457</td>
<td>431</td>
<td>482</td>
<td>432</td>
<td>487</td>
<td>448</td>
<td>0.320</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>1.3</td>
<td>1.6</td>
<td>1.7</td>
<td>2.0</td>
<td>3.0</td>
<td>2.3</td>
<td>0.026</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.8</td>
<td>1.1</td>
<td>2.0</td>
<td>1.3</td>
<td>2.5</td>
<td>1.4</td>
<td>0.004</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.18</td>
<td>1.25</td>
<td>1.19</td>
<td>1.16</td>
<td>1.06</td>
<td>1.07</td>
<td>0.358</td>
</tr>
</tbody>
</table>

All parameters but lipids were obtained in patients 3 months after the index infarction and at enrolment of controls. * measured within 24 hours after patient admission; Insulin resistance by homeostasis model assessment; PAI-1 Plasminogen activator inhibitor type 1; hs-CRP high sensitivity C- reactive protein; Proins/Ins ratio - Proinsulin / Insulin ratio; $ statistical comparison between patients and controls was made separately within each glucose tolerance category. Levels of significance are marked in the respective columns as ns - not significant; * p<0.05; *** p<0.001.
three months later (Figure 10; Tables 4 and 5). The most prominent differences comprised increased plasma proinsulin ($p < 0.001$), fibrinogen ($p < 0.001$), HbA1c ($p < 0.001$) and triglycerides ($p < 0.01$), which separated patients from controls even when controlled for glucose tolerance (Figure 10; Table 5).

**Prevalence of abnormal glucose regulation in CAD. Study II.**

Out of 4,961 patients, 2,107 were recruited at the occasion of an acute hospital admission due to coronary artery disease that was newly diagnosed in 50% of the cases. The remaining 2,854 subjects were enrolled during an elective consultation, of out of whom 60% were seen in the outpatient clinic (Figure 7, Table 6).

**Previously known diabetes**

Previously known diabetes as revealed by medical records, patient interviews or the use of specific glucose lowering medication was reported in 1,524 (31%) patients. There were certain differences in the prevalence of prior diabetes as well as basic characteristics among patients enrolled in the four European regions (150) as shown in Table 7.

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**Figure 10.** Comparison of metabolic features across glucose tolerance categories between patients assessed before discharge (black boxes), after three months (gray boxes) and controls (white boxes): HbA1c (a), Proinsulin (b), Insulin resistance (c), Triglycerides (d) and Fibrinogen (e). Study I. Boxes span the 25% to 75% percentiles and whiskers non-outlier minimum and maximum values; numbers are median values (outliers, extremes not displayed).
Table 6. Study II population: medical history and pharmacological treatment at enrolment.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient group</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td></td>
<td>Acute 2107 (42.5%)</td>
<td>Elective 2854 (57.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>1044 (50)</td>
<td>2577 (89)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>685 (33)</td>
<td>1505 (53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary intervention (PCI, CABG)</td>
<td>451 (21)</td>
<td>1318 (46)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>404 (19)</td>
<td>704 (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1329 (63)</td>
<td>1917 (67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>1022 (49)</td>
<td>2057 (72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>136 (7)</td>
<td>140 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>233 (11)</td>
<td>513 (18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus previous diagnosis</td>
<td>664 (32)</td>
<td>860 (30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>type 1; type 2; other type (%)$</td>
<td>36 (5); 625 (94); 3 (1)</td>
<td>59 (7); 796 (93); 5 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>795 (38)</td>
<td>2006 (70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE- inhibitors or ARBs</td>
<td>961 (46)</td>
<td>1729 (61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>509 (24)</td>
<td>802 (28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>541 (26)</td>
<td>958 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>735 (35)</td>
<td>1933 (68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>926 (44)</td>
<td>2062 (72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel or Ticlopidine</td>
<td>183 (9)</td>
<td>448 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Treatment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drugs/ Insulin/ OAH/ Combined</td>
<td>16 / 29 / 50 / 5</td>
<td>13 / 25 / 56 / 6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as count (%); $ proportion out of patients with diabetes diagnosed prior to enrollment; OAH - Oral Anti-Hyperglycaemic agents.

Table 7. Patients characteristics in relation to the geographical region of recruitment. Study II.

<table>
<thead>
<tr>
<th>Region</th>
<th>Centres number</th>
<th>Patients</th>
<th>Age median</th>
<th>Acute $^1$</th>
<th>DM $^2$</th>
<th>HF</th>
<th>Smoking</th>
<th>OGGT $^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>6</td>
<td>272</td>
<td>66</td>
<td>51</td>
<td>27</td>
<td>13</td>
<td>12</td>
<td>87</td>
</tr>
<tr>
<td>Central</td>
<td>39</td>
<td>1 381</td>
<td>63</td>
<td>52</td>
<td>30</td>
<td>19</td>
<td>23</td>
<td>75</td>
</tr>
<tr>
<td>Western</td>
<td>23</td>
<td>1 359</td>
<td>68</td>
<td>29</td>
<td>24</td>
<td>18</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>42</td>
<td>1 949</td>
<td>68</td>
<td>44</td>
<td>36</td>
<td>23</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>4 961</td>
<td>66</td>
<td>2 107</td>
<td>1 524</td>
<td>20</td>
<td>21</td>
<td>1 920</td>
</tr>
</tbody>
</table>

Data are presented as count and proportion (%) of patients enrolled in each region.

1 Acute - proportion of acute admissions; 2 DM - diagnosis of diabetes mellitus established before enrollment; HF - known heart failure; Smoking - current smoking; 3 OGGT - proportion of patients without previously known diabetes in whom an oral glucose tolerance was performed within 2 months since recruitment.

Regions defined as: Northern (Finland, Sweden and UK), Central (Belarus, Bulgaria, Czech Republic, Estonia, Georgia, Hungary, Lithuania, Macedonia, Poland, Romania and Slovenia), Western (Austria, France, Germany, the Netherlands and Switzerland) and Mediterranean (Cyprus, Greece, Italy, Portugal, Spain and Egypt), ref 150.
Table 8. Glucose regulation in patients with acute or stable CAD presentation in relation to the region of enrolment. Study II.

<table>
<thead>
<tr>
<th>Region</th>
<th>NGR (row %)</th>
<th>IFG (row %)</th>
<th>IGT (row %)</th>
<th>DM (row %)</th>
<th>count</th>
<th>NGR (row %)</th>
<th>IFG (row %)</th>
<th>IGT (row %)</th>
<th>DM (row %)</th>
<th>count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>47.5</td>
<td>2.5</td>
<td>38.8</td>
<td>11.3</td>
<td>80</td>
<td>62.0</td>
<td>4.3</td>
<td>26.1</td>
<td>7.6</td>
<td>92</td>
</tr>
<tr>
<td>Central</td>
<td>53.6</td>
<td>3.3</td>
<td>29.4</td>
<td>13.6</td>
<td>360</td>
<td>59.2</td>
<td>6.3</td>
<td>22.7</td>
<td>11.8</td>
<td>365</td>
</tr>
<tr>
<td>Western</td>
<td>38.7</td>
<td>6.5</td>
<td>33.9</td>
<td>21.0</td>
<td>62</td>
<td>47.7</td>
<td>3.9</td>
<td>34.2</td>
<td>14.2</td>
<td>155</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>31.8</td>
<td>5.0</td>
<td>32.3</td>
<td>30.9</td>
<td>421</td>
<td>36.1</td>
<td>4.4</td>
<td>41.6</td>
<td>17.9</td>
<td>385</td>
</tr>
<tr>
<td>Total count</td>
<td>389</td>
<td>39</td>
<td>294</td>
<td>201</td>
<td>923</td>
<td>486</td>
<td>50</td>
<td>320</td>
<td>141</td>
<td>997</td>
</tr>
<tr>
<td>Total %</td>
<td>42.1</td>
<td>4.2</td>
<td>31.9</td>
<td>21.8</td>
<td></td>
<td>48.7</td>
<td>5.0</td>
<td>32.1</td>
<td>14.1</td>
<td></td>
</tr>
</tbody>
</table>

Hidden abnormalities of glucose metabolism
Out of 3,437 patients without previously known diabetes, 3,041 (88%) had blood glucose concentration measured at enrolment (random or fasting) and 1,920 (56%) underwent an OGTT. The OGTT outcomes with respect to geographical region and clinical condition at enrolment are presented in Table 8. The proportion of normal glucose regulation was somewhat lower among patients with acute than stable presentation of CAD while the opposite was true for newly detected diabetes. If glucose metabolism would have been assessed by fasting glycaemia only, as suggested by ADA (7), less than half of patients with an abnormal glucose regulation revealed by an OGTT, recommended by WHO (6), would have been disclosed. According to WHO the diagnosis of

Table 9. Glucometabolic classification according to the WHO (OGTT) and ADA criteria (FPG). Study III.

<table>
<thead>
<tr>
<th>Classification by 1999 WHO criteria</th>
<th>ADA criteria 1997</th>
<th>WHO total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>IFG</td>
</tr>
<tr>
<td>1999 WHO criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGR</td>
<td>870 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>IGR (IGT± IFG)</td>
<td>494 (72.9)</td>
<td>184 (27.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>145 (45.4)</td>
<td>88 (27.6)</td>
</tr>
<tr>
<td>ADA Total (%)</td>
<td>1509 (80.8)</td>
<td>272 (14.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1999 WHO criteria</th>
<th>ADA criteria 2004</th>
<th>WHO total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>IFG</td>
</tr>
<tr>
<td>1999 WHO criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGR</td>
<td>717 (82.4)</td>
<td>153 (17.6)</td>
</tr>
<tr>
<td>IGR (IFG ± IGT)</td>
<td>385 (56.8)</td>
<td>293 (43.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>93 (29.1)</td>
<td>140 (43.9)</td>
</tr>
<tr>
<td>ADA Total (%)</td>
<td>1195 (64.0)</td>
<td>586 (31.4)</td>
</tr>
</tbody>
</table>

Data are presented as counts and row percent (%). FPG - Fasting Plasma Glucose; NGR - Normal Glucose Regulation; IGT - Impaired Glucose Tolerance; NFG - Normal FPG; IFG - impaired FPG according to ADA or WHO criteria respectively (mmol/L).

Among those with IFG according to ADA criterion 1997: 87 (32.0%) IFG only and 97 (35.7%) IGT+IFG; 2004: 109 (18.6%) IGT only and 97 (16.6%) IGT+IFG.
diabetes does not require testing with a glucose load in case of overt hyperglycaemia. Out of 1170 patients who were not tested with OGTT but had blood glucose measured at least at enrolment, 86 (7.4%) with a random plasma glucose $\geq 11.1$ or fasting plasma glucose $\geq 6.1$ mmol/L got a final diagnosis of diabetes mellitus. Thus, the total prevalence of hidden diabetes was somewhat higher than that estimated based on performed OGTT.

**Projection of glucometabolic state in the entire patient population**

Assuming that the results of OGTT would have been similar among all patients without previously known glucose disturbances in this survey as in those without any previously known glucose abnormalities in which an OGTT was performed (study III; Table 9) and accounting also for patients with already known diabetes mellitus the complete pattern of glucose metabolism amongst patients with CAD would have been as presented in Figure 11. Overall 46% of the patients with acute and 40% with stable manifestation of CAD would have been classified as having diabetes mellitus while only 29 and 34% respectively would have had normal glucose metabolism.

**Comparison of diagnostic approaches for glucometabolic assessment. Study III.**

**Fasting glycaemia or OGTT**

The outcome of glucometabolic classification of patients with CAD without previous glucose disturbances according to WHO 1999, ADA 1997 and ADA 2004 is summarised in Table 9. Elevated fasting glucose concentrations $> 6.1$ or $> 5.6$ mmol/L were found in 19% (n = 358) and 36% (n = 672) of the patients, respectively, while abnormal glucose regulation recognised by means of OGTT comprised 53% (n = 997) of all participants. The proportion of patients with IGT (n = 591) who had IFG varied from 16% (n = 97) to 35% (n = 206) following the ADA 1997 or 2004 criterion. The prevalence of different stages of glucose regulation among patients who underwent an OGTT is shown in Figure 12, while the prevalence of various categories of fasting and post load glycaemia is presented in Figure 13. If only fasting blood glucose had been used for glucometabolic evaluation glucose disturbances would have remained undetected in 21% of all patients having an isolated IGT and additional 5% with a post load glycaemia in the diabetic range (Figure 13).

**Mathematical modelling to reduce the need for glucose tolerance testing**

Several variables related to the metabolic status such as age, fasting plasma glucose, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure and BMI or waist and hip circumferences are ordinarily included within laboratory and examination routines at cardiology wards and outpatient clinics. Attempts were made to improve identification of subjects with hidden hyperglycaemia by means of algorithms including commonly available

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**Figure 11.** Estimated pattern of glucose regulation in the entire patient population in Study II.
clinical and laboratory parameters together with age, gender and HbA1c as candidate predictors. All possible combinations of these variables were fitted and the models were compared with respect to the proportion of misclassified patients. In a subsequent attempt to improve the diagnostic model the finally selected variables were used as input to a neural network.

A single hidden layer back-propagation network model including fasting glycaemia, HDL-cholesterol and age reached a high diagnostic accuracy, correctly identifying 96% of all patients, who by means of the OGTT were classified as having abnormal glucose regulation (Table 10). The discriminative property of the neural network model with the hidden variables \( h_1 - h_3 \) is demonstrated by a three dimensional scatter-plot, Figure 14, where \( h_1 \) is a weighted mean of fasting plasma glucose, age and HDL-cholesterol (the latter with reversed sign), \( h_2 \) is a function of age while \( h_3 \) is a function of fasting plasma glucose. The neural network algorithm may identify patients with abnormal glucose regulation (IGR or DM) and thereby reduce the need for OGTT by 25%.
Glucose regulation and coronary artery disease

During 34 months of follow-up there were eight cardiovascular deaths, six strokes, 15 recurrent myocardial infarctions and 10 cases of severe heart failure. All patients who died from cardiovascular causes had an abnormal glucose tolerance before hospital discharge. Out of 168 patients, in whom glucometabolic status was classified before discharge, 31 (18%) experienced at least one major cardiovascular event. The relative frequencies of various cardiovascular events are shown in Figure 15.

Abnormal glucose tolerance predictor of long-term prognosis

The probability of remaining free from any cardiovascular event was significantly poorer in patients with abnormal than normal glucose tolerance (p=0.0017). As revealed in Figure 16 Kaplan-Meier curves presenting time to the first cardiovascular event diverged widely for patients with normal and abnormal glucose tolerance. Apart from previous myocardial infarction, abnormal glucose tolerance (newly detected IGT or DM) was the strongest predictor of future cardiovascular events (Table 11).

**Table 10.** Glucose regulation predicted by neural network model, including fasting plasma glucose, age and HDL-cholesterol applying ten-fold cross validation. Study III.

<table>
<thead>
<tr>
<th>OGTT</th>
<th>Neural network</th>
<th>Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGR</td>
<td>446 (95.5)</td>
<td>21 (4.5)</td>
</tr>
<tr>
<td>IGR</td>
<td>236 (67.6)</td>
<td>102 (29.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>59 (33.9)</td>
<td>51 (29.3)</td>
</tr>
<tr>
<td>Total</td>
<td>741 (74.8)</td>
<td>174 (17.6)</td>
</tr>
</tbody>
</table>

Data presented as counts (row %); NGR - normal glucose regulation; IGR - impaired glucose regulation.

**Glucose tolerance and long-term prognosis after MI. Study IV.**

**Figure 14.** Glucometabolic classification by means of the neural network model with three hidden variables. The first hidden variable (h1) is a function of a weighted mean of fasting plasma glucose, age and HDL-cholesterol (the last with negative sign). The second (h2) is a function of age and the third (h3) is a function of fasting plasma glucose with negative sign.
Figure 15. Major cardiovascular events in relation to glucose tolerance. Study IV.
Relative frequency of each cardiovascular event recorded among patients in different glucose tolerance categories. Reported events comprising severe heart failure, nonfatal re-infarction (Re-MI), nonfatal stroke, cardiovascular (CV) death and total number of events (Any) are presented as crude proportions (number of events displayed as labels within bars).

Figure 16. Time to the first major cardiovascular event. Study IV.
Kaplan-Meier curves for patients with normal (dashed line) and abnormal glucose tolerance (solid line). The Wilcoxon test for difference between groups, p=0.0017. Numbers below graph represent number of patients at risk at different times of observation.

Table 11. Adjusted risks for major cardiovascular events. Cox proportional hazard regression. Study IV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Myocardial Infarction</td>
<td>0.001</td>
<td>3.38</td>
<td>1.62 – 7.04</td>
</tr>
<tr>
<td>Abnormal Glucose Tolerance</td>
<td>0.019</td>
<td>4.18</td>
<td>1.26 – 13.84</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>0.037</td>
<td>3.68</td>
<td>1.08 – 12.49</td>
</tr>
</tbody>
</table>
Abnormal glucose regulation is very common among patients with coronary artery disease. Since this condition does not cause specific symptoms and as a majority of patients do not have overt hyperglycaemia the inadequate glucose homeostasis usually remains unrecognised in clinical practice. Hidden diabetes and impaired glucose tolerance are almost twice as common in patients with myocardial infarction as in subjects without cardiovascular disease. An abnormal glucose regulation is indeed more common than a normal glucose metabolism in patients with various manifestations of coronary artery disease. Measuring fasting glycaemia only does not permit proper identification of a majority of affected patients even when applying the most recent, diagnostic criteria proposed by ADA in 2004 (8). Sophisticated diagnostic algorithms, based on commonly available clinical and laboratory data, do not replace the need for glucometabolic classification by means of a glucose tolerance test.

Newly detected abnormal glucose tolerance is one of the strongest predictors of long-term prognosis after myocardial infarction. Thus, early assessment of glucose regulation is important in cardiology practice, enabling identification of patients at high risk for subsequent major cardiovascular events, adequate risk stratification and the initiation of intensive secondary preventive measures.

The prevalence of known diabetes
The prevalence of previously known diabetes accounting for 31% patients in Study II, is higher than the 18 to 20% usually reported from controlled clinical trials (GUSTO-IIb; 131) and registries (OASIS; 130; RIKS-HIA; 76). This discrepancy may have several explanations. It is well recognised that patients enrolled in clinical trials are selected and not entirely representative of a general population. It is common to exclude from clinical trails elderly and sicker patients, among whom diabetes is more frequent. The Swedish RIKS-HIA does not include patients above the age of 80 years. Moreover the Euro Heart Survey required a thorough and focused medical history regarding a prior diagnosis of diabetes or IGT, previous gestational diabetes and the use of defined blood glucose lowering medication. This may have contributed to an improved awareness of the glucometabolic state than that obtained in ordinary clinical routine. An alternate explanation is a changing phenotype of patients with myocardial infarction with an increasing prevalence of diabetes in this population. As reported by Gu et al (127), in the United States there has been a successive decline of cardiovascular mortality in patients with CAD and without diabetes, however, not among those with concomitant diabetes. This may contribute to an increase in the proportion of patients with diabetes in the population with coronary artery disease. An increasing prevalence of diabetes over time was recently described by Takaishi et al (151) who studied coronary risk factors of hospitalised patients with coronary artery disease. During the decade 1993 to 2003 the prevalence of diabetes increased from 25 to 45% and the corresponding proportions of IGT were 6 and 11%. It may be possible that the present findings represent a similar trend in Europe. It is noteworthy that in the EUROASPIRE II survey an unrecognised diabetes was revealed in 8% of 4 489 patients with stable coronary artery disease, only by reviewing fasting blood glucose measurements, increasing the prevalence from 20 to 28% (152).

The prevalence of hidden hyperglycaemia
The coincidence of disturbed glucose homeostasis and acute myocardial infarction has been
recognised since a first report by Levine 1922 (62). It was initially experienced as a transitory phenomenon related to stress caused by the acute condition (67). Interpretation of these early observations were, however, complicated by several reasons including varying, not yet standardised methods for glucose loads, lacking definitions for hyperglycaemic states and rather small groups of not always well defined patients. Furthermore observations made during the initial phase of the disease were not systematically followed over time. The report by Norhammar et al (78) that two thirds of patients with acute myocardial infarction and no prior diabetes had abnormal glucose tolerance not only in the early phase following a myocardial infarction but also three months thereafter, supported the conclusion that this observation represents truly impaired glucose homeostasis. It did, however, also raise questions regarding the glucometabolic state in the population from which these patients originated. This was the reason to investigate control individuals without cardiovascular disease originating from the respective local municipal registries as reported in Study I. The majority of these subjects had normal glucose homeostasis. A similar observation was reported by Gerstein et al (153), who investigated patients with acute myocardial infarction and controls in a South Asian population. However, their study included individuals with known diabetes. Recent reports from Swedish epidemiological studies confirm that normal glucose tolerance is the most common state (59 - 93%) in the general population, varying with age and gender (154-158). The data from international study populations in which the 1999 WHO criteria were applied the prevalence of hidden diabetes ranged between 3 – 18 % and IGT between 7 - 29 % (Table 12; 158-164), varying with age, gender and ethnicity. These proportions are considerably lower than those found among the patients in study I.

The somewhat surprising outcome of Study I, which recruited a relatively modest number of patients from a defined geographical area in Sweden, made it important to study the relation between glucose metabolism and coronary artery disease in a broader perspective. This was the background to the multicenter European Heart Survey on diabetes and the heart (studies II and III) recruiting 4 961 patients with acute and stable manifestations of coronary artery disease from 110 centres in 25 countries. This survey confirmed that hidden hyperglycaemia is very common in patients with acute coronary syndromes and disclosed that this is true even among patients with stable manifestations of coronary artery disease. Reviewing the reports concerning patients with CAD, in all but one (166) IGT was the most prevalent category of the clinical stages of hyperglycaemia comprising 18 to 37% of the patients with a relatively low variation between clinical manifestation and geographical area (Table 13; 153, 165-170). The frequency of newly detected diabetes, assessed by an OGTT, ranged from 17 to 43%. Indeed, the overall prevalence of newly detected abnormal glucose regulation accounted for more than half of the patients subjected to an OGTT in Study II. These results are concordant with recent reports from various patient cohorts with different disease manifestations, including several ethnic groups (153, 165-170). In studies that reported only on fasting glycaemia, the prevalence of newly recognised diabetes ranged from 6 to 18% (Table 13; 152, 171-173), what is actually higher than the 5% found in study III. These data indicate that if anything the prevalence of previously undetected diabetes in studies II and III is underestimated. However, according to WHO, an OGTT is not required in the presence of an overt hyperglycaemia or at least two recordings of fasting or random blood glucose in the diabetic range (6). Among participants, not tested with a glucose load in the Euro Heart Survey, diabetes was newly diagnosed in 7%, who had elevated fasting or random blood glucose reported at enrolment.

**Methodological concerns**

An important question is whether the patients in the Euro Heart Survey on Diabetes and the Heart are representative for a general population of patients with coronary artery disease. It may be difficult to ensure correct enrolment of patients in a survey. Great emphasis was therefore put on correcting and completing the database
Table 12. Glucose regulation in the general populations described in different studies (based on OGTT).

<table>
<thead>
<tr>
<th>First author (ref. number)</th>
<th>publication year country</th>
<th>Time period</th>
<th>Inclusion criteria</th>
<th>Number</th>
<th>Age (years)</th>
<th>F (%)</th>
<th>Diabetes (%)</th>
<th>IGT (%)</th>
<th>NGT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlsson S (154)</td>
<td>2000 Sweden</td>
<td>1992-1994</td>
<td>Men aged 35-56 from 4 municipalities of Stockholm</td>
<td>3 128</td>
<td>35-56</td>
<td>0</td>
<td>Excl.</td>
<td>1.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Rolandsson S (155)</td>
<td>1999 Sweden</td>
<td>1988-1992</td>
<td>Västerbotten County Health Project (Lycksele)</td>
<td>2 157</td>
<td>30-60</td>
<td>49</td>
<td>Excl.</td>
<td>0.8</td>
<td>19.3</td>
</tr>
<tr>
<td>Welin L (156)</td>
<td>2003 Sweden</td>
<td>1980</td>
<td>Men born in 1913, 1923 (100g-OGTT)</td>
<td>833</td>
<td>57, 67</td>
<td>0</td>
<td>5.2</td>
<td>4.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Byberg L (157)</td>
<td>2000 Sweden</td>
<td>1990-1994</td>
<td>Uppsala Longitudinal Study on Adult Men (ULSA)</td>
<td>734</td>
<td>70</td>
<td>0</td>
<td>14</td>
<td>27</td>
<td>59</td>
</tr>
<tr>
<td>Eliasson M (158)</td>
<td>2002 Sweden</td>
<td>1999</td>
<td>Västerbotten Intervention Project (VIP), MONICA</td>
<td>2 224</td>
<td>25-64 (45)</td>
<td>50</td>
<td>Excl.</td>
<td>2.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Saydah SH (159)</td>
<td>2001 the USA</td>
<td>1976-1980</td>
<td>NHANES II</td>
<td>3 174</td>
<td>30-74</td>
<td>55</td>
<td>7.8</td>
<td>6.5</td>
<td>14.6</td>
</tr>
<tr>
<td>DECODE (160)</td>
<td>1999 Europe</td>
<td>NA</td>
<td>Europe, 20 countries</td>
<td>29 108</td>
<td>30-89</td>
<td>35</td>
<td>Excl.</td>
<td>5.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Rojo-Martinez G (161)</td>
<td>2004 Spain</td>
<td>NA</td>
<td>Pizzara Municipal register</td>
<td>1 023</td>
<td>18-65</td>
<td>NA</td>
<td>4.5</td>
<td>9.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Tripathy D (162)</td>
<td>2000 Finland</td>
<td>1990 onwards</td>
<td>Botnia Study: DM in the family (≥ 2 pers)</td>
<td>5 396</td>
<td>18-70</td>
<td>53</td>
<td>Excl.</td>
<td>18.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Schmidt MI (163)</td>
<td>2003 the USA</td>
<td>1996-1998</td>
<td>The Atherosclerosis Risk in Communities (ARIC) study</td>
<td>8 286</td>
<td>53-75</td>
<td>56</td>
<td>Excl.</td>
<td>11.7</td>
<td>9.1</td>
</tr>
<tr>
<td>Bonora E (164)</td>
<td>2004 Italy</td>
<td>1990</td>
<td>The Bruneck Study</td>
<td>919</td>
<td>40-79</td>
<td>50</td>
<td>Excl.</td>
<td>8.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>

NA - not available (not reported); Excl. - excluded from the study; *Diabetes defined by fasting plasma glucose ≥ 7.8 or 2 hour post load glucose ≥ 11.1 mmol/L and IGT respectively.
Table 13. Studies including evaluation of clinical stages of hyperglycaemia in patients with coronary artery disease.

<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>publication year country</th>
<th>Time period</th>
<th>Inclusion criteria</th>
<th>Patients</th>
<th>Age (years)</th>
<th>Women (%)</th>
<th>Diabetes (%) known</th>
<th>IGT (%)</th>
<th>IFG (%)</th>
<th>Normal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerstein H (153)</td>
<td>1999 India</td>
<td>NA</td>
<td>Patients: first acute MI Controls: No CAD</td>
<td>296</td>
<td>47</td>
<td>7</td>
<td>20.6</td>
<td>16.6</td>
<td>18.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Kowalska I (165)</td>
<td>2001 Poland</td>
<td>1996-1998</td>
<td>Elective C-angiography Stable CAD</td>
<td>302</td>
<td>53</td>
<td>0</td>
<td>Excl. 18.5</td>
<td>36.1</td>
<td>--</td>
<td>45.4</td>
</tr>
<tr>
<td>Piatti PM (166)</td>
<td>2003 Italy</td>
<td>NA</td>
<td>6 months after PCI + stent</td>
<td>120</td>
<td>57</td>
<td>0</td>
<td>Excl. 42.5</td>
<td>21.7</td>
<td>--</td>
<td>35.8</td>
</tr>
<tr>
<td>Kim HK (167)</td>
<td>2003 South Korea</td>
<td>1999</td>
<td>Confirmed CAD</td>
<td>230</td>
<td>61</td>
<td>46</td>
<td>20.9</td>
<td>26.1</td>
<td>30.0</td>
<td>--</td>
</tr>
<tr>
<td>Wascher TC (168)</td>
<td>2004 Austria</td>
<td>NA</td>
<td>Elective C-angiography: (CAD confirmed 71%)</td>
<td>160</td>
<td>65</td>
<td>34</td>
<td>31.9</td>
<td>23.1</td>
<td>30.0</td>
<td>--</td>
</tr>
<tr>
<td>Meier JJ (169)</td>
<td>2002 Germany</td>
<td>1991-1997</td>
<td>Acute MI survivors OGTT performed</td>
<td>562</td>
<td>68</td>
<td>41</td>
<td>27.0</td>
<td>14.8</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Gray CS (170)</td>
<td>2004 the UK</td>
<td>1997-1999</td>
<td>Acute stroke survivors Enrolled in the GIST trial</td>
<td>62</td>
<td>76</td>
<td>55</td>
<td>(14)</td>
<td>(68)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Taubert G (171)</td>
<td>2003 Germany</td>
<td>1997-1999</td>
<td>Elective C-angiography</td>
<td>3 266</td>
<td>65</td>
<td>30</td>
<td>17.0</td>
<td>17.9</td>
<td>NA</td>
<td>--</td>
</tr>
<tr>
<td>Fisman EZ (172)</td>
<td>2000 Israel</td>
<td>1990-1992</td>
<td>confirmed CAD / prior MI Screened for BIP study</td>
<td>11 853</td>
<td>45 - 74</td>
<td>18</td>
<td>Excl. 6.9</td>
<td>10.6</td>
<td>82.5</td>
<td>--</td>
</tr>
<tr>
<td>Rubins HB (173)</td>
<td>2002 the USA</td>
<td>1991-1993</td>
<td>VA-HIT CAD and lipid criteria</td>
<td>2 531</td>
<td>&lt; 74</td>
<td>0</td>
<td>24.8</td>
<td>5.6</td>
<td>12.8</td>
<td>56.3</td>
</tr>
<tr>
<td>Pyöälä K (152)</td>
<td>2004 Europe</td>
<td>1999-2000</td>
<td>EUROASPIRE II: previous hospitalisation for CAD</td>
<td>4 489</td>
<td>≤ 70</td>
<td>24</td>
<td>19.5</td>
<td>8.5</td>
<td>18.9</td>
<td>53.0</td>
</tr>
</tbody>
</table>

Classifications based on OGTT - the WHO 1999 criteria (6)

Classification based on fasting blood glucose - the ADA criteria 1997

C-angiography - coronary angiography; ~ about; NA - not available; ( ) - numbers in the brackets refer to the whole population from which the patients studied originate.
and to exclude patients recruited in violation to the protocol. Intentionally the period of recruitment was kept short, up to twelve weeks per centre, and the number of patients asked for from each of them was modest, to simplify the process and to help ensure high quality of data and that consecutive patients were enrolled. Moreover domestic laboratory investigations were harmonised by recalculating glucose concentrations according to standards established by the DECODE investigators (136) and by analysing HbA1c at a core laboratory. A drawback with central analysis was that some countries did not allow transport of the blood specimen across the border, explaining the loss of data in that perspective. Strength with surveys of the present kind is that they recruit patients seen in everyday clinical practice without any exclusion criteria. Since most patients originated from hospital settings, it should, however, be acknowledged that they may not be completely representative for those cared for in primary care. Still, the size of the current survey, comprising almost 5 000 individuals with a wide spectrum of clinical presentations of coronary artery disease, makes it likely that patterns disclosed represent a true picture of the actual situation.

Categorisation of glucose regulation was, as recommended by WHO, based on OGTT. Such tests were available from 56% of the eligible patients i.e. those without previously known diabetes. An important reason for the lack of data was that some National Ethics Committees did not approve the performance of an OGTT. In addition the survey built on voluntary, unpaid participation which, together with lack of local routines for performing OGTT in a cardiology setting, may have decreased the willingness to perform the test at some centres. It should, however, be sufficient with 1 920 (study II) and 1 867 (study III) completed tests for the purpose of assessing the prevalence of different stages of glucose regulation in patients with coronary artery disease. In this context the characteristics of eligible patients without an OGTT are of interest. They were somewhat older, more often females, more frequently diagnosed with heart failure, had wider waist circumference and higher fasting blood glucose at enrolment. Thus these patients were more likely to have an impaired glucose homeostasis and the proportion of hidden hyperglycaemia is if anything underestimated.

**Glucose regulation in CAD**

The prevalence of hidden hyperglycaemia assessed in the large and diverse population of patients with coronary heart disease recruited in Study II and subjected to an OGTT comprised IGT in 32%, IFG in 5% and previously unknown diabetes in 18%. As outlined above one may assume that hidden hyperglycaemia is at least as common in eligible patients not investigated with an OGTT. Adding the 31% of the total survey population with already known diabetes the proportions of normal and abnormal glucose regulation in the complete patient population of 4 961 subjects with stable and unstable coronary artery disease would distribute as presented in Figure 17. Only one third of the total patient cohort had a normal glucose homeostasis. In conclusion abnormal glucose regulation is indeed much more common than normal glucose homeostasis in patients with coronary artery disease.

**The metabolic features that distinguish patients from controls**

The most important biochemical parameters discriminating patients from controls in Study I were higher levels of fibrinogen, triglycerides, plasma proinsulin and HbA1c among patients. Interestingly insulin resistance as estimated by HOMA did not differ significantly between the two groups following adjustment for glucose tolerance.

An important question is whether the control population may be considered representative. The 185 controls originated from 500 individuals randomly selected from the population registry (37%). A majority of drop-outs related to unwillingness or absence of response to the invitation letters (44%) while 16% of those invited were excluded by medical reasons, a proportion that, based on common knowledge, reasonably had been higher among the non responders. Further analysis of the drop-outs was perceived unethical although it may have
added information of importance. As already discussed it was reassuring to note that the prevalence of previously undiagnosed diabetes and impaired glucose tolerance was similar in the present control group and previous Swedish epidemiological studies. The relatively low prevalence of hypertension may raise questions. However, in patients as for controls, only previously treated hypertension was recorded. A blood pressure exceeding 140/90 mmHg was recorded in 43% of the control population.

Most of the metabolic features which were identified in patients before hospital discharge remained unchanged after three months of patient follow up, suggesting that they are related to the underlying coronary artery disease rather than mirroring the acute condition. A multiple regression model, adjusting for pharmacological treatment, distinguished patients from controls by smoking and a set of biochemical parameters including fibrinogen, HDL-cholesterol, triglycerides, hsCRP, proinsulin and HbA1c. Interestingly HbA1c was significantly higher in patients than in controls even within the same glucose tolerance category. This indicates an overall impaired glycaemic homeostasis perhaps due to a more advanced dysglycaemic condition. Inadequate glycaemic control together with increased fibrinogen, hsCRP and triglycerides were the most distinctive features remaining significant even after adjustment for the actual levels of glucose tolerance.

The lack of difference in insulin resistance between patients and controls following adjustment for glucose tolerance supports the hypothesis that it is rather postprandial, not the fasting state metabolic abnormalities that relate to coronary artery disease. In addition the significantly higher proinsulin levels that were found in patients irrespective of glucose tolerance category, indicate that beta-cell dysfunction is an important part of the difference between patients with coronary artery disease and controls of similar age and gender composition. Put into the context of the association between post load proinsulin concentrations and the severity of global coronary atherosclerosis (57, 174, 175) and observations that plasma proinsulin is an independent predictor of coronary heart disease incidence and mortality (176, 177) this definitely deserves further evaluation.

**Glucometabolic categorisation**

The Euro Heart Survey population contains to our knowledge, one of the largest populations

---

**Figure 17.** Estimated pattern of glucose regulation in patients with CAD including patients with known diabetes. Studies II and III (n= 4 961).
of patients with coronary artery disease without previously known glucose disturbances in whom both fasting and post challenge glycaemia were tested. This enabled a comparison of glucometabolic classification according to WHO, recommending an OGTT if fasting or random glucose do not exceed a certain level (6), and according to ADA, based on fasting glycaemia only (7, 8). The pattern of glucose homeostasis recognised by means of fasting glycaemia was strikingly different from the outcome based on a combination of fasting and post load glucose measurements (Figure 18). Applying the original (1997) and the most recent (2004) ADA criteria normal fasting glucose was found in 81 and 64% of the patients without any previous glucose disturbances, out of whom only 58 and 60% respectively had normal post load glucose. Only 47% of the patients had a normal glucose regulation.

Impaired glucose tolerance was the most common hyperglycaemic state among patients with coronary artery disease. The concordance between IFG, as defined by ADA, and IGT defined by WHO was quite modest. Lowering the level for normal fasting glucose from < 6.1 to < 5.6 mmol/L only caused it to increase from 5 to 11%. At least every fourth patient would have been misclassified as normal by the use of the updated ADA criteria, 21% with IGT and 5% with newly detected diabetes respectively. The new ADA criteria evoke concerns by logistic and medical reasons by introducing a new category of prediabetic patients, comprising 8% of the actual population, namely those with a normal post load glucose and fasting glucose between 5.6 and 6.1 mmol/L (178, 179). Their risk for developing diabetes and cardiovascular complications is still unknown. Moreover post load glycaemia is a more sensitive predictor for cardiovascular outcomes than fasting glycaemia, especially in patients above the age of 65 years (136, 180-182), comprising a majority of those with coronary artery disease.

Taken together these factors advocate that the clinical usefulness of the new ADA criterion should be further evaluated before it is adopted as a common tool for glucometabolic classification of patients with coronary artery disease. An evaluation of glucose metabolism based solely on fasting glycaemia fails to identify almost half of the patients with diabetes.

**Figure 18.** Glucometabolic characterisation of patients with CAD by fasting plasma glucose according to ADA 2004 (FPG\textsuperscript{ADA}) and WHO criteria (OGTT) respectively. Study III (n= 1 867). The arrows indicate proportion of patients with normal or impaired fasting glucose according to ADA 2004 who would be classified as having impaired glucose tolerance or diabetes based on WHO criteria.
or impaired glucose regulation and is therefore unsatisfactory for the assessment of glucose metabolism in coronary patients. An OGTT is still irreplaceable for an accurate assessment of glucose metabolism. It is concluded that an OGTT deserves to become a diagnostic routine in cardiology practice.

**Classification without OGTT**

During the planning of the Euro Heart Survey it was recognised that an OGTT, although not difficult or expensive to perform, was perceived with hesitancy by some of the participating cardiologists. This was also reflected by failure to deliver such data from some centres. Several variables related to the metabolic status such as age, fasting plasma glucose, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure and BMI or waist and hip circumferences that are ordinarily included within laboratory and examination routines at cardiology wards and outpatient clinics were used for constructing an algorithm for predicting the metabolic status. The final model was chosen on clinical grounds from a set of almost equal models and included FPG, HDL-cholesterol, HbA1c and age. Such algorithm may perhaps be experienced faster and easier to accommodate than an OGTT. Due to a high misclassification rate of nearly 45% the original ordinal logistic regression model was not feasible. In a subsequent attempt to improve the diagnostic model the finally selected variables were used as input to a neural network. The best algorithm obtained by this model reached 96% specificity in identifying patients with abnormal glucose regulation according to OGTT. The model did unfortunately disclose only 25% of the patients with an abnormal OGTT. For the remaining 75%, an OGTT is still required for appropriate glucometabolic characterisation since many of them do indeed have abnormal glucose regulation.

**Prognostic implications of hidden hyperglycaemia**

Abnormal glucose tolerance, newly recognised before hospital discharge, was associated with a four times higher risk for the composite of cardiovascular death, re-infarction, stroke or severe heart failure during long-term follow-up of patients with myocardial infarction. The GAMI trial assessed glucose metabolism by means of OGTT already four to five days after onset of symptoms in a contemporary population with myocardial infarction. The possibility to make such characterisation soon after the onset of the cardiac event, as shown by Tenerz et al (183) and in study I, was of crucial importance. Many events occurred already early during follow up, in similarity to previous observations (169, 171, 172). The present findings further underline that glucometabolic classification by means of OGTT seems to be of particular value for cardiovascular risk prediction in elderly patients (181, 182, 184, 185). Another important observation is that a majority of the cardiovascular events occurred in patients with impaired glucose tolerance and not among those with diabetes. Similar observations were made in the general population by the DECODE investigators (186) underlining the continuity of risk that follows increasing blood glucose, especially 2-hour post load glycaemia, apparent already at levels considered fairly normal (87, 187, 188). The role of fasting glycaemia and the unexpected strength of its impact on the mortality rate after percutaneous coronary interventions has also been discussed by Muhlestein et al (189).

A total mortality of 11% during a median follow up period of 34 months may seem low. However, the GAMI cohort did not include any patients with previously known diabetes or renal insufficiency thereby representing a rather healthy subgroup of those admitted with myocardial infarction. In the multivariate analysis abnormal glucose tolerance together with a previous myocardial infarct and stroke were the only appreciable risk predictors of the composite of major cardiovascular events: death, non-fatal re-infarction, stroke or severe heart failure. Neither reperfusion therapy, age nor the use of statins or classical risk factors improved the Cox multiple regression model. Study IV supports the assumption that abnormal glucose tolerance may be an important player in processes promoting or initiating factors contributing to acute cardiovascular events. This may be linked to multiple mechanisms, inflammatory response, pro-oxidative stress and pro-thrombotic properties, (117, 121, 175,
The completeness of follow-up and the extended metabolic characterisation, including among others hs-CRP, proinsulin and fibrinogen can be seen as advantages with the GAMI study that, in this perspective, is well suited to generate hypotheses to be confirmed in larger patient materials.

The relatively small patient cohort has to be recognised as a limitation of study IV. The seemingly convincing message needs confirmation in a larger study. The one-year follow-up of the population in Study II offers such opportunity. Preliminary data from the 2,000 initial participants showed an increased mortality among patients with newly detected abnormal glucose regulation (Rydén et al: Data on file).

**Future challenges**

Considering the accumulating evidence for a continuous relation between increasing blood glucose and atherosclerotic disease and cardiovascular events it seems reasonable to undertake actions towards improved glycaemic control in individuals with hyperglycaemia below what is presently labelled as diabetes including hidden abnormal glucose regulation (192, 193). It is possible to prevent or at least retard the progress from IGT to diabetes by means of several measures. Among them lifestyle-oriented interventions, already with a modest weight reduction and increase of physical activity, seem to be particularly effective, however, difficult to achieve and notoriously hard to maintain (194-196). Pharmacological interventions are also available according to recent reports on the use of Acarbose (197), Metformin (196) and Trioglitazone (198). None of these studies were, however, powered to address the important question whether such treatment will influence morbidity and mortality.

The outcome of the present series of studies clearly underlines the importance of further research in the field. One obvious aim, for which the outcome of studies I and IV provides a comprehensive background, is a clinical trial testing the hypothesis that morbidity and mortality will improve by the use of life-style interventions supplemented by pharmacological treatment. Insulin, Metformin, Acarbose, Glitazones or perhaps Glucagon Like Peptide-I may be useful alternatives to test alone or in combinations.

Another line of research should aim at exploring a potential common denominator behind beta-cell dysfunction and atherosclerosis taking the particular risk associated with postprandial hyperglycaemia into account. One possibility may be hyperglycaemia induced activation of protein kinase C altering the function of endothelial NO synthase into a superoxide generator, thereby enhancing the production of free oxygen radicals stimulating programmed cell death, which is enhanced in diabetic hearts (199). A similar activation may affect the pancreatic beta-cells, compromising their function adding to the glucometabolic disturbance and to the relation between cardiovascular disease and disturbed glucose regulation (112, 117, 200). As outlined more in detail in the introduction, the oxidative stress hypothesis comprises mechanisms involved in endothelial dysfunction, the haemostatic homeostasis and platelet function, inflammatory processes, oxidised lipoproteins, insulin resistance and deterioration of the pancreatic beta-cell function, all elements in the pathogenesis of atherosclerosis and diabetes (91, 109, 112, 120).
CONCLUSIONS

The prevalence of abnormal glucose tolerance is almost two times higher among patients with coronary artery disease than in the population from which they are derived.

Metabolic differences, comprising glycaemia, HbA1c, proinsulin, triglycerides and fibrinogen, distinguish patients from controls more than differences in conventional risk factors.

Abnormal glucose regulation is more common than normal glucose homeostasis among patients with both acute and stable manifestations of coronary artery disease.

Fasting plasma glucose has a limited capacity to identify abnormal glucose metabolism in patients with coronary artery disease. An oral glucose tolerance test is still irreplaceable for the appropriate evaluation of glucose metabolism in such patients.

Abnormal glucose tolerance is a strong risk factor for future major cardiovascular events after an acute myocardial infarction.

Assessment of glucose regulation should be incorporated in routine risk evaluation and in future clinical trials on patients with coronary artery disease.

It is assumed that interventions that effectively improve glucose metabolism will have a potential to improve the outcome in patients with coronary artery disease.
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