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DIABETES MELLITUS AND CORONARY ARTERY SURGERY
CLINICAL AND EPIDEMIOLOGICAL STUDIES

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ABSTRACT

Objectives: Assess early and late mortality and incidence of acute myocardial infarction (AMI) after coronary artery bypass grafting (CABG) in patients with and without diabetes mellitus (DM) in relation to type of treatment. Analyse mortality after CABG in patients with and without DM to examine if any difference was influenced by changes in prognosis related to time-period. Measure glycosylated haemoglobin 1 (HbA1c) before CABG to determine correlation to postoperative outcome. Determine if the use of thoracic epidural analgesia (TEA) during and after CABG reduced insulin requirements and hyperglycaemia in patients with and without DM. Seek novel markers for morbidity and hospital stay after CABG by using gene expression techniques.

Methods and Results: The risk of early mortality (≤30 days) was increased in patients with insulin-treatment (odds ratio [OR] 4.6, 95% Confidence Interval [CI]: 2.5-8.4) and in those on oral antidiabetic drugs (OR 2.0, 95% CI 1.0-3.8), but not in diet treated patients compared with patients without DM among 6,707 patients who had CABG during 1980-1995. At 10 years the relative risk of death or AMI was 1.8 (95% CI 1.5-2.2) in insulin-treated patients and 1.4 (95% CI 1.2-1.7) in patients on oral drugs but there was no increased risk in diet treated patients compared with patients without DM. Survival at 10 years without AMI was 40% in patients with insulin-treatment, 48% if on oral drugs, 59% if diet managed, compared with 66% in patients without DM.

Early mortality was 3.4% in patients with DM versus 1.8% in patients without DM (OR 2.0, 95% CI 1.4-2.7) among 12,557 patients who had CABG during 1970-2003. Early mortality was reduced in patients operated on 2000-03 compared with 1970-89 in patients with DM (OR 0.3, 95% CI 0.1-0.9) and in those without DM (OR 0.4, 95% CI 0.2-0.7). Five-year mortality was 14.6% in patients with DM versus 8.3% in those without DM (hazard ratio 1.8, 95% CI 1.5-2.0). Five-year mortality was reduced 40% in patients operated on 2000-03 compared to 1970-89 in patients with and without DM.

Superficial sternal wound infection after CABG occurred in 13.9% of patients with preoperative HbA1c level ≥6% versus in 5.5% if HbA1c <6% (p=0.007). Mortality at an average of 3.5 years after CABG was 18.9% in patients with HbA1c ≥6% compared with 4.1% if HbA1c <6% (p<0.001, hazard ratio 5.4, 95% CI 3.0-10.0). TEA was used during and three days after CABG in half of 44 patients with DM and 60 without DM. TEA reduced mean blood glucose (BG) and insulin requirements (p<0.02) during the initial 24 hours in patients without DM whereas in patients with DM mean BG level was reduced (p=0.017) with unchanged insulin requirements. TEA did not attenuate hyperglycaemia during the first three postoperative days or diminish the increased fasting BG on the third postoperative day in patients without DM. Metabolic gene expression profiles were analysed in biopsies obtained during CABG in 66 patients. Patients with DM and not diagnosed DM had prolonged hospitalization time. Levels of the anti-inflammatory gene dual-specificity phosphatase 1 (DUSP1) in skeletal muscle differed in patients with normal (≤8 days) versus long hospitalization (>8 days, p=0.003).

Conclusions: DM was associated with an increased risk of early and late mortality. Early and late mortality was reduced in patients with and without DM operated on more recently but the mortality disadvantage associated with DM was not eliminated. HbA1c level ≥6% was associated with increased risk of wound infection and higher mortality at three years after CABG. TEA improved glucose homeostasis minimally during the initial 24 postoperative hours but did not attenuate hyperglycaemia during subsequent three postoperative days. Levels of DUSP1 expression predicted hospitalization time and may be of use to predict outcome after CABG.

KEYWORDS: Acute myocardial infarction, Coronary Artery Bypass Grafting, Diabetes mellitus, Mortality, Wound infection, Thoracic Epidural Analgesia, Hyperglycaemia, Gene expression, Dual specificity phosphatase-1, Hospitalization.

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LIST OF ORIGINAL ARTICLES

This thesis is based on the following original articles which are referred to in the text by their Roman numerals:

I. Alserius T, Hammar N, Nordqvist T, Ivert T.
   Risk of death or acute myocardial infarction ten years after coronary artery bypass surgery in relation to type of diabetes.
   *American Heart Journal, 2006;152:599-605.*

II. Alserius T, Hammar N, Nordqvist T, Ivert T.
    Improved survival after coronary artery bypass grafting has not influenced mortality disadvantage in patients with diabetes mellitus.
    *Submitted Journal of Thoracic and Cardiovascular Surgery.*

III. Alserius T, Anderson R.E, Hammar N, Nordqvist T, Ivert T.
    Elevated glycosylated haemoglobin (HbA1c) is a risk marker in coronary artery bypass surgery.

    Effects of thoracic epidural analgesia on glucose homeostasis after cardiac surgery in patients with and without diabetes mellitus.

    Dual-Specificity Phosphatase-1—An Anti-Inflammatory Marker Predicts Prolonged Postoperative Stay after Coronary Artery Bypass Grafting.
    *Submitted Journal of the American College of Cardiology.*
LIST OF ABBREVIATIONS

ACE  Angiotensin converting enzyme
AMI  Acute myocardial infarction
ARTS Arterial Revascularization Therapy Study
BARI Bypass Angioplasty Revascularization Investigation
CABG Coronary artery bypass grafting
CAD Coronary artery disease
CARDIA Coronary Artery Revascularization in Diabetes
CPB Cardiopulmonary bypass
CVD Cardiovascular disease
DM Diabetes mellitus
ERACI Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease
FFA Free fatty acids
FREEDOM The Future Revascularization Evaluation in Patients with Diabetes Mellitus Optimal management of Multivessel Disease
GIP Glucose dependent insulinotropic polypeptide
GLP-1 Glucagon-like peptide-1
HbA1c Glycosylated haemoglobin 1
HR Hazard ratio
IMA Internal mammary artery
NO Nitric oxide
OR Odds ratio
PCI Percutaneous Coronary Intervention
RR Relative risk
TEA Thoracic epidural analgesia
INTRODUCTION

Clinical experiences from coronary artery bypass grafting (CABG) in patients with diabetes mellitus (DM) particularly those insulin treated are that the operation is more technically demanding because of extensive coronary artery pathology and the results inferior regarding both survival and complications compared to in patients without DM. Clinical outcome in patients with DM and hyperglycaemia have been observed, reported and discussed by several Swedish authors. The impetus to write this thesis was generated from dismal experience after operations performed on patients with DM. Extent and magnitude of the complex of problems associated with CABG in patients with DM are elucidated.

Type 2 diabetes mellitus
An epidemic nature of DM is predicted in the world during the first quarter of the 21st century. The prevalence of DM is rapidly increasing worldwide and more than 300 million people are projected to suffer from DM in 2025. The prevalence of DM in Sweden is 4% and 85-90% is type 2 DM. Environmental lifestyle factors as obesity and low physical activity level superimposed on genetic predisposition will cause β-cell failure, insulin resistance and hyperglycaemia. DM will develop overtime accompanied by cardiovascular risk factors including hypertension and dyslipidaemia. DM is a chronic condition and cardiovascular disease is the most common cause of death. Hyperglycaemia and specifically the post-load hyperglycaemia resulting from post-prandial glucose excursions is the main factor associated with increasing the risks of morbidity and mortality in DM. As aggressive atherosclerosis develop prematurely an early diagnosis of DM is important. There are initially limited symptoms and the condition may go undiagnosed for long times. Patients with type 2 DM have similar risk of suffering an acute myocardial infarction (AMI) as patients without DM with history of a previous AMI.

Effects of hyperglycaemia
DM impart severe metabolic derangements. Hyperglycaemia is associated with insulin resistance, hypertension, dyslipidaemia with elevated triglyceride and decreased high density lipoprotein (HDL) levels, inflammation and exuberance of growth factor. There is also a prothrombotic state with impaired fibrinolysis and activated platelets that aggregate more easily. Plasma concentration of fibrinogen, factor VII, von Willebrand factor, plasminogen activator inhibitor are elevated and thrombin activity is increased. Hyperglycaemia and advanced glycation end-products result in endothelial cell dysfunction that activate protein C, block production of nitric oxide (NO) and increases oxidative stress by generating active oxygen radicals. DM affects the vessel wall by influencing synthesis of collagen and increased production of matrix metalloproteinase. Mechanisms such as synthesis of collagen, elevated low-density lipoproteins and tumor necrosis factor promote development of atherosclerosis. An impaired NO mediated endothelial relaxation is observed prior to the development of overt atherosclerosis. Vasoconstriction is enhanced by reduced production of prostacyclin and increased endothelin-1. During euglycemic hyperinsulinemic clamps in obese women an increased insulin level correlated to increment in endothelin-1 indicating that insulin modulates endothelin level.

Insulin resistance and hyperinsulinemia may precede the onset of type 2 DM. The main sites for insulin resistance seem to be extrahepatic tissues, probably skeletal muscle, where preliminary data suggest that the glucose transporting system is involved. Insulin resistance results in excessive liberation of free fatty acids from adipose tissue that enhances oxidative stress and reduce production of NO, a condition associated with increased neointimal hyperplasia and restenosis following percutaneous coronary intervention (PCI). Elective surgery causes a marked, tran-
sient reduction in insulin sensitivity related to the magnitude of the operation.32

An elevated admission plasma glucose in patients with an AMI not only reflects acute stress, but may also be a marker of disturbed glucose metabolism that worsens the prognosis and requires intervention.3 Elevated blood glucose level is a strong, independent predictor of long-term mortality in type 2 diabetic patients following myocardial infarction underlining that glucose control is an important part of their management.31

Aggressive atherosclerosis and myocardial failure
Atherosclerosis is ubiquitous in adults with DM and portends a poor prognosis.34 A diagnosis of DM is equivalent to established coronary artery disease. The multiple metabolic abnormalities associated with DM contribute to endothelial dysfunction, hypertension, rapid acceleration of an atherosclerosis process and eventually plaque rupture and coronary artery thrombosis.35 The plaques in patients with DM are lipid rich, unstable and are more prone to rupture.35 The ulcerated plaques and intracoronary thrombus frequent in patients with DM result in a disproportionately high risk for development of acute coronary syndromes.36

Patients with DM have more severe left main coronary artery stenosis and more frequently extensive multivessel coronary artery disease with small size vessels, long lesions and diffuse atherosclerosis than in patients without DM (Figures 1a and 1b).37,38 Pajunen and co-workers from Finland reported similar coronary artery disease in patients with and without noninsulin-dependent DM, who have similar symptoms at a given age.39

DM is associated with increased risk for developing heart failure. Diabetic cardiomyopathy is the presence of myocardial dysfunction in the absence of coronary artery disease and hypertension. Hyperglycemia seems to be central to the pathogenesis of diabetic cardiomyopathy and to trigger a series of maladaptive stimuli that result in myocardial fibrosis and collagen deposition.40 Contributing factors to heart failure are alterations of cardiomyocyte metabolic substrate switching between free fatty acid (FFA) and glucose metabolism i.e. increased FFA exposure and cellular accumulation and alterations in peroxisome proliferator-activated receptor-(PPAR-)alpha activity, among others.41 FFAs are increased in obese patients and contribute to DM, hepatic steatosis and several cardiovascular diseases. The elevated FFA levels in patients with heart failure and acute coronary syndromes are a consequence of an increased lipolysis due to a surge in catecholamines and natriuretic peptides. FFAs contribute to myocardial dysfunction and are proarrhythmic and their oxidation requires more oxygen than does glycolysis.42 There are in most patients with DM commonly

Figure 1a. Coronary angiography in a patient without diabetes showing proximal stenosis and arteries with good run-off.

Figure 1b. Coronary angiography in a patient with diabetes showing small vessels with distal lumen caliber changes.
coincident dyslipidaemia, hypertension, left ventricular hypertrophy and ischemic heart disease.

**Revascularization in patients with DM**

The preferred revascularization strategy in patients with diabetes mellitus has been under debate. CABG was the gold standard treatment for patients with multivessel coronary artery disease that was challenged by the introduction of PCI. The main difference between the two treatments is that grafts are placed distally on the coronary arteries whereas PCI attacks the proximal lesion. CABG bypasses a large amount of plaque burden in the coronary arteries and inherently prevents reinterventions caused by progression of disease proximal to the site of the coronary anastomoses whereas PCI does not preclude progression of lesions close to a stent. CABG deals not only with the immediate culprit lesion but also with future lesions as the graft is placed to the distal coronary artery. Further advantages of CABG are that complete revascularization is more often achieved; that the arterial grafts if used have excellent long-term patency rates and bilateral internal mammary artery (IMA) grafts can be used safely in patients with DM.\(^44-46\)

The aggressive accelerated atherosclerosis in patients with DM inextricably connected to multivessel coronary artery disease with vulnerable plaques causes higher rates of restenosis and inferior survival after PCI compared with nondiabetic patients.\(^47-49\) The presence of platelet derived and insulin mediated growth factors that stimulate smooth muscle growth are pivotal in the process of restenosis after PCI.\(^50\) Advanced glycation end-products cause cell activation and proliferation.\(^51\) An imbalance in the fibrinolytic system may also contribute to restenosis after PCI.

In one randomized trial coronary stenting for multivessel disease was less expensive than CABG and offered the same degree of protection against death, stroke and myocardial infarction after one year, but was associated with a greater need for repeated revascularization.\(^52\) The randomized Bypass Angioplasty Revascularization Investigation (BARI) conducted before the era of glucoprotein IIb/IIIa inhibition and novel coronary stent technologies, showed inferior survival rates and higher need for repeat revascularization in patients with diabetes mellitus treated with PCI than in those undergoing CABG.\(^53\) In the BARI mortality at five years was significantly higher after PCI than CABG in the subset of patients with DM.\(^54\) There was a 15% survival advantage for CABG at five years. The survival benefit in the BARI trial that has received most attention was limited to patients with IMA grafts.\(^53\) The introduction of drug eluting stent (DES) reduced the rate of restenosis after PCI. In the Arterial Revascularization Therapy Study (ARTS) patients with DM treated with PCI and DES required more repeat revascularization than after CABG.\(^55\) At one year, diabetic patients treated with DES had lower event-free survival rate (63.4%) because of a higher incidence of repeat revascularization compared with both diabetic patients CABG treated (84.4%). Also in the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI-III) trial of PCI with DES the need for repeat revascularisation after one year was higher than after CABG. Hannan and co-workers concluded that both risk adjusted survival and revascularization was higher three years after CABG than after PCI in a review of almost 60,000 patients.\(^56\)

No randomized trial specifically compares the effect of PCI and CABG in patients with DM. In an observational study ten-year survival, corrected for baseline differences, in patients with insulin treated DM was 36% after PCI and 47% after CABG, raising further questions about angioplasty in insulin requiring diabetic patients with multivessel disease.\(^57\) In a prospective study Barsness and associates found no significant differential effect of diabetes on outcome at five years between patients treated with PCI and those treated with CABG.\(^58\) Two ongoing randomized trials the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) and the Coronary Artery Revascularisation in Diabetes (CARDIA) studies addresses specifi-
cally the effect of use of PCI with DES versus CABG in patients with DM.\textsuperscript{59}

**Survival after CABG in patients with diabetes**

In large number of reports the outcome after CABG has been inferior in patients with DM compared to in nondiabetics. There are conflicting observations regarding mortality with reports of a higher\textsuperscript{1,60,67} as well as similar early mortality\textsuperscript{1,68-71} after CABG in patients with DM compared with in patients without DM. Similar results were reported by Hakala and colleagues from Kupio in Finland who matched 866 diabetic patients with non-diabetic controls. Thirty-day mortality was equally low in diabetic and non-diabetic patients with severe coronary artery disease but long-term survival was significantly lower in the diabetic group than in the non-diabetic group.\textsuperscript{69} DM is in most reports recognized an independent predictor of five-year mortality.\textsuperscript{59,64,66,68,69,72-74}

Conversely, Calafiore who used multiple arterial grafts did not find that DM, exclusive of patients with diet treatment, was associated with a worse five-year mortality.\textsuperscript{62} There is agreement that the prognosis is worse in patients with insulin treated DM than in those having oral medication.\textsuperscript{1,61,64,71,73,74}

**Morbidity after CABG in patients with diabetes and hyperglycemia**

A review of 1,369,961 cardiac procedures in the Society of Thoracic Surgeons Database revealed higher rates of 30-day mortality, sternal wound infection, stroke and longer length of hospital stay in patients with DM than in a non diabetic population.\textsuperscript{75} Postoperative infection\textsuperscript{1,61,67,71,76,77} and morbidity rates has been reported to be higher\textsuperscript{1,60,61,71,77} as well as not increased in patients with DM.\textsuperscript{68,69}

Male gender, emergency, diabetes mellitus, obesity, redo operations were identified by Valla et al as risks factors for mediastinitis in 9,814 patients undergoing heart surgery.\textsuperscript{78} Zsabo and colleagues found that patients with DM undergoing CABG did not have higher 30-day mortality but suffered more renal failure, stroke and wound infections than patients without DM and that 5-year survival was 84.4% versus 91.3%.\textsuperscript{1} McAlister documented that 1 mmol/L increase blood glucose on the first postoperative day correlated to increased risk of the adverse outcomes stroke, AMI, infection or death.\textsuperscript{79}

Hyperglycaemia is itself an independent risk factor for the development of infection. Hyperglycemia is associated with, impaired leukocyte function, granulocyte adherence, chemotaxis, host resistance and phagocytosis.\textsuperscript{80} As postoperative hyperglycaemia and previously undiagnosed diabetes are associated with development of wound infection, screening for diabetes and hyperglycaemia among patients planned to undergo cardiothoracic surgery may be warranted to prevent postoperative and chronic complications of this metabolic abnormality.\textsuperscript{81} Efforts to improve perioperative glucose homeostasis in diabetic patients is one clue to reduce the incidence of nosocomial infection and thereby improve outcome.\textsuperscript{80}

**Prolonged hospital stay**

DM and elevated blood glucose level correlates to longer hospital stay and thereby increased hospitalization costs.\textsuperscript{75,76,82,83} Estrada and coworkers found that every 50mg/dL (2.78 mol/L) increase of blood glucose was associated with longer postoperative days and increase of hospitalization charges.\textsuperscript{76} DM is one of several factors that increase the risk of readmission after CABG.\textsuperscript{4}

**Perioperative hyperglycaemia**

Elevated fasting blood glucose prior to surgery correlates to mortality after CABG.\textsuperscript{84} Also elevated glucose levels during surgery correlates to higher mortality and postoperative complications in patients with and without diabetes.\textsuperscript{61,79,85-87}

Continuous insulin infusion regardless of diagnosis of DM during surgery and until the third day after the operation to target level 100-150 mg/dl (5.6-8.4 mmol/L) has significantly reduced hospital mortality and sternal wound infection.\textsuperscript{65,88,89} There are some conflicting observations regarding management of blood glucose level during cardiac surgery. Butterworth and colleagues failed to demonstrate improved clinical outcome by keeping blood glucose level <100 mg/dl during CPB in patients without DM.\textsuperscript{90} Gandhi and co-
workers observed a tendency for more deaths and stroke in a randomized trial in a group receiving insulin to maintain blood glucose level at 80-100mg/dL.91

Metabolic control, as reflected by normoglycaemia, rather than the infused insulin dose, is related to the beneficial effects of intensive insulin therapy.92
AIMS OF THE THESIS:

I. Assess early and late mortality and incidence of nonfatal AMI up to ten years after CABG in patients with DM compared to in patients without DM and relate the risk to type of treatment with insulin, oral drugs or diet only at the time of the operation.

II. Analyse mortality up to five years after CABG performed during more than three decades in patients with and without type 2 DM to examine if mortality differed in the two groups and if any difference was influenced by changes in survival prognosis related to time-period of the operation.

III. Measure glycosylated haemoglobin 1 (HbA1c) before CABG regardless of diagnosis of DM to determine if the HbA1c concentrations correlated to postoperative infections and mortality rates.

IV. Determine if the use of thoracic epidural analgesia (TEA) during and three days after CABG would reduce perioperative insulin requirements and postoperative hyperglycaemia in patients with and without type 2 DM.

V. Seek novel markers for morbidity and prolonged hospital stay after CABG by using the gene expression compendium of the Stockholm Atherosclerosis Gene Expression Study (STAGE) cohort consisting of transcriptional profiles from tissues obtained during CABG.
PATIENTS

During the entire period 1970 through 2006 a total of 14,481 patients underwent a first isolated CABG with the aid of cardiopulmonary bypass at the Karolinska University Hospital in Stockholm, Sweden. Demographic variables and clinical characteristics were continuously recorded in the department database. All medical records were reviewed to validate the information in the database and to extract more detailed clinical information. Patients from this cohort were included in the studies listed. These studies were approved by the Ethics committee in Stockholm and informed consent was obtained from the patients to include data in the database. All patients in study V gave written informed consent. For the gene expression study approval was also obtained by the Ethics committees at the Tartu University Hospital in Estonia.

Study I includes 6727 patients operated on during 1980 up to 1995, 856 (13%) of whom had DM. Patients with DM were classified as type 1 in 56 (6%) or type 2 treated with insulin in 246 (29%), oral antidiabetic drugs in 393 (46%), or diet only in 161 patients (19%).

Study II includes 12,557 patients from June 1970 through December 2003. Totally 2,034 patients (16%) had DM. The analyses were confined to the 1892 patients with type 2 DM and the 10,523 patients without a diagnosis of DM.

Study III is a prospective observational study. HbA1c concentration was measured regardless of diagnosis of DM in 605 patients who underwent elective CABG. None of the patients had type 1 DM and 161 patients (27%) had a diagnosis of type 2 DM.

Study IV is a prospective, interventional study of the effect of TEA in 104 patients undergoing elective CABG for stable angina pectoris. Patients with type 1 DM, a history of heart failure or severely reduced myocardial or kidney function were excluded. All patients fasted overnight and received their normal anti-anginal and betablocking medications on the morning of surgery but hypoglycaemic (both oral and insulin) medication was withheld until the day after surgery. Four patient groups were studied: non-diabetic without TEA (n=30), non-diabetic with TEA (n=30), diabetic without TEA (n=22), diabetic with TEA (n=22).

Study V Metabolic gene expression profiles were used to find correlation to morbidity after CABG in 66 patients. Patients with comorbidities, such as malignancy, kidney disease, and chronic systemic inflammatory diseases were excluded. Gene-expression profiles of liver, skeletal muscle, and visceral fat from 66 patients were finally included. For the purpose of validation, 54 patients undergoing CABG at the Tartu University Hospital in Estonia were collected.

METHODS

Operative procedures

During the more than three decades of CABG covered by this study major changes of the operative technique were introduced. All operations included in this thesis were performed via a median sternotomy with the aid of CPB. Bubble oxygenators replaced initially used disc oxygenators in 1975 and were completely discarded in favour of membrane oxygenators in 1988. Heparin was given before cardiopulmonary bypass (3mg/kg) to maintain activated clotting time above 400 s. During the last years core temperature was normothermia or was allowed to drift to 34°C. Intermittent aortic cross clamping was used up to 1976. Subsequently the most common method of myocardial protection was cold crystalloid modified St. Thomas' cardioplegia with procainamide 5 mmol/L given antegrade into the aortic root. During the 1990s cold diluted blood cardioplegia was administered either antegrade into the aorta or in patients with high-grade proximal coronary artery obstruction retrograde into the coronary sinus or various combinations of these two techniques were used. The distal anastomoses were constructed first with a continuous running 7-0 polypropylene suture and the proximal vein anastomoses to the aorta sutured over a partially occluding clamp while reperfusing the heart and rewarming the patient.

In Studies III-V the patients were premedicated with morphine (7.5–15 mg intramuscu-
During induction the patients received 1000 mL Ringer acetate solution. Anaesthesia was induced with 3–4 μg/kg fentanyl, 30–40 μg/kg midazolam and variable amounts of propofol. Patients were paralysed with 0.5–0.7 mg/kg atracurium to facilitate intubation. Anaesthesia was maintained with isoflurane until cardiopulmonary bypass and thereafter with 0.1–0.3 mg fentanyl boluses and a continuous infusion of propofol until completion of surgery.

All patients were put on acetylsalicylic acid 160 mg/d from the first postoperative day. During the 1990s additional antithrombotic treatment of dalteparin (Fragmin®, Pharmacia & Upjohn, Stockholm, Sweden) 5000 U was administered once daily subcutaneously until discharge from hospital.

Epidural catheter
The epidural catheter was inserted the day before surgery by one anaesthetist when logistically possible. An epidural catheter was inserted on the evening before surgery at level T2 or T3 and the position was confirmed with a bolus dose of lidocaine. At least 20 min before surgery, a bolus dose of 8–10 mL bupivacaine (5mg/mL) was given. A second 6 mL bolus was given after 1½ hour at which time a continuous infusion of bupivacaine 2.5mg/mL with sufentanil 1 μg/mL was started (5–7ml/h). Paracetamol 1 g intravenously (i.v.) was given at the end of CPB. Patients were discharged to the wards with a continuous TEA infusion of bupivacaine 1.25mg/mL and sufentanil 1μg/mL (4–8ml/L/h). TEA was continued at least until the end of the study period. All patients received oral paracetamol 1 g four times daily. Patients without TEA received i.v. ketobemidone (1mg/mL) via a patient-controlled analgesia pump.

Definitions
Diabetes mellitus In Studies I–V a clinical diagnosis of DM on admittance treated with diet restriction only or requiring oral medication and/or insulin was used to classify a patient as having DM. In patients with DM, the year of diagnosis as well as the dose and type of medication were recorded. Study I included both type 1 and type 2 DM whereas in Studies II–V patients with type 2 DM only were analysed. Onset of diabetes was defined as the year of diagnosis and start of treatment. Patients with type 1 DM had their diagnosis before the age of 40 years and were initially insulin-dependent, whereas type 2 DM appeared later in life, was usually initially not insulin-dependent and frequently associated with insulin resistance.

A patient was defined as hypertensive if admitted on anti-hypertensive medication and having hyperlipidaemia if taking lipid-lowering drugs. Unstable angina was chest pain at rest on admittance to the hospital or new onset or accelerated angina within four weeks of the operation. Unstable patients were operated on urgently, whereas all other patients underwent elective surgery. Peripheral vascular disease was a history of exertional claudication and/or prior revascularization to the legs. The number of obstructed coronary vessels was grouped into four categories as single-, two- or three-vessel disease, or stenosis of the left main coronary artery. Left ventricular function was categorized as normal, reduced or severely reduced according to the preoperative assessment by the physician performing contrast ventriculography or echocardiography. Normal left ventricular function was defined as an ejection fraction of >50% without dilatation of the ventricle. A reduced left ventricular function was defined as an ejection fraction of <50% but >30%. A severely reduced left ventricular function was defined as a markedly dilated ventricle with akinetic or hypokinetic segments and an estimated ejection fraction of <30%. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Serum creatinine was measured at the time of hospital admission. Creatinine clearance was calculated using the equation of Cockroft and Gault. Normal renal function was defined as a creatinine clearance of 80 mL/min or more.
Table I. *Plasma glucose levels and definitions*

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<tr>
<th>Study III</th>
<th>Study V</th>
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<tr>
<td><strong>Fasting plasma glucose</strong></td>
<td><strong>Fasting blood glucose</strong></td>
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<td>&lt; 5.6 mmol/L</td>
<td>&lt; 5.6 mmol/L</td>
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<td>6.1 &lt; 7.0 mmol/L</td>
<td>5.6 &lt; 6.1 mmol/L</td>
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<td>≥ 7.0 mmol/L</td>
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**Blood glucose**

Plasma glucose levels were analyzed in Study III. Blood glucose values were used in Studies IV and V (Table I). 53,95,133

Fasting blood glucose (B-gluc) was determined before anaesthesia on the morning of surgery from whole blood by the glycodydrogenase method (HemoCue Inc; Ängelholm, Sweden). No glucose was given before or during surgery, but patients received 100 mg/kg, h postoperatively in the intensive care unit (ICU). Regular insulin (1 unit/mL; Actrapid®; Novo Nordisk AB, Malmö, Sweden) via a motor syringe infuser was initiated in the operating room or ICU when B-gluc exceeded 6 mmol/L with the goal of maintaining all values of B-gluc < 6.9 mmol/L (local clinical policy at time of study); ICU nurses adjusted insulin infusion rates in response to B-gluc values without the aid of a nomogram. Patients returned to the ward mid-morning on the first postoperative day. Local clinical ward policy at the time of this study was to use subcutaneous insulin injections when B-gluc exceeded 10 mmol/L. On the day of surgery, B-gluc was measured at four specific times (before anaesthesia, midday, 18 h and midnight) in addition to whenever clinically indicated.

In Study V blood glucose was measured by a glucose oxidase method (Kodak Ektachem).

**Glycosylated haemoglobin (HbA1c)**

The American Diabetes Association and the European Association for the Study of Diabetes have recommended a target concentration of glycosylated haemoglobin (HbA1c) concentration <7%. 95 In our studies HbA1c was determined by chromatography (Bio-Rad Laboratories AB, Sundbyberg, Sweden). The normal reference limits were 3.6-5.3% with the Swedish Mono-S high resolution HPLC method. 96,97 This correspond to HbA1c<6% by the Swedish Mono-S method, the recommended target concentration by the Swedish Diabetes Association. 96,97 We therefore compared the postoperative course in patients with HbA1c <6% versus in those with HbA1c ≥6%.

**Wound infection**

At discharge all patients were encouraged to contact our out-patient clinic in case of wound infection. Information of postoperative wound infection was obtained in all patients from questionnaires and by scrutinizing patient charts. Superficial sternal wound infection was defined as positive cultures and a local infection requiring reopening of a few cm of the skin incision and involving subcutaneous tissue only. Mediastinitis was defined as positive cultures from sternum and/or mediastinum during the postoperative course and the need for surgical revision of the entire wound.

**Tissue biopsies**

Small pieces of tissue were obtained from the skeletal muscle, mediastinal fat and the anterior hepatic edge via a small incision in the diaphragm taken after weaning from CPB and reversal of heparin effect. The biopsies were preserved in RNAlater (Qiagen), and frozen at -80°C. At follow-up blood samples were drawn into precooled sterile tubes (Vacutainer, Becton Dickinson) containing NaEDTA and placed on ice. Plasma was recovered within 30 min by centrifugation (2750 g, 20 min, 4°C) for analysis of cholesterol, triglyceride, and lipoproteins as described. 98
Gene Expression Profiling in STAGE
Trizol (BRL-Life Technologies) and FastPrep (MP Biomedicals), purified with RNeasy Mini kit (Qiagen), and treated with RNase-Free DNase Set (Qiagen). Sample quality was assessed with an Agilent Bioanalyzer 2100. cRNA yield was assessed with a spectrophotometer (ND-1000, NanoDrop Technologies) before hybridization to HG-U133 Plus 2.0 arrays (Affymetrix). The arrays were processed with a Fluidics Station 450, scanned with a GeneArray Scanner 3000, and analyzed with GeneChip Operational Software 2.0.

RT-PCR Analyses
For cDNA synthesis, 150 ng of total RNA was reverse transcribed with Superscript III (Invitrogen) according to the manufacturer’s protocol. After 4-fold dilution, cDNA (3 µL) was amplified by real-time PCR with 1xTaqMan universal PCR master mix (Applied Biosystems, Foster City, CA) on an ABI Prism 7000 (PE Biosystems) and software according to the manufacturer’s protocol. Assay-On-Demand Kits containing corresponding primers and probes from Applied Biosystems were used, and expression values were normalized to acidic ribosomal phosphoprotein P0. Each sample was analyzed in duplicate.

Western Blot Analyses
The samples were resolved by 8 % SDS-polyacrylamide gels and then transferred onto a HYBOND-PVDF membrane filter after protein separation. Immunoblots were incubated with goat polyclonal to DUSP1 primary antibodies and then incubated with rabbit polyclonal to goat IgG-H&L (HRP) as secondary antibody. As a control we used rabbit polyclonal to β-Tubulin and anti-rabbit IgG-H&L as secondary antibody (HRP) (Abcam). The signals were detected with enhanced chemiluminescence ECL advance western blotting detection kit (Health Care).

Coronary Atherosclerosis Measurements in STAGE
All CABG patients in the STAGE cohort underwent preoperative biplane coronary angiography (Judkins technique). Angiograms were evaluated with quantitative coronary angiography (QCA) techniques (Medis). In brief, the left and right coronary arteries and their branches were divided into segments. Each segment was measured during end-diastole, and plaque area determined as a percentage of total area of the segment. In some patients, right coronary artery occlusion prohibited QCA evaluation. In addition, a coronary stenosis score was calculated from all major lesions in the coronary arteries (1 point, 20–50% luminal obstruction; 2 points >50% obstruction).

Follow-up
All cause mortality was included in the analyses of early and late deaths. Follow-up of mortality was performed by linking each subject’s Swedish personal identification number to the National Cause of Death Register 1970-2002 and to the National Population Register for deaths occurring between 2003 up to December 2006. Early mortality was defined as death occurring within 30 days of surgery. Information of incident AMI occurring after the operation was obtained from the Stockholm and the National Myocardial Infarction registers. These registers are based on information from registrations that cover all deaths and all hospital discharges from hospitals treating acute medical cases in Sweden. All hospitalizations and deaths for the same individual within 28 days of onset of symptoms were considered to reflect the same myocardial infarction episode. This method has been found to identify incident cases of AMI in Sweden with a high sensitivity and specificity.

Using a standard questionnaire, a research nurse obtained a medical history and information on lifestyle factors (e.g., smoking, alcohol consumption and physical activity) 3-months after surgery from 66 STAGE patients but pre-operatively from the Tartu cohort. At these occasions, the STAGE and Tartu patients underwent a physical examination and venous blood samples were taken.

The total number of days spent in hospital after surgery were recorded. Post-operative health related quality of life questionnaires were sent by mail to the STAGE patients on average 3.3 (range 2.7-4.3) years after surgery.
Statistical analyses

Early mortality was determined for patients with different types of treatment of DM, and comparisons were performed crude and adjusted by odds ratios (ORs) obtained from logistic regression analyses. The relative risk (RR) (or hazard ratios (HR) in Studies II and III) of late death was estimated crude and in multivariate analysis using Cox proportional hazards regression.

In the multivariate analyses, adjustment was made for age and other factors associated with the outcome. Only variables that when added to the model changed the point estimate of the RR for diabetes by at least 10% were retained in the final model. Estimates of RRs were accompanied by asymptotic 95% CIs. In the multivariate analyses age, BMI and creatinine clearance were included in the models as continuous variables and all other variables as dichotomous representing presence or absence of the characteristic. Year of surgery was subdivided into the categories 1980 to 1984, 1985 to 1989, and 1990 to 1995. Left ventricular function was categorized as normal, reduced, or severely reduced. Euroscore was used as a general indicator of the risk of the patient undergoing surgery. The Cochran-Armitage test was used to assess trends in risk when comparing subgroups of HbA1c. Survival curves were calculated according to Kaplan-Meier methods.

Continuous variables are presented using means with 1 SD or range and categorical variables with numbers and percentages. The Student’s t test was used to compare differences in means between 2 patient groups. The x2 test or the 2-tailed Fisher exact test, where applicable, was used to compare qualitative data. Analysis of variance with repeated measures was used to compare group differences over time.

In Study V gene expression values were pre-processed using Quantile Normalization and the Robust Multichip Average. Of 604, 258 perfect-match Affymetrix probe signals; 280,523 could be mapped to 16,685 Entrez genes without using cross-hybridizing probes. The correlation analysis was performed using Spearman rank correlation with p-values from Student’s t test following a Fisher transformation. Mathematica 5.1, StatView 5.0.1 or SAS for Windows (Cary, NC, version 6.12) were used for the statistical analyses. Regression analyses were performed according to Draper and Smith.
Table II. Characteristics of 12,415 patients undergoing coronary artery bypass grafting during 1970-2003 in relation to time period of the operation and diagnosis of type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>Not Diabet n=10523 (85%)</th>
<th>Type 2 Diabetes n=1892 (15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1970-89 (n = 3488)</td>
<td>1970-89 (n=319)</td>
</tr>
<tr>
<td></td>
<td>1990-99 (n=5166)</td>
<td>1990-99 (n=989)</td>
</tr>
<tr>
<td></td>
<td>2000-03 (n=1869)</td>
<td>2000-03 (n=584)</td>
</tr>
<tr>
<td>Age (Yr)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>57.9±8.1</td>
<td>64.9±9.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>26.3±3.1</td>
<td>26.2±3.5</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>82.4±22.9</td>
<td>79.4±26.9</td>
</tr>
<tr>
<td>Female gender</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>14.2</td>
<td>20.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>23.7</td>
<td>31.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Insulin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oral drugs</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diet treated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>7.3</td>
<td>33.8</td>
</tr>
<tr>
<td>Previous myocardal infarction</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>52.0</td>
<td>51.2</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>6.1</td>
<td>27.4</td>
</tr>
<tr>
<td>History of stroke</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>No. obstructed vessels</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>15.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Two vessel disease</td>
<td>32.5</td>
<td>22.3</td>
</tr>
<tr>
<td>Three vessel disease</td>
<td>50.3</td>
<td>70.5</td>
</tr>
<tr>
<td>Missing</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>59.0</td>
<td>54.7</td>
</tr>
<tr>
<td>Reduced</td>
<td>35.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Severely reduced</td>
<td>3.8</td>
<td>7.0</td>
</tr>
<tr>
<td>No information</td>
<td>2.3</td>
<td>5.7</td>
</tr>
<tr>
<td>No. coronary anastomoses</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>39.0</td>
<td>15.6</td>
</tr>
<tr>
<td>3-4</td>
<td>50.5</td>
<td>69.7</td>
</tr>
<tr>
<td>5-8</td>
<td>10.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Use of internal mammary graft</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>73.4</td>
<td>95.2</td>
</tr>
</tbody>
</table>

BMI, body mass index * P-Value for trend. Age, BMI and Creatinine clearance are calculated with crude model in regression analysis. Other p-values are calculated from Mantel-Haenszel Chi-Square. † P-Value for global difference between patients with versus without diabetes <0.001.
Table III. Medication at discharge during three time-periods after CABG.

<table>
<thead>
<tr>
<th></th>
<th>1996-1999 (n=2737)</th>
<th>2000-2003 (n=2505)</th>
<th>2004-2006 (n=1924)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitor</td>
<td>603 (22.0%)</td>
<td>887 (35.4%)</td>
<td>813 (42.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blockers</td>
<td>2125 (77.6%)</td>
<td>2161 (86.3%)</td>
<td>1742 (90.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>1340 (49.0%)</td>
<td>1774 (70.8%)</td>
<td>1524 (79.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACE, Angiotensin-converting enzyme

RESULTS

There was a continuous increased of prevalence of DM among patients undergoing CABG from the first operation performed in 1970 up to 30% during 2006 (Fig. 2).

The largest cohort of 12,415 patients included in Study II was used to describe characteristics of the patients. The initial 19 years up to 1989 included only 17% of the patients with type 2 DM. Throughout three time periods 1970-89, 1990-99 and 2000-2003 average age increased and cardiovascular risk factors, acute coronary syndrome, three vessel disease and left main stem stenosis became increasingly more common in patients with as well as without DM. BMI, creatinine clearance, history of previous myocardial infarction and peripheral vascular disease remained essentially unchanged (Table II). In Patients with DM medication with ACE-inhibitors, β-blockers and statins has increased during more recent time-periods (Table III).

![Figure 2. Annualized proportion of patients with type 2 diabetes mellitus among 14,481 patients undergoing isolated artery bypass grafting during 1970 through 2006](image-url)
BMI, creatinine clearance, history of previous myocardial infarction and peripheral vascular disease remained essentially unchanged. An increasing proportion of the patients with DM had insulin treatment or oral medication. Among 722 patients with insulin treatment 202 (27%) in addition had oral hypoglycaemic medication. Year of diagnosis of DM until year of CABG was significantly longer in patients operated on during 1990-99 (15.6±16.0 years) than during 2000-03 (9.5±8.9 years). Single vessel disease became less common. During 2000-03 almost 80% of the patients received 3-4 or more distal coronary anastomoses. An internal mammary artery graft was inserted in more than 90% of patients operated on after 1989.

**Study I**
This study included patients with type 1 DM. These few patients usually had their diagnosis as teenagers and were on average 10 years younger than nondiabetic patients and those with type 2 DM. Type 1 diabetic patients had less BMI, less frequently hypertension, hyperlipidaemia, unstable angina, and left main coronary artery obstruction, whereas female sex, triple-vessel disease, previous AMI and percutaneous coronary intervention were more common than in patients with type 2 DM.

**Early deaths**
In the entire group of patients with type 2 DM, the adjusted risk of early death was three times higher (OR 2.9, 95% CI 1.8-4.4) than in patients without diabetes (Table IV). The risk of early death in insulin-treated patients with type 2 DM was substantially higher than in patients without diabetes after multivariate adjustment for confounding factors (OR 4.6, 95% CI 2.5-8.4). There was an increased risk of early death also in patients on oral drugs (OR 2.0, 95% CI 1.0-3.8), but the risk in patients on diet only did not differ significantly from that in patients without diabetes.

Table IV. Risks of death within 30 days, within five and ten years after coronary artery bypass surgery in patients with diabetes mellitus in relation to patients without diabetes mellitus.

<table>
<thead>
<tr>
<th>Treatment of type 2 DM (n = 800)</th>
<th>Not diabetes (n = 5871)</th>
<th>All type 2 DM (n = 800)</th>
<th>Insulin (n = 246)</th>
<th>Oral drugs (n = 393)</th>
<th>Diet only (n = 161)</th>
<th>Type 1 DM (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 30 d</td>
<td>103 (1.8%)</td>
<td>34 (4.3%)</td>
<td>16 (6.5%)</td>
<td>15 (3.8%)</td>
<td>3 (1.9%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>2.5 (1.7-3.7)</td>
<td>3.9 (2.3-6.7)</td>
<td>2.2 (1.3-3.9)</td>
<td>1.1 (0.3-3.4)</td>
<td>1.3 (0.1-7.4)</td>
</tr>
<tr>
<td>Adjusted for age and year of surgery</td>
<td>1.0</td>
<td>2.5 (1.7-3.7)</td>
<td>4.2 (2.4-7.3)</td>
<td>2.2 (1.2-3.8)</td>
<td>1.1 (0.3-3.5)</td>
<td>2.9 (0.4-21.8)</td>
</tr>
<tr>
<td>Multivariate adjustment*</td>
<td>1.0</td>
<td>2.9 (1.8-4.4)</td>
<td>4.6 (2.5-8.4)</td>
<td>2.0 (1.0-3.8)</td>
<td>1.3 (0.4-4.2)</td>
<td>3.0 (0.4-23.3)</td>
</tr>
<tr>
<td>Death between 30 d and 5 y</td>
<td>504 (8.7%)</td>
<td>117 (15.3%)</td>
<td>46 (20.0%)</td>
<td>55 (14.6%)</td>
<td>16 (10.1%)</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>n = 5678</td>
<td>n = 766</td>
<td>n = 230</td>
<td>n = 378</td>
<td>n = 158</td>
<td>n = 55</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.8 (1.5-2.2)</td>
<td>2.2 (1.6-3.0)</td>
<td>1.4 (1.1-1.8)</td>
<td>1.2 (0.7-1.9)</td>
<td>1.4 (0.7-3.0)</td>
</tr>
<tr>
<td>Adjusted for age, year of surgery</td>
<td>1.0</td>
<td>1.8 (1.5-2.2)</td>
<td>2.3 (1.7-3.1)</td>
<td>1.4 (1.0-1.8)</td>
<td>1.2 (0.7-1.9)</td>
<td>2.6 (1.2-5.5)</td>
</tr>
<tr>
<td>Multivariate adjustment</td>
<td>1.0</td>
<td>1.6 (1.3-2.0)</td>
<td>2.0 (1.4-2.8)</td>
<td>1.3 (1.0-1.7)</td>
<td>0.9 (0.5-1.6)</td>
<td>2.6 (1.2-5.6)</td>
</tr>
<tr>
<td>Death between 30 d and 10 y</td>
<td>1151 (20.0%)</td>
<td>241 (31.5%)</td>
<td>62 (35.7%)</td>
<td>124 (22.0%)</td>
<td>35 (22.2%)</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>n = 5676</td>
<td>n = 766</td>
<td>n = 230</td>
<td>n = 379</td>
<td>n = 158</td>
<td>n = 55</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.8 (0.8-3.3)</td>
<td>2.0 (1.6-2.5)</td>
<td>1.7 (1.4-2.0)</td>
<td>1.1 (0.8-1.6)</td>
<td>1.4 (0.8-2.3)</td>
</tr>
<tr>
<td>Adjusted for age, year of surgery</td>
<td>1.0</td>
<td>1.8 (1.6-2.1)</td>
<td>2.1 (1.6-2.6)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.1 (0.8-1.6)</td>
<td>2.4 (1.4-4.2)</td>
</tr>
<tr>
<td>Multivariate adjustment</td>
<td>1.0</td>
<td>1.7 (1.5-2.0)</td>
<td>2.1 (1.6-2.6)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.1 (0.8-1.6)</td>
<td>2.4 (1.4-4.2)</td>
</tr>
</tbody>
</table>

*Adjusted for age, year of surgery, sex, previous AMI, peripheral vascular disease, hypertension, hyperlipidaemia, and number of obstructed coronary arteries.
†Adjusted for age, year of surgery, creatinine clearance, and peripheral vascular disease.
‡Adjusted for age, year of surgery, number of obstructed coronary arteries, creatinine clearance, and body weight.
Late mortality and nonfatal AM

The RRs of death at 5 and 10 years exclusive of early deaths and after correction for confounding factors were higher in insulin-treated patients with type 2 DM than in patients without diabetes (RR 2.0, 95% CI 1.4-2.8 and RR 2.1, 95% CI 1.6-2.6, respectively) (Table IV).

The increased long-term mortality in patients with insulin-treated type 2 DM was thus not explained from factors such as age, year of surgery, creatinine clearance or peripheral vascular disease. The RRs of death at 5 and 10 years in patients on oral antidiabetic drugs were 30% and 60% increased, respectively, compared with that in patients without diabetes, but was not significantly increased in the diet-treated group. Survival at 10 years without an AMI was 40% (95% CI 32%–48%) for patients with insulin-treated type 2 DM, 48% (95% CI 42%–54%) for those on oral drugs, and 59% (95% CI 51%–67%) for patients with DM with diet restriction only compared with 66% (95% CI 65%–67%) in patients without diabetes (Figure 3). Analyses of the composite end point death or having a nonfatal AMI yielded similar results as the analyses of deaths only (Table V). At 10 years the adjusted risk was 80% higher in insulin-treated type 2 DM and 40% higher in patients with type 2 DM on oral drugs than in patients without diabetes, but not significantly increased in diet treated patients.

Table V. Risks of nonfatal acute myocardial infarction or death within five and ten years after coronary artery bypass surgery in patients with diabetes mellitus in relation to those without diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 856)</th>
<th>Treatment of type 2 DM (n = 800)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not diabetes (n = 5871)</td>
<td>All type 2 DM (n = 800)</td>
</tr>
<tr>
<td>Death or AM between 30 d and 5 y</td>
<td>723 events (12.7%), n = 5704</td>
<td>159 events (20.9%), n = 762</td>
</tr>
<tr>
<td>Crude</td>
<td>RR</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Adjusted for age, year of surgery</td>
<td>1.0</td>
<td>1.7 (1.4-2.0)</td>
</tr>
<tr>
<td>Multivariate adjustment*</td>
<td>1.0</td>
<td>1.5 (1.3-1.9)</td>
</tr>
<tr>
<td>Death or between 30 d and 10 y</td>
<td>1587 events (27.8%), n = 5704</td>
<td>312 events (40.1%), n = 762</td>
</tr>
<tr>
<td>Crude</td>
<td>RR</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Adjusted for age, year of surgery</td>
<td>1.0</td>
<td>1.7 (1.5-2.0)</td>
</tr>
<tr>
<td>Multivariate adjustment*</td>
<td>1.0</td>
<td>1.6 (1.4-1.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age, year of surgery, number of obstructed coronary arteries, creatinine clearance, previous AMI, and peripheral vascular disease.

**Adjusted for age, year of surgery, creatinine clearance, previous AMI, and peripheral vascular disease.
Study II

Early mortality during 1970-2003 after a first isolated CABG was 3.4% in patients with DM versus 1.8% in patients without DM yielding a two-fold higher risk in DM patients after multivariable correction for age and other confounders (Table VI). There was no clear trend over time periods in the odds ratio for early mortality in DM vs. non-DM patients but in the latest time period (2000-2003) the odds ratio was somewhat lower with a 95% confidence interval including 1.0 (OR 1.5; 95%CI 0.8-2.5). The multivariable adjusted risk of early death during 2000-03 compared to 1970-89 was significantly reduced both in patients with DM (OR 0.3, 95%CI 0.1-0.9) and those without DM (OR 0.4, 95%CI 0.2-0.7) taking changes in patients characteristics during the three decades into account (Table VII). Overall crude all-cause mortality until five years was higher in patients with DM particularly in those operated on during the early period 1970-89 (Fig. 4). Late mortality occurring in survivors after 30 days until five years after operations was almost two times higher after multivariable correction in patients with DM versus in patients without DM (HR 1.8, 95%CI 1.5-2.0) (Table VIII). This disadvantage in patients with a diagnosis of DM was essentially unchanged across the three time-periods.
Table VI. Early Mortality after coronary artery bypass grafting during three time-periods in patients with type 2 diabetes mellitus (DM) compared to in patients without DM.

<table>
<thead>
<tr>
<th>Time-period</th>
<th>Early deaths &lt;30 days</th>
<th>Age</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM Deaths</td>
<td>Not DM Deaths</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>1970-2003</td>
<td>1892</td>
<td>187</td>
<td>1.8</td>
</tr>
<tr>
<td>1970-1989</td>
<td>319</td>
<td>72</td>
<td>2.1</td>
</tr>
<tr>
<td>1990-1999</td>
<td>989</td>
<td>79</td>
<td>1.5</td>
</tr>
<tr>
<td>2000-2003</td>
<td>584</td>
<td>36</td>
<td>1.9</td>
</tr>
</tbody>
</table>

OR, Odds ratio; 95% CI, 95% confidence interval.
Adjusted for age, unstable angina pectoris, left ventricular function, creatinine clearance, history of myocardial infarction, use of internal mammary artery graft, length and weight.

Table VII. Early mortality after coronary artery bypass grafting in patients with and without type 2 diabetes. Mortality during a time-period compared to operations performed during 1970 through 1989.

<table>
<thead>
<tr>
<th>Time-period</th>
<th>Deaths</th>
<th>Age adjusted</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>OR 95%CI</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1892</td>
<td>64</td>
<td>3.4</td>
</tr>
<tr>
<td>1970-1989</td>
<td>319</td>
<td>11</td>
<td>3.5</td>
</tr>
<tr>
<td>1990-1999</td>
<td>989</td>
<td>35</td>
<td>3.5</td>
</tr>
<tr>
<td>2000-2003</td>
<td>584</td>
<td>18</td>
<td>3.1</td>
</tr>
<tr>
<td>Not diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>10523</td>
<td>187</td>
<td>1.8</td>
</tr>
<tr>
<td>1970-1989</td>
<td>3488</td>
<td>72</td>
<td>2.1</td>
</tr>
<tr>
<td>1990-1999</td>
<td>5166</td>
<td>79</td>
<td>1.5</td>
</tr>
<tr>
<td>2000-2003</td>
<td>1869</td>
<td>36</td>
<td>1.9</td>
</tr>
</tbody>
</table>

OR, Odds ratio; 95% CI, 95% confidence interval.
Adjusted for age, unstable angina pectoris, left ventricular function, creatinine clearance, history of myocardial infarction, use of internal mammary artery graft, length and weight.

Table VIII. Mortality 30 days until five years after coronary artery bypass grafting during three time-periods in patients with type 2 diabetes compared to in patients without diabetes.

<table>
<thead>
<tr>
<th>Time-period</th>
<th>Diabetes Deaths</th>
<th>Not diabetes Deaths</th>
<th>Age</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>No.</td>
<td>n</td>
</tr>
<tr>
<td>1970-2003</td>
<td>1828</td>
<td>14.6</td>
<td>10336</td>
<td>859</td>
</tr>
<tr>
<td>1970-1989</td>
<td>308</td>
<td>19.2</td>
<td>3416</td>
<td>293</td>
</tr>
<tr>
<td>1990-1999</td>
<td>954</td>
<td>13.7</td>
<td>5087</td>
<td>444</td>
</tr>
<tr>
<td>2000-2003</td>
<td>566</td>
<td>13.6</td>
<td>1833</td>
<td>122</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval.
Adjusted for age, unstable angina pectoris, left ventricular function, creatinine clearance, history of myocardial infarction, use of internal mammary artery graft, length and weight.
Five-year survival after artery bypass grafting performed during 1970-89, 1990-99 and 2000-03, respectively, in patients with and without type 2 diabetes mellitus. The y-axis ranges from 50% survival.

The multivariable corrected risk of late death was similarly reduced 40% in patients with and in those without DM after CABG performed during 2000-2003 compared to in patients operated on during 1970-89 (Table IX).

Study III
HbA1c concentrations in the 605 patients ranged from 3.4% to 12.3%. HbA1c was <5% in 56% of the patients and only 11% had HbA1c ≥7% (Table X).

Table IX. Late mortality in survivors at 30 days until five years after coronary artery bypass grafting in patients with and without type 2 diabetes. Mortality during different time-periods compared to operations performed during 1970 through 1989.

<table>
<thead>
<tr>
<th>Time-period</th>
<th>Deaths</th>
<th>Age adjusted</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1828</td>
<td>267</td>
<td>14.6</td>
</tr>
<tr>
<td>1970-1989</td>
<td>308</td>
<td>59</td>
<td>19.2</td>
</tr>
<tr>
<td>1990-1999</td>
<td>954</td>
<td>131</td>
<td>13.7</td>
</tr>
<tr>
<td>*2000-2003</td>
<td>566</td>
<td>77</td>
<td>13.6</td>
</tr>
<tr>
<td><strong>Not diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>10336</td>
<td>859</td>
<td>8.3</td>
</tr>
<tr>
<td>1970-1989</td>
<td>3416</td>
<td>293</td>
<td>8.6</td>
</tr>
<tr>
<td>1990-1999</td>
<td>5087</td>
<td>444</td>
<td>8.7</td>
</tr>
<tr>
<td>2000-2003</td>
<td>1833</td>
<td>122</td>
<td>6.6</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval.
*Adjusted for age, unstable angina pectoris, left ventricular function, creatinine clearance, history of myocardial infarction, use of internal mammary artery graft, length and weight.
Table X. Clinical characteristics in 605 patients undergoing coronary artery bypass grafting in relation to concentration of glycosylated haemoglobin (HbA\textsubscript{1c}) before surgery.

<table>
<thead>
<tr>
<th>HbA\textsubscript{1c} concentration</th>
<th>All (n=605)</th>
<th>&lt;5% (n=339)</th>
<th>5&lt;6% (n=144)</th>
<th>6&lt;7% (n=54)</th>
<th>≥ 7% (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>100</td>
<td>56</td>
<td>24</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Percent of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 9</td>
<td>65 9</td>
<td>68 9</td>
<td>66 9</td>
<td>63 10</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>31 3</td>
<td>31 3</td>
<td>31 3</td>
<td>31 2</td>
<td>31 2</td>
</tr>
<tr>
<td>Euroscore</td>
<td>3.6 2.7</td>
<td>3.3 2.6</td>
<td>3.2 2.8</td>
<td>3.8 2.4</td>
<td>4.0 3.0</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>5.9 1.7</td>
<td>5.1 0.9</td>
<td>5.9 1.1</td>
<td>7.4 1.4</td>
<td>8.7 2.6</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>98 28</td>
<td>100 26</td>
<td>93 27</td>
<td>99 29</td>
<td>102 36</td>
</tr>
<tr>
<td>No. anastomoses (%)</td>
<td>3.1 1.0</td>
<td>3.1 1.0</td>
<td>3.2 0.8</td>
<td>3.1 1.0</td>
<td></td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>21 19</td>
<td>22 27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27 3</td>
<td>30 89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin treatment (%)</td>
<td>31 0</td>
<td>42 59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>21 19</td>
<td>38 26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>38 39</td>
<td>27 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMCA stenosis (%)</td>
<td>8 6</td>
<td>11 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>68 75</td>
<td>62 69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td>26 21</td>
<td>32 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely reduced</td>
<td>6 3</td>
<td>6 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMA used (%) (%)</td>
<td>92 92</td>
<td>90 87</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI=body mass index; DM=diabetes mellitus; FPG = Fasting plasma glucose; IMA internal mammary artery; LMCA left main coronary artery stenosis.

Only nine of the 339 patients (3%) with HbA\textsubscript{1c} <5% had DM in contrast to in 109 of those 122 (89%) with HbA\textsubscript{1c} ≥6% (p<0.001). Thus, 11% of the patients had HbA\textsubscript{1c} ≥6% without having a diagnosis of DM. The 68 patients with a HbA1c concentration ≥7% had higher FPG, more frequently diabetes and more often a severely reduced left ventricular function than those with HbA\textsubscript{1c} concentration <5%. With increasing HbA\textsubscript{1c} concentrations an increasing proportion of the patients with DM required insulin treatment. A total of 74 patients (12%) had FPG ≥7.0 mmol/L as well as HbA\textsubscript{1c} ≥6% on admittance. In 38 patients (6%) HbA\textsubscript{1c} was ≥6% but with FPG <7.0 mmol/L. Thirty-five of these patients had DM diagnosis and 4 (10%) died during follow-up. Length of hospital stay and length of follow-up were similar in patients with different preoperative HbA\textsubscript{1c} concentrations (Table XI).

Superficial sternal wound infections occurred more frequently if HbA\textsubscript{1c} concentration was ≥6% (13.9%, 17/122) than if HbA\textsubscript{1c} <6% (5.2%, 25/483) (p=0.007). It seemed that the risk of suffering mediastinitis increased in patients with higher HbA\textsubscript{1c} concentrations. The rate of mediastinitis was 4.9% (5/122) in patients with HbA\textsubscript{1c} ≥6% versus 2.1% (10/483) if HbA\textsubscript{1c} <6% (p=0.20) (HR 1.9, 95% CI 0.6-5.9) after multivariable adjustment for age, Euroscore and BMI. Mediastinitis occurred after the operation in 5% of the patients with DM (8/161) versus in 1.8% of the patients without DM (8/444) (p=0.03).
Table XI. Outcome after coronary artery bypass grafting in 605 patients in relation to preoperative concentration of glycosylated haemoglobin (HbA$_{1c}$).

<table>
<thead>
<tr>
<th>HbA$_{1c}$ concentration</th>
<th>All (n=605)</th>
<th>&lt;5% (n=339)</th>
<th>5&lt;6% (n=144)</th>
<th>6&lt;7% (n=54)</th>
<th>≥7% (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>7.7 6.8</td>
<td>7.5 6.0</td>
<td>8.1 7.7</td>
<td>7.6 7.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>3.5 0.9</td>
<td>3.5 0.8</td>
<td>3.6 0.9</td>
<td>3.6 1.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Sternal wound infection**
- Superficial (%) 43 (7.1) 19 (5.6) 6 (4.2) 11 (20.4) 6 (8.8)
- Mediastinitis (%) 16 (2.6) 5 (1.5) 5 (3.5) 3 (5.6) 2 (4.4)

**Mortality**
- <30 days (%) 10 (1.7) 2 (0.6) 2 (1.4) 5 (9.3) 1 (2.4)
- Total deaths (%) 43 (7.1) 12 (3.5) 8 (5.6) 12 (22.2) 11 (16.2)

Figure 5. Survival after coronary artery bypass grafting in relation to preoperative glycosylated haemoglobin 1 (HbA$_{1c}$) concentration in 605 patients.
Survival at four years was 96% in patients with HbA1c concentration <5% (Figure 5). It was 93% in patients with HbA1c in the interval 5<6%, 80% in those with HbA1c 6<7% and 78% in patients with HbA1c ≥7%. Forty-three patients died during the follow-up an average of 3.5 years after the operation. All cause mortality was 18.9% (23/122) in patients with HbA1c ≥6% compared to 4.1% (20/483) if HbA1c <6% (p<0.001). The risk of death was substantially higher, both at univariate analysis and after multivariable adjustment, if the preoperative HbA1c was ≥6% compared to if HbA1c was <6% (HR 5.4, 95%CI 1.3-10.0) (Table XII). There was a similar risk regardless of DM diagnosis.

**Study IV**

The preoperative patient characteristics are listed in Table XIII. TEA groups did not differ from non-TEA groups for any preoperative or surgical parameter. Patients with and without DM did differ in fasting B-glut and HbA1c concentration. The average BMI ≥25 kg/m² indicates that all patient groups were overweight. All patients were using beta-adrenergic blocking agents except one in the non-TEA, non-DM group; two in the TEA, non-DM group and five in each DM group.

| Table XIII. Characteristics of patients with and without diabetes mellitus (DM) undergoing coronary surgery without (Controls) or with thoracic epidural analgesia (TEA). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Non-DM groups:  | DM groups:      |                  |                  |
|                  | Controls        | TEA             | Controls-DM     | DM-TEA          |
| No. patients     | 30              | 30              | 22              | 22              | p              |
| Age (years)      | 68 ± 8          | 67 ± 8          | 62 ± 13         | 63 ± 7          | 0.12           |
| EuroSCORE        | 2.5 ± 1.7       | 2.4 ± 1.8       | 2.9 ± 2.5       | 3.5 ± 2.3       | ns             |
| BMI (kg/m²)      | 26 ± 3          | 27 ± 4          | 26 ± 4          | 28 ± 4          | ns             |
| fB-glut (mmol/L) | 5.0 ± 0.5       | 4.9 ± 0.4       | 7.1 ± 1.2       | 7.2 ± 1.7       | <0.001*        |
| HbA1c (% Hb)     | 4.8 ± 1.5       | 5.0 ± 1.3       | 6.4 ± 1.5       | 6.6 ± 2.0       | <0.001*        |
| No. anastomoses  | 2.9 ± 0.9       | 3.1 ± 0.9       | 3.3 ± 1.0       | 3.0 ± 0.8       | ns             |
| CPB (min)        | 41 ± 23         | 39 ± 23         | 39 ± 16         | 35 ± 17         | ns             |
| Surgery (min)    | 162 ± 31        | 166 ± 41        | 165 ± 28        | 196 ± 59        | ns             |
| Fluid balance (L)| 3.7±1.1         | 4.2±1.3         | 3.8 ± 1.0       | 3.6 ± 1.0       | ns             |
| LOS (days)       | 6.8 ± 2.2       | 6.5±1.3         | 6.5 ± 1.2       | 6.9 ± 2.7       | ns             |
| Norepi (min)     | 0(0-66)         | 18(0-130)       | 0(0-18)         | 9(0-130)        | p=0.04         |
| Norepi (mg)      | 0(0-2.6)        | 0.7(0-5.2)      | 0(0-0.7)        | 0.3(0-5.2)      | p=0.02         |
| Ventilator (hours)| 0(0-15)        | 5(0-22)         | 0(0-9)          | 3.5(0-18)       | p=0.02         |

*Comparison all groups. SD = standard deviation; BMI = body mass index; fB-glut = fasting blood glucose; HbA1c = glycosylated haemoglobin; CPB = cardiopulmonary bypass; Norepi = norepinephrine, LOS = length of hospital stay.


**Day of surgery**

There was no difference between groups for number of anastomoses, time on CPB, surgery time, fluid balance during the surgical day, nor length of hospital stay. Both TEA groups required more and longer use of vasopressors, and less ventilator support (Table XIII). All patients required a continuous insulin infusion during the perioperative 24 h period. For non-diabetics, the departmental goal of always maintaining B-glu <6.9 mmol/L was attained in 33% of those with TEA and 16% of those without TEA. In diabetics 23% of patients with TEA achieved that goal but not one patient without TEA. Maintaining an average B-glu <6.9 mmol/L during the day of surgery was achieved in 78% with TEA vs. 54% without TEA in non-diabetics, and 64% with TEA and 32% without TEA for diabetics. TEA reduced both insulin requirements (by about 36%, p=0.004) and mean B-glu (by about 8%, p=0.02) during the day of surgery for non-DM groups. For patients with DM, TEA resulted in a lower mean B-glu during the day of surgery with the same amount of insulin. TEA did not result in a significantly lower mean B-glu at any single time for either non-DM or DM groups (Figs 6). The insulin required during the day of surgery and the mean B-glu were significantly higher (p<0.001 and p=0.02) in DM patients than in non-DM patients.

**Postoperative days 1–3**

There was prominent postoperative hyperglycaemia (Fig. 6). B-glu was still elevated on day 3 (23–31%, p<0.001) relative to preoperative times; this increase was not altered by TEA. Half (52%) of controls had fasting B-glu ≥6.1 mmol /L (threshold for DM) on day 3. TEA was not able to attenuate hyperglycaemia during the first 3 postoperative days in either DM or non-DM groups. The small differences seen when only the surgical day was averaged are no longer significant when the whole study period is analyzed. All patients with DM received insulin in addition to their oral medications during the 3 postoperative days (mean 18, 28, 27 units/day on days 1–3, respectively) while only one non-diabetic with TEA and two non-diabetics without TEA each received insulin once on the ward.

![Figure 6. Whole blood glucose concentrations (standard deviations) are shown versus sampling time of day (from day of surgery (Op) until the third postoperative day (POD-3)) in patients with diabetes mellitus (DM) undergoing coronary artery bypass grafting with or without use of thoracic epidural analgesia (TEA). Fasting blood glucose (fB-glu) values are shown before surgery and at 6 o’clock on POD-2 & 3.](image-url)
Study V

The CABG patients of the STAGE cohort were classified into four groups with increasing evidence of diabetes. Seventeen percent of the patients had a clinical diagnosis of type 2 diabetes on admittance (n=11; 2 oral drugs, 6 insulin treated, 3 diet only), 15 % had undiagnosed DM as indicated by pre-operative fasting blood glucose (FBG) level of ≥ 6.1 mmol/L (n=10) and 11 % was defined as pre-DM since their FBG levels were in the range of 5.6 < 6.1 mmol/L (n=7). The remaining patients (57 %) had a normal FBG < 5.6 mmol/L (n=38). Patients with DM and those with undiagnosed DM had longer total rehabilitation and hospitalization than patients without DM (Figs. 1A and 1B). The underlying reasons for the prolonged stay at the hospital and rehabilitation homes were mainly atrial fibrillation (AF) but also infection, bleeding, kidney failure, stroke and pneumothorax (Figure 7C).

We postulated that patients with already ongoing but subtle inflammation at the time of CABG operation would be more prone to these complications. We used the STAGE gene expression compendium to seek changes in gene activity in the liver, skeletal muscle and visceral fat that could predict CABG patients at risk of prolonged post-operative stay including rehabilitation (“rehabilitation”) or not (“hospitalization”). Hence, we examined correlations between post-operative stay and mRNA levels obtained from each of the tissues isolated during CABG. The gene, dual specificity phosphatase 1 (DUSP1), had the highest positive correlation with rehabilitation days. Using stepwise regression, we found that this correlation was independent of FBG levels as well as patient age. The mRNA levels of DUSP1 did not only segregate the STAGE patients with the longest and shortest rehabilitation (Figure 8A) and hospitalization (Figure 8B) but also discriminated all patient into those with normal (8 days) and prolonged (>8 days) rehabilitation (P< 0.003, Figure 8C) as well as hospitalization (P< 0.004, Figure 8D). RT-PCR confirmed the difference in DUSP1 mRNA levels in skeletal muscle between those with the shortest and longest rehabilitation and hospitalization (Figures 8E and F).
**Validation of DUSP1 as a Marker of Post-Operative Complications and Stay.**

Of the ~17,000 genes examined in the STAGE study, we identified DUSP1 activity (i.e. mRNA levels) in skeletal muscle as the strongest predictor of post-operative stay and thus risk of complications. Now despite the fact that this observation was confirmed by RT-PCR, the relation between DUSP1 and post-operative stay may still be a chance observation. Furthermore, gene expression in skeletal muscle is not a feasible source for biomarker. For these reasons, we sought ethical approval to collect pre-operative blood samples from patients elected for CABG at the Tartu University hospital in Estonia. We collected 54 CABG patients in Tartu. The characteristics of this group of patients were similar to the STAGE cohort. We then isolated RNA from whole blood and performed RT-PCR analyses of the CABG patients with the longest and shortest hospitalization. DUSP1 blood mRNA levels clearly separated these two groups whereas the level of the established blood marker of early inflammation – high sensitive C-reactive protein (hCRP) did not.

**Figure 8. DUSP1 mRNA levels and Postoperative Stay in the STAGE Cohort.**

Box plots of number of rehabilitation (A) and hospitalization (B) days of patients with low (n=10) and high (n=10) mRNA levels of DUSP1 in skeletal muscle as indicated by the GeneChip. Bar grafts of DUSP1 mRNA levels in skeletal muscles of all patients with normal (≤8 days) and long (>8 days) rehabilitation (C) and hospitalization (D). Box plots of mRNA levels of DUSP1 in skeletal muscle as indicated by RT-PCR in patients with normal (n=13) and long (n=12) rehabilitation (E) and normal (n=10) long (n=8) hospitalization (F). “Rehabilitation” includes both days in hospital and at rehabilitation wars whereas “hospitalization” only include days in hospital. The boxes enclose values between the 25th and 75th percentiles and the bars between the 10th and 90th percentiles. Dots show extreme values. Bar graph plots show means and SDs.
DISCUSSION

Increase of DM in CABG
A variety of causes may explain a marked increase of patients with DM having CABG as also observed by other authors. During the initial experience surgeons were hesitant to accept patients for CABG with peripherally located coronary artery obstructions often observed in patients with DM. Randomized trials have shown that CABG is a better alternative than PCI in patients with DM and multivessel coronary artery disease because of higher rates of complete revascularization and less risk of repeat revascularization. Cardiac death, myocardial infarction or angina requiring revascularization occur less frequently following CABG than after PCI in patients with DM and multivessel coronary artery disease. Surgical revascularization is an effective treatment for patients with DM whose coronary artery lesions do not qualify for endovascular revascularization. The advantages seen with CABG over balloon-only PCI in early trials may not be applicable in the era of drug-eluting stents, glycoprotein IIb/IIIa inhibitors, and the latest medical therapies. PCI may be a treatment of choice in DM in case of discrete lesions in large vessels, severe co-morbidities and if the internal mammary artery cannot be used. The number of patients with DM undergoing revascularization is expected to increase as the prevalence of DM is increasing globally with a high incidence of coronary artery disease.

Patients
In consistency with other reports we found in Study II that patients with DM accepted for CABG were more likely to be female and more often have co-morbidities such as higher BMI, previous stroke, history of hypertension, peripheral vascular disease, unstable coronary syndrome, worse LV function, and more widespread coronary artery disease than patients without DM. Type 2 DM with insulin resistance is closely linked with the metabolic syndrome. Echahidi and co-workers reported a 2.7-fold increase of risk of death within 30 days of CABG in patients with DM and metabolic syndrome, and a 2.4-fold increased risk patients with metabolic syndrome without DM but no increased risk in the patients with DM but not metabolic syndrome. Our observational study includes all 12,415 first-time isolated CABG procedures performed at one institution during more than three decades. During this period there was substantial increase of type 2 DM, of patient age and of cardiovascular risk factors. Throughout the long time-period major improvements were introduced regarding operative technique, myocardial protection, perioperative patient management and pharmacological treatment of diabetes and cardiovascular risk factors. The internal mammary artery was almost routinely used in our series. From 1983 all patients routinely received lifelong treatment with acetylsalicylic acid 160 mg daily from the first post-operative day after CABG. The use of angiotensin-converting enzyme (ACE) inhibitors increased from 22% during 1996-1999 to 35% during 2000-2003 and the corresponding use of statins from 49% to 71%.

Mortality
Overall early and five-year multivariable adjusted mortality was about two-fold higher in patients with DM than in those without DM and possibly somewhat lower in patients operated on more recently. During 2000-03 early and five-year multivariable adjusted mortality was substantially reduced compared to after operations performed earlier during 1970-89 irrespective of DM status. A significant reduction of early mortality after adjustment for confounders was a result of improvements in the perioperative management of patients undergoing open heart surgery such as technical development of pumps and oxygenators, shorter operative times, less cooling, a refined and more careful surgical technique and handling of grafts, methods of myocardial protection, anaesthesiological and intensive care monitoring and practices to deal with heart, pulmonary and renal failure in addition to the understanding and introduction of effective antithrombotic regimens.
Early mortality is influenced by factors such as operative technique and events occurring during the early recovery period whereas late mortality should be more influenced by patient’s cardiovascular risk factors, the extent of coronary artery disease, and degree of left ventricular impairment and patency of inserted grafts. Survival after CABG in patients with diabetes is greatly affected by associated co-morbidities of peripheral vascular disease and renal failure. Diabetic patients treated with an early invasive strategy for unstable angina and non-ST-segment elevation myocardial infarction have a higher in-hospital and long-term mortality that is largely explained by their less favourable baseline characteristics including more advanced coronary artery disease. Observed differences in survival between CABG-treated patients with and without diabetes may be a result of differential risk of mortality from non-cardiac causes. Patients with insulin-dependent type II DM who undergo CABG have a high rate of major complications and an extremely unfavourable short- and long-term prognosis.

Improved survival over time

An improved prognosis of survival after CABG over time in patients with DM was anticipated because continuous dramatic advances in the medical treatment of patients with ischemic cardiovascular disease and DM have occurred. As a consequence of guidelines there is an increased awareness to treat modifiable risk factors and co-morbidities. Patients are encouraged to reduce cardiovascular risk by means of cessation of smoking, dietary modifications and physical exercise to treat obesity, control of hyperlipidaemia, hypertension and renal failure. Angiotensin-converting enzyme inhibitors reduce risk of cardiovascular complications in patients with DM regardless of the anti-hypertensive effect. Similarly statins reduce the cardiovascular risk in patients with DM irrespective of cholesterol lowering effect. Use of these two drugs increased with time in our patients. In the UKPDS the use of metformin reduced the risk of myocardial infarction.

\( HbA_{1c} \)

In study III almost 70% of the patients with a diagnosis of DM had \( HbA_{1c} \) concentrations ≥6% and half of these patients also had FPG higher than 7 mmol/L. Fasting hyperglycaemia and elevated Hba1 were also found in the patient group without a diagnosis of DM. In a survey of 4662 men \( HbA_{1c} \) showed a continuous relation to all cardiovascular mortality with the lowest mortality rate in those with concentration <5%, but no exact cut-off concentration above which there is a disproportional increase of macrovascular risk has yet been defined. Elevated concentrations of \( HbA_{1c} \) predict an increased probability of developing DM. There were among our patients those with elevated concentrations of \( HbA_{1c} \) but without a diagnosis of DM. These patients with elevated \( HbA_{1c} \) need vigilant surveillance and possibly a more forceful treatment of risk factors to reduce a future risk to develop DM. In the United Kingdom Prospective Diabetes Study elevated \( HbA_{1c} \) was a negative prognostic factor whereby each 1% decrease in \( HbA_{1c} \) was associated with a significant reduction of both macrovascular and microvascular complications. We and others have documented an increased risk of death and adverse outcome in patients with DM after CABG. In our study length of postoperative hospital stay was similar in patients with different concentrations of Hba1c but we were not able to include in our analyses the entire duration of rehabilitation spent in other hospitals. However, Medhi and co-authors found Hba1c >7% to be a strong predictor of a length of hospital stay of 6 days or longer in 135 patients after CABG, suggesting the correctness of Hba1c as a surrogate marker for cardiac and non-cardiac morbidity. Postprandial blood glucose level may influence \( HbA_{1c} \) to a greater extent than fasting levels.

TEA

Study IV shows that TEA can improve glycaemic control during the 24h period starting with surgery for CABG, but did not improve the postoperative hyperglycaemia the following 3 days after surgery in either diabetic or non-diabetics and the use of TEA for
CABG is therefore, in respect to glycaemic control, doubtful.

Postprandial hyperglycaemia in patients with DM and the incretin effect
When analyzing data in the TEA study we observed higher postprandial plasma glucose levels in patients with than in those without DM. The phenomenon that oral glucose intake elicits higher insulin response that iv infusion of glucose is called incretin effect.\textsuperscript{118} The two hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) stimulate insulin secretion in response to meal ingestion. Both are metabolized quickly by dipeptidyl peptidase-IV (DPP-IV).\textsuperscript{119} In patients with DM glucagon concentrations fail to decrease or may even increase after carbohydrate ingestion and will increase hepatic glucose production resulting in pronounced postprandial hyperglycaemia.\textsuperscript{118}

DUSP1
In several reports hyperglycaemia and DM are associated prolonged hospital stay after CABG compared to in patients.\textsuperscript{124,125,129} In accordance with DM and not previously DM in the STAGE cohort also had prolonged hospitalization compared to the non-diabetics, regardless if rehabilitation days were included. Many postoperative complications are related to inflammatory processes.\textsuperscript{122,123} DUSP1 has in previous studies been highlighted as an early marker of inflammatory processes and has also been associated to extent of carotid atherosclerosis.\textsuperscript{124-128} DUSP1 has previously been reported to be expressed by white blood cells and activated in cases of subtle inflammation.\textsuperscript{129}

Unsatisfying diagnosis of hyperglycaemia
Previously undiagnosed diabetes and impaired glucose tolerance are common in patients with an acute myocardial infarction. Among 181 patients with acute myocardial infarction, 35% had impaired glucose tolerance and 31%, had undiagnosed diabetes mellitus at discharge.\textsuperscript{130} Blood glucose, even within the normal range, is a strong independent predictor of 2-year mortality in nondiabetic subjects with CVD and therefore of prognostic significance for these high-risk patients.\textsuperscript{131} The preclinical diagnosis of CAD is effective in reducing the risk of cardiac events, especially major events, in subjects with type 2 diabetes mellitus at high cardiovascular risk.\textsuperscript{132}

Hyperglycaemia increases the risk of suffering an AMI and significantly worsens the prognosis once the patient has an AMI. For this reason, it was strongly recommended to treat diabetic patients more aggressively, not only those with symptomatic IHD, but also asymptomatic patients. Actually, survival of asymptomatic diabetic patients is similar to non-diabetic patients who suffered an AMI.\textsuperscript{133}

Methodological considerations
Strength of studies I-III was the complete follow-up by using a unique personal number linked to national registers allowing every patient to be traced. Thus, with regard to vital status there was essentially no misclassification in these studies. Limitations were incomplete data of diagnosis of DM after hospital discharge. The information of DM reflected the situation at the time of the operation. It goes without saying that during the years following the operation DM was diagnosed in many patients who were originally not classified as having DM.\textsuperscript{134} Assumed inferior results in these patients may tend to attenuate the true differences in observed long term mortality between DM and non-DM patients. During recent years information has evolved that many patients not having a diagnosis of DM on admission have dysglycaemia and a pre-diabetic state with IFG and or impaired OGTT. The important implication is that many patients listed as non-diabetic have a disturbed glucose homeostasis and an increased risk after CABG.\textsuperscript{84}

Only a few potential confounders were consistently available in the entire database and changed the multivariable adjusted point estimate at least 10%. Patients in whom medication with beta blockers and statins was started after treatment for unstable coronary syndrome were classified as having hypertension and hyperlipidaemia, respectively, although we did not have more detailed information about blood pressures and lipid levels. We did not have valid information of smoking
habits. Diabetes is associated with dyslipidemia, in particular by increased triglyceride levels and low HDL cholesterol, as well as hypertension. Failure to fully adjust for these factors in analyses of mortality most likely resulted in residual confounding in estimates of odds ratios and hazard ratios reflecting the increased risk associated with diabetes. The net effect of residual confounding from major cardiovascular risk factors may have been an overestimate of the risk associated with diabetes.

**Future optimizing of glycaemia and risk factors** Because potentiation of atherogenesis and cardiac dysfunction occurs in the presence of early diabetic symptoms as well as in the established disease, early implementation of strategies to reduce cardiovascular risk factors and to slow diabetes progression may help to improve long-term outcomes for at-risk individuals. Such interventions may include well-established treatments for hypertension and dyslipidemia, diet improvements, weight loss, and exercise as well as novel pharmacologic interventions aimed at newly identified therapeutic targets.

Treatment of hypertension in patients with DM will reduce macro- and microvascular complications and mortality but not stroke. Randomized trials have shown that decreasing glycemic level is effective to reduce long-term vascular and neuropathic complications. Preventive strategies should be very aggressively applied to diabetic patients, including the use of β-blockers, statins and optimization of glycemic and/or metabolic control with insulin if diet and/or general measures or oral hypoglycemic drugs are not enough. Routine treatment of patients with type 2 DM with aspirin seems logic based on the prothrombotic state and platelet physiology but hard evidence from randomized trials are lacking. Particularly in the elderly with type 2 DM treatment of important modifiable risk factors for cardiovascular disease is suboptimal.

The most appropriate target levels for blood glucose and HbA1c have not been assessed. The HbA1c level should be as close to normal (6%) without episodes of hypoglycemia. Halkos and associates documented HbA1c greater than 8.6% was associated with a 4-fold increase in mortality and that increase in HbA1c increased the risk of myocardial infarction, deep sternal wound infection, renal failure and cerebrovascular accident. Patients with normal HbA1c have a low incidence of DM whereas patients with elevated HbA1c who do not have DM need more careful follow-up and possibly aggressive treatment to reduce the risk of DM. Assiduous attention to risk factors overweight, hypertension and dyslipidaemia will improve the prognosis.

In patients with DM it is imperative to carefully monitor glycemic control and lipid concentrations to achieve optimal outcome. Despite revascularization with PCI the mortality risk of even mild elevations in FBG is substantial, emphasizing the importance of early detection and treatment of glycaemia-related risk. Poor glycemic control during and after heart surgery is a pervasive problem. Implementation of subcutaneous insulin orders and use of a targeted standardized insulin algorithm should result in improved glycemic control. Sliding scale regimen may result in roller coaster effect with increased hyperglycaemia as well as hypoglycaemia.

Caffeine is a counter regulatory hormone that increase blood pressure, heart rate and stress and increase 2 hour postprandial blood glucose and insulin levels. A 20% reduction of postprandial blood glucose can be achieved by avoiding caffeine. However, in a Swedish population high consumers of coffee had a reduced risk of DM and impaired glucose tolerance assumed to be. The beneficial effects may involve both improved insulin sensitivity and enhanced insulin response.

Thus strict monitoring of risk factors with optimal medication and treatment of hyperglycemia will improve prognosis in patients with type 2 DM.

Bariatric surgery is an efficient procedure for controlling type 2 DM in morbidly obese patients. In order to improve the incretin effect that is either greatly impaired or absent De Paula and associates laparoscopically interposed a segment of ileum into the proximal
jejenum in 39 obese patients with DM and obtained glycemic control in 87%.

Despite an increased risk compared to in patients without DM CABG is definitely indicated in patients with obstructive coronary artery disease. It should be stressed that silent ischemia is not uncommon in patients with DM. In the large cohort of patients with left main stem stenosis or triple vessel disease and often an impaired left ventricular function survival prognosis will be improved compared to if revascularization was not performed. CABG in DM will improve the patients symptoms and make physical activity possible in patients who have been limited from angina pectoris.

CONCLUSIONS

We conclude that type 1 DM was rare in patients undergoing CABG compared to type 2 DM. Type 2 DM requiring insulin treatment or oral antidiabetic drugs was associated with an increased early and long-term risk of death or AMI after CABG whereas diet treated patients had a risk similar to that in patients without diabetes. Type 2 DM requiring insulin treatment or oral antidiabetic drugs at the time of surgery was a risk factor for death and AMI after CABG but not in diet treated patients, who had a lower risk similar to that in patients without diabetes. The long-term outcome was worst in insulin treated type 2 DM patients. Our findings support intense metabolic monitoring and attempt to reduce cardiovascular risk factors in patients with diabetes in particular those requiring insulin after CABG in order to reduce the risk of death or acute myocardial infarction.

Multivariable adjusted early mortality and late mortality until five-years after CABG was about two-fold higher in patients with than in those without DM. The adjusted risk of early and late death during 2000-03 compared to 1970-89 were strongly reduced both in patients with and without DM. Despite medical advances late mortality after CABG in patients with DM operated on recently remained increased.

HbA1c ≥6% was associated with an increased risk of postoperative superficial sternal wound infections and a trend for higher mediastinitis rate and a significantly higher mortality three years after CABG in patients with DM as well as in those without DM.

Epidural analgesia improved glucose homeostasis minimally during the initial 24 postoperative hours but did not attenuate the marked hyperglycaemia during the subsequent three postoperative days which occurred even in patients without DM. These marginal benefits of TEA do not in themselves strengthen the indication for TEA for CABG.

In a well-characterized CABG cohort, mRNA levels of DUSP1, an anti-inflammatory gene, predicted postoperative stay. This marker may be of general use for predicting risk for postoperative complications and prolonged hospital stay. Our study support that even subtle preoperative inflammation may be detrimental in increasing the risk of postoperative complications prolonging hospitalization. The clinical significance of measuring DUSP1 expression in blood may very well be proven useful as a general marker for postoperative complications.
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REFERENCES


81. Latham R, Lancaster AD, Covington JF, Pirola JS, Thomas CS. The association of diabetes and glucose...


