Randomized Trial of Insulin-Glucose Infusion Followed by Subcutaneous Insulin Treatment in Diabetic Patients With Acute Myocardial Infarction (DIGAMI Study): Effects on Mortality at 1 Year

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Objectives. We tested how insulin-glucose infusion followed by multidose insulin treatment in diabetic patients with acute myocardial infarction affected mortality during the subsequent 12 months of follow-up.

Background. Despite significant improvements in acute coronary care, diabetic patients with acute myocardial infarction still have a high mortality rate.

Methods. A total of 620 patients were studied: 306 randomized to treatment with insulin-glucose infusion followed by multidose subcutaneous insulin for ≥ 3 months and 314 to conventional therapy.

Results. The two groups were well matched for baseline characteristics. Blood glucose decreased from 15.4 ± 4.1 to 9.6 ± 3.3 mmol/liter (mean ± SD) in the infusion group during the 1st

24 h, and from 15.7 ± 4.2 to 11.7 ± 4.1 among control patients (p < 0.0001). After 1 year 57 subjects (18.6%) in the infusion group and 82 (26.1%) in the control group had died (relative mortality reduction 29%, p = 0.027). The mortality reduction was particularly evident in patients who had a low cardiovascular risk profile and no previous insulin treatment (3-month mortality rate 6.5% in the infusion group vs. 13.5% in the control group [relative reduction 52%, p = 0.046]; 1-year mortality rate 8.6% in the infusion group vs. 18.0% in the control group [relative reduction 52%, p = 0.020]).

Conclusions. Insulin-glucose infusion followed by a multidose insulin regimen improved long-term prognosis in diabetic patients with acute myocardial infarction.

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Patients with diabetes mellitus have a considerably higher short- and long-term mortality rate after myocardial infarction than do nondiabetic patients (1–7). This difference has remained despite the introduction of new therapeutic measures that have decreased overall morbidity and mortality after acute myocardial infarction (8–12). Because diabetes mellitus is rather common among patients with infarction, its relative impact on mortality in ischemic heart disease seems to be increasing (13,14). It has been suggested that diabetic patients have a more extensive and distal coronary artery disease with preexisting cardiac dysfunction due to diabetic cardiomyopathy and autonomic imbalance (15–17). Such factors could explain the increased mortality in diabetic patients with acute myocardial infarction. In diabetes, fatty acid metabolism is presumably increased, compromising glycolysis not only in ischemic but

also in nonischemic areas (18). Beta-adrenergic blocking agents reduce lipolysis and the amount of circulating free fatty acids. Subgroup analyses from postmyocardial infarction studies demonstrate that beta-blockade seems to be of special benefit in diabetic patients (19,20). Another way to suppress free fatty acid oxidation is by the infusion of insulin-glucose (21). On the basis of a small study and the use of historical control subjects, Clark et al. (22) suggested that improved metabolic control by means of intravenous insulin could reduce the high initial complication rate and mortality among diabetic patients with acute myocardial infarction. Another similar study reached contradictory results (23). Prospective studies designed and powered to demonstrate mortality reduction by means of insulin-glucose infusion in diabetic patients with acute myocardial infarction have so far not been reported (24).

The impairment of platelet and fibrinolytic function in patients with diabetes mellitus (25,26) also may contribute to the high rate of early recurrent infarction. Insulin treatment has recently been shown (25,27) to reduce thromboxane A production and to decrease plasma plasminogen activator inhibitor-I activity. These observations give further theoretic support to the hypothesis that insulin therapy in the immediate

Table 1. Protocol Used by the Coronary Care Unit Nurses for the Insulin-Glucose Infusions

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

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

If blood glucose is stable and ≤10.9 mmol/liter after 10 PM, reduce infusion rate by 50% during night.

Blood Glucose Level (mmol/liter)	
>15 mmol/liter:	Give 8 IU of insulin as an intravenous bolus injection and increase infusion rate by 6 ml/h.
11 to 14.9 mmol/liter:	Increase infusion rate by 3 ml/h.
7 to 10.9 mmol/liter:	Leave infusion rate unchanged.
4 to 6.9 mmol/liter:	Decrease infusion rate by 6 ml/h.
<4 mmol/liter:	Stop infusion for 15 min. Then test blood glucose and continue testing every 15 min until blood glucose is ≥7 mmol/liter. In the presence of symptoms of hypoglycemia, administer 20 ml of 30% glucose intravenously. The infusion is restarted with an infusion rate decreased by 6 ml/h when blood glucose is ≥7 mmol/liter.

peri-infarction period may improve the ischemic damage and prognosis.

The DIGAMI study (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) was initiated to test the hypothesis that rapid improvement of metabolic control in diabetic patients with acute myocardial infarction by means of insulin-glucose infusion decreases the high initial mortality rate and that continued good metabolic control during the early postinfarction period improves the subsequent prognosis.

Methods

Definitions. *Diabetes mellitus.* Diabetes mellitus was considered present if a patient had been given this diagnosis and was receiving treatment (diet, tablets or insulin). Patients with no previous diagnosis of diabetes mellitus but with a blood glucose level ≥11 mmol/liter on admission were classified as having newly detected diabetes mellitus and were also included. The patients were classified as non–insulin-dependent or insulin-dependent by clinical history and according to the definitions of the National Diabetes Data Group (28). Thus, patients considered non-insulin dependent were usually >40 years old at diagnosis, had not required insulin for 2 years after the diagnosis and were not prone to ketosis.

Myocardial infarction. The diagnosis "definite myocardial infarction" required fulfillment of at least two of the following criteria: 1) chest pain of at least 15 min duration; 2) at least two values of serum creatine kinase and serum creatine kinase B above the normal range (normal value +2 SD) 10 to 16 h after the onset of symptoms or at least two serum lactic dehydrogenase values +2 SD above the normal range 48 to 72 h after onset of symptoms, including an isoenzyme pattern typical of myocardial infarction; 3) development of new Q waves in at least 2 of the 12 standard ECG leads. The diagnosis "possible myocardial infarction" was made if typical chest pain was combined with only one serum creatine kinase or serum lactic dehydrogenase value above the normal range or if Q waves

appeared in only 1 of the 12 standard ECG leads, or both. A reinfarction was defined as an event fulfilling the criteria given for a myocardial infarction but appearing >72 h after the index infarction.

Study design. In the multicenter DIGAMI study all patients admitted to the coronary care units of 19 Swedish hospitals (see Appendix) were considered for inclusion. Inclusion criteria were suspected acute myocardial infarction within the preceding 24 h combined with previously known diabetes mellitus and a blood glucose level >11 mmol/liter or a blood glucose level >11 mmol/liter even without known diabetes mellitus. The following exclusion criteria were applied: inability to participate for reasons of health (e.g., too sick to give informed consent or unable to manage multidose insulin treatment), refusal to participate, residence outside the hospital catchment area, enrollment in other studies and previous participation in DIGAMI. Subjects without any exclusion criteria were randomized in blinded manner to one of two groups: insulin-glucose or control. In addition to standard coronary care unit therapy, patients in the insulin-glucose group received an insulin-glucose infusion according to a predefined protocol for ≥24 h (Table 1), then subcutaneous insulin four times daily for ≥3 months. Control patients were treated according to standard coronary care unit practice and did not receive insulin unless it was deemed clinically indicated.

The patients were classified as being at high risk if they fulfilled two or more of the following criteria: age >70 years, history of previous myocardial infarction, history of congestive heart failure, current treatment with digitalis. Before randomization the patients were stratified into one of four groups according to risk classification (high; low) and to previous antidiabetic treatment (insulin; no insulin). Predefined strata were: 1) no insulin, low risk; 2) no insulin, high risk; 3) insulin, low risk and 4) insulin, high risk.

The DIGAMI protocol was approved by the ethical com-

mittees at the Karolinska Institute and the Universities of Gothenburg, Linköping, Lund and Uppsala, Sweden.

The insulin-glucose infusion was started by the nurse in charge of the coronary care unit as soon as possible after the patient's arrival. Samples for determination of blood glucose were drawn from an intravenous cannula at time intervals outlined in the protocol (Table 1). The accuracy and feasibility of the method used have been previously described (29). The infusion was continued until stable normoglycemia was attained and always for ≥24 h. Subcutaneous administration of insulin was instituted immediately after cessation of the infusion, according to a multidose regimen, with the aim of maintaining stable normoglycemia. It consisted of soluble insulin administered through an insulin pen three times daily before meals combined with medium–long-acting insulin in the evening (Isuhuman Rapid, Isuhuman Basal; Optipen, Hoechst AG, Sweden). Subcutaneous insulin treatment was withdrawn if serious hypoglycemic events occurred despite repeated dose adjustments. In patients who proved unable to manage the insulin treatment because of a physical or psychiatric handicap, attempts were made to obtain the assistance of a district nurse or a relative before treatment was stopped.

Serum potassium (normal range 3.5 to 5.0 mmol/liter) was measured immediately before the insulin-glucose infusion and then after 6, 12 and 24 h. Serum potassium was checked immediately in patients who developed any kind of clinically significant arrhythmia.

Concomitant therapy. The patients received treatment other than glucose-insulin infusion according to predefined guidelines. If there were no contraindications, thrombolytic treatment was administrated to patients with onset of symptoms within 6 h and an electrocardiogram (ECG) with ST segment elevation ≥1 mm in the limb leads or ≥2 mm in the chest leads or with left bundle branch block. Streptokinase (Behring, Germany), 1.5 × 10^6 IU, was infused over 60 min. Unless contraindicated, intravenous beta-blockade was initiated by repeated injections of metoprolol (Seloken, ASTRA, Sweden; up to 3 × 5 mg over 60 min) immediately after admission. This treatment was followed by administration of oral metoprolol, up to 200 mg daily, according to a previously described protocol, with the aim of obtaining optimal beta-blockade as early as possible (9).

Statistics. The primary aim of this study was to evaluate whether the insulin-glucose infusion followed by multidose insulin for 3 months reduced mortality at 3 months in diabetic patients with acute myocardial infarction. An earlier retrospective analysis of postinfarction patients with diabetes discharged from a Swedish hospital (4) revealed a 3-month mortality rate of 35%. With some variations, other studies (22,23,30) usually reported even higher mortality rates. We hypothesized that insulin-glucose infusion followed by multidose subcutaneous insulin for 3 months would reduce the mortality rate by 30%, from a 35% mortality rate in the control group. On the basis of this assumption, ~600 patients had to be randomized to demonstrate the expected mortality reduction with a 5% significance level and a power of 80%.
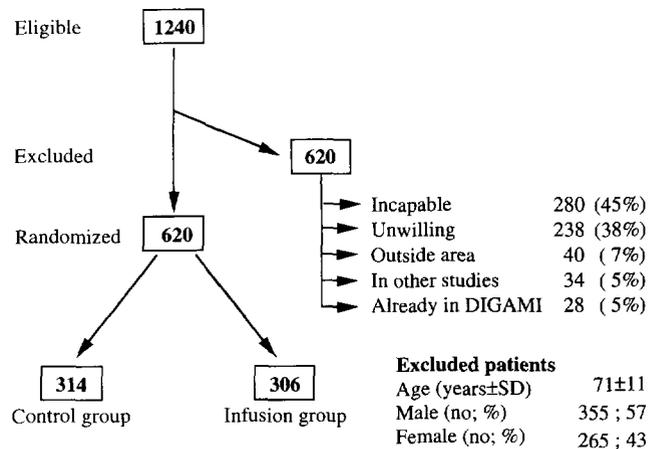

Figure 1. Schematic presentation of logged, excluded and included patients in the present Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study.

Standard statistical methods were used. The significance of the differences between the two groups were tested by Student t test and Fisher exact test. Differences within groups were tested by a paired test. For survival data the log-rank test was used. The effect and its confidence interval were estimated by the relative hazards rate in a Cox analysis (31). Cumulative mortality curves were estimated by the Kaplan-Meier method. To adjust simultaneously for other factors the Cox model was used. A two-tailed p value < 0.05 was considered statistically significant.

Results

Between January 1, 1990 and December 18, 1993 a total of 1,240 patients fulfilled the inclusion criteria. Fifty percent (n = 620) were excluded, the vast majority because of inability or unwillingness to participate (Fig. 1). Compared with patients in the study, excluded subjects were somewhat older and more of them were women.

Of the 620 included patients, 306 were randomly allocated to insulin-glucose infusion followed by multidose subcutaneous insulin treatment (infusion group) and 314 to the control group. The mean time from onset of symptoms to randomization was 13 ± 7 h. The two groups were well matched in baseline characteristics (Table 2). More than 80% of the patients were characterized clinically as non-insulin dependent; 13% were not previously known to have diabetes mellitus. At hospital admission a relatively large proportion were already being treated for cardiovascular disorders (Table 2). The body mass index of 27 in both groups indicated that the patients were slightly overweight.

At hospital admission 226 patients (74%) in the infusion group and 232 (74%) in the control group showed ECG signs of ongoing myocardial ischemia, and during the hospital stay, definite myocardial infarction developed in 270 patients (88%) in the infusion group and 264 (84%) in the control group (p = NS). The respective proportion of patients with possible

Table 2. Prehospital Characteristics*

	Control Group (n = 314)		Infusion Group (n = 306)	
	No.	%	No.	%
Age (yr)	68 ± 9		67 ± 9	
Male	197	63%	191	62%
Female	117	37%	115	38%
BMI (kg/m²)	27 ± 4		27 ± 4	
Previous disease				
Myocardial infarction	117	37%	121	40%
Angina pectoris	164	52%	176	58%
Hypertension	154	49%	143	47%
Congestive heart failure	70	22%	69	23%
Type of diabetes mellitus				
Non-insulin dependent	265	84%	251	82%
Insulin dependent	49	16%	55	18%
Previously unknown	47	15%	31	10%
Duration (yr)	10 ± 10		10 ± 10	
Antidiabetic treatment				
None	47	15%	31	10%
Diet	39	12%	33	11%
Tablets	115	37%	140	46%
Insulin	113	36%	102	33%
Other treatment				
Beta-blockers	112	36%	121	40%
Aspirin	111	35%	93	30%
Nitrates	80	25%	81	26%
ACE inhibitors	54	17%	45	14%
Digoxin	56	18%	49	16%
Smoker	73	23%	70	23%

*There were no significant differences between groups. Data are expressed as number or percent of patients or mean value ± SD. ACE = angiotensin-converting enzyme; BMI = body mass index.

Table 3. Biochemical Variables During the In-Hospital Period

	Control Group (n = 314)	Infusion Group (n = 306)	p Value
HbA$_{1c}$ at randomization (%)*	8.0 ± 2.0	8.2 ± 1.9	NS
Blood glucose (mmol/liter)			
At randomization	15.7 ± 4.2	15.4 ± 4.1	NS
24 h after randomization	11.7 ± 4.1	9.6 ± 3.3	< 0.0001
At hospital discharge	9.0 ± 3.0	8.2 ± 3.1	< 0.01
Serum potassium (mmol/liter)			
At randomization	4.3 ± 0.5	4.3 ± 0.5	NS
24 h after randomization	4.2 ± 0.5	4.0 ± 0.4	< 0.001
Hypoglycemia during infusion (no. [%] of patients)	0	46 [15]	< 0.0001
Serum lactate dehydrogenase 48 h after onset of symptoms (μkat/liter)†	10.1 ± 9.5	9.3 ± 8.8	NS

*n = 266 and 257 in the infusion and control groups, respectively. †n = 210 and 201 in the infusion and control groups, respectively. Data are presented as mean value ± SD, unless otherwise indicated.

myocardial infarction was 9 (3%) and 23 (7%) (p = NS). Only <2% of patients lacked evidence of ischemic heart disease. The proportion of patients with anterior wall infarction was 50% in both groups.

In-hospital metabolic variables are given in Table 3. During the 1st 24 h blood glucose decreased significantly in both groups, with a greater decrease in the infusion group (5.8 ± 4.9 vs. 4.0 ± 3.9 mmol/liter, p < 0.0001). In the insulin-glucose group the blood glucose decreased relatively rapidly during the first hours, with a nadir of 7.1 ± 3.1 mmol/liter 6 h after the start of the infusion. During the 1st 24 h hypoglycemia developed in 46 patients (15%) in the infusion group compared with none in the control group (p < 0.0001). During the hospital stay 172 control patients (55%) received an extra bolus of soluble insulin at least once.

At hospital discharge 87% of patients in the insulin-glucose group were receiving insulin treatment, compared with 43% in the control group (p < 0.0001). After the 3-month visit these proportions were 80% and 45%, respectively (p < 0.0001); after the 1-year visit (n = 376) they were 72% and 49%, respectively (p < 0.0001).

At the 3-month follow-up study the fasting blood glucose level was 8.5 ± 3.1 mmol/liter in the infusion group and 9.0 ±

3.2 mmol/liter in the control group (p = NS). At that time glycosylated hemoglobin HbA$_{1c}$ (n = 459) was 7.0 ± 1.6% in the infusion group and 7.5 ± 1.8% in the control group (p < 0.01). The HbA$_{1c}$ level decreased significantly in both groups during the follow-up period but significantly more in the infusion group (1.1 ± 1.6% vs. 0.4 ± 1.5% after 3 months [p < 0.0001] and 0.9 ± 1.9% vs. 0.35 ± 1.8% after 1 year [p < 0.05]). Fasting blood glucose 1 year after randomization did not differ between the two groups.

During the in-hospital period almost 50% of the patients were given thrombolysis and intravenous nitroglycerin and 17% were fully heparinized. At the time of hospital discharge 80% of the patients were receiving aspirin and 70% were receiving beta-blockers. Angiotensin-converting enzyme inhibitors were given to 31% of patients. Except for antidiabetic treatment including insulin, there were no significant differences in the in-hospital or follow-up treatment between the two groups. During the follow-up year 13 patients in each group underwent percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery was performed in 30 patients in the infusion group and in 29 in the control group.

In-hospital morbidity. The hospital stay was 11.3 ± 13.3 days in the infusion group and 9.5 ± 9.4 days in the control group (p = 0.043). During the hospital period the control group did not differ from the infusion group regarding reinfarction (4% vs. 5%), ventricular fibrillation (5% vs. 3%), high degree atrioventricular conduction disturbances (3% vs. 7%) or congestive heart failure (48% vs. 50%).

Mortality. Mortality data are presented in Table 4. The mean follow-up time for all patients was 344 days (range 91 to 365). The overall mortality rate was considerably lower than expected and was lower at each checkpoint in the infusion group than in the control group (Fig. 2). The 3-month mortality rate was 12.4% in the infusion group versus 15.6% in the control group (p = NS); the corresponding data at 1 year were

Table 4. Mortality at Various Follow-Up Times

Time	Total (n = 620) No.	Total (n = 620) %	Control Group (n = 314) No.	Control Group (n = 314) %	Infusion Group (n = 306) No.	Infusion Group (n = 306) %	Mortality Reduction %	Mortality Reduction p Value
In-hospital	63	10.2	35	11.1	28	9.1	18	NS
3 months	87	14.0	49	15.6	38	12.4	21	NS
1 year*	139	22.4	82	26.1	57	18.6	29	0.0273

*See text for follow-up time. Log-rank test used.

18.6% and 26.1% (p = 0.0273). The relative reduction in mortality was 29% by the crude method and 31% with the Cox model. The corresponding confidence interval was 4% to 51%.

The mortality rates within the prestratified risk groups are presented in Table 5. In stratum 1, consisting of patients with a low cardiovascular risk profile and no previous insulin treatment, the mortality reduction was 52% after 3 months (p = 0.046). This difference persisted at 1 year, with a mortality rate of 8.6% in the infusion group and 18.0% in the control group (relative risk reduction 52%, p = 0.020).

Discussion

The main conclusion from this study is that the long-term overall mortality in diabetic patients with acute myocardial infarction could be further reduced by the administration of insulin-glucose infusion followed by multidose subcutaneous insulin. The mortality rate was reduced by 30% after 1 year. Patients without previous insulin treatment and with a relatively low risk profile benefited the most.

Mortality in diabetic patients with myocardial infarction. The mortality rate in the present study is lower than that previously reported (4,30). This finding is especially encouraging because the patients' prehospital characteristics show that many were at high risk. Almost 40% had a previous infarction and >50% had angina pectoris. Approximately 20% were receiving therapy for congestive heart failure. In-hospital treatment was active and half of the patients received thrombolytic therapy. In the International Study of Infarct Survival (ISIS) II trial (32), diabetic patients benefited more than nondiabetic patients from streptokinase. Other studies (7,33,34) have also shown at least as good an effect of thrombolytic therapy among diabetic as among nondiabetic patients. A recent study (35) reported a 42% reduction in in-hospital mortality among diabetic patients after the introduction of thrombolytic therapy.

The high proportion of patients given beta-blockers (70%) probably also contributed to the good prognosis in our study. We and others (19,20,36) have reported on the excellent secondary preventive effect of beta-blockers in diabetic post-myocardial infarction patients. Traditionally, diabetic patients have been considered less suitable for beta-blockade because of fear of worsening of metabolic control and of more severe hypoglycemic attacks with diminished hypoglycemic warning
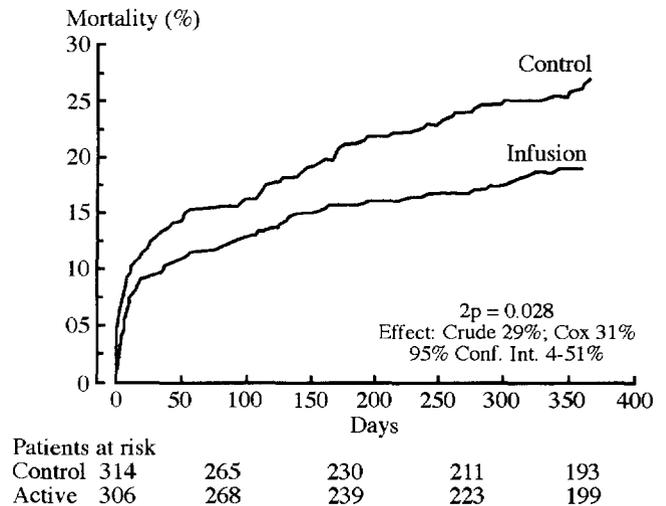

Figure 2. Actuarial mortality curves in the patients receiving insulin-glucose infusion and in the control group of the present Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study during 1 year of follow-up. **Numbers below graph** = number of patients at different times of observation. Active = patients receiving infusion; Conf. Int. = confidence interval.

signs (37–42). However, these drawbacks have not been confirmed with beta₁-selective blocking agents (40,41,43).

Eighty percent of our patients were discharged on a regimen of aspirin therapy. Thromboxane A production and platelet aggregability are increased in diabetic patients (25). Furthermore, such patients are thought to require larger doses of aspirin to inhibit platelet aggregation than those needed by nondiabetic patients (33). For example, in ISIS-II (32) there was no reduction in mortality among diabetic patients receiving aspirin (160 mg daily) compared with a 20% reduction among nondiabetic patients. In the present study most patients received only 75 mg of aspirin daily but even so the mortality was low. According to Davi and co-workers (25), insulin treatment decreases thromboxane A production in patients with type II diabetes mellitus; however, this observation cannot explain the rather low mortality in our control group.

Study limitations. It was not considered feasible or safe to design a nurse-based blinded protocol for administration of insulin-glucose treatment in a multicenter trial. Great care was taken to keep the study blinded until the patients were allocated to the predefined strata, and, in fact, the two groups were well matched at randomization. If it had any effect, the lack of blinding may have blunted a possible beneficial outcome because of a carryover effect. Altogether 55% of the control patients received at least one extra bolus of insulin during the hospital stay and HbA_{1c} decreased significantly among the control patients during follow-up, indicating improved metabolic control. However, only a few of these patients were transferred to treatment with subcutaneous insulin at hospital discharge. Institution of insulin therapy may be paralleled by a general improvement in the care of the patient, contributing to the beneficial outcome. However, this

Table 5. Mortality in Prestratified Risk Groups

	Stratum 1	Stratum 2	Stratum 3	Stratum 4
Patient mortality	272 (44%)*	129 (21%)*	119 (19%)*	100 (16%)*
3 month	9.9%	16.3%	12.6%	24.4%
1 year	13.2%	29.5%	20.9%	41.0%
Mortality by group†				
Control group				
3 month	18 (13.5%)	10 (15.2%)	8 (12.3%)	13 (26.0%)
1 year	24 (18.0%)	21 (31.8%)	14 (21.5%)	23 (46.0%)
Insulin group				
3 month	9 (6.5%)	11 (17.5%)	7 (13.0%)	11 (22.0%)
1 year	12 (8.6%)	17 (27%)	10 (18.5%)	18 (36.0%)
Mortality reduction				
3 month	52%‡	−11%	0%	15%
1 year	52%‡	15%	14%	22%

*Percent of total patients. †Number (%) of patients. ‡p = 0.046, p = 0.020 log-rank test. Stratum 1 = no insulin, low risk; Stratum 2 = no insulin, high risk; Stratum 3 = insulin, low risk; Stratum 4 = insulin, high risk.

should not be seen as a bias but rather as part of a comprehensive care program for diabetic patients with myocardial infarction. Arguing against such an effect is that concomitant therapy including revascularization procedures did not differ between the two groups.

The considerably lower than predicted overall mortality rate has already been emphasized. Therefore, the sample size turned out to be relatively small, a factor that explains the wide confidence intervals. Nevertheless, there was a consistent and continuous mortality reduction, which became significant after 1 year of follow-up. Although the study group was small in the light of the present mortality findings, the study is by far the largest clinical trial exploring the possibility that good metabolic control may influence prognosis in diabetic patients. A 50% exclusion rate before randomization is fairly modest in a study involving an initial insulin-glucose infusion followed by ≥3 months of four injections daily. During the time of the study angiotensin-converting enzyme inhibitors became recommended treatment for patients with compromised left ventricular function after a myocardial infarction (44,45); however, the use of these agents did not differ between the two groups.

Mechanisms of action. This study was based on the assumption that a rapidly achieved and persistent improvement in metabolic control should reduce morbidity and mortality in diabetic patients with myocardial infarction. It was not designed to study detailed mechanisms of action, and it is difficult to separate immediate from long-term effects. Nevertheless, some possibilities may be discussed.

During the acute phase of a myocardial infarction there is a dramatic increase of catecholamines in blood and ischemic myocardium (46), whereas plasma insulin levels are low (47,48). At the same time, cortisol and glucagon levels increase (47,49,50). This decreases insulin sensitivity, which contributes to impaired glucose utilization. The net effect of these hormonal alterations is an increased turnover of free fatty acids. Patients with diabetes mellitus, particularly those with poor metabolic control, are characterized by markedly increased plasma levels of free fatty acids and extreme sensitivity to catecholamine stimulation (51,52). Normally free fatty acids

are the primary myocardial substrate, accounting for 60% to 70% of oxygen consumption (53). In diabetic animals that have a reduced glucose utilization, free fatty acids may account for 90% (54,55). There is no anaerobic pathway for the metabolism of free fatty acids. Experimental and clinical observations (56,57) suggest that free fatty acids and their intermediates potentiate ischemic injury through several mechanisms such as direct toxicity, increased oxygen demand and direct inhibition of glucose oxidation. There is a well recognized relation between high levels of free fatty acids and complications during acute myocardial infarction (58,59). However, free fatty acids were not measured in the present study and the possible importance of a reduction may only be speculated on.

As early as 1962 Sodi-Pallares et al. (60) advocated the use of insulin-glucose-potassium infusion during acute myocardial infarction on the basis that potassium loss was an important factor behind cellular response to ischemia. This group (61,62) demonstrated that insulin-glucose-potassium increased intracellular potassium in the ischemic zone. Subsequent clinical studies (21) demonstrated a reduction in the plasma levels of free fatty acids and of the complication rate during acute myocardial infarction. In addition to an enhanced segmental ejection fraction in the infarcted area, there was evidence of improved global left ventricular function after glucose-insulin-potassium infusion (63,64).

In patients with diabetes mellitus and acute myocardial infarction, ejection fraction in the noninfarcted area is lower than that in nondiabetic patients (7,65,66). The insulin-glucose infusion may have improved untoward metabolic changes during the acute phase of the myocardial infarction, thereby preserving myocardium and causing less extensive myocardial damage. Some support for this view comes from the finding that the enzymatically estimated infarct size tended to be larger in the control than in the infusion group. Presumably this observation does not fully explain the beneficial results as the mortality reduction at the time of hospital discharge was still rather small.

Although many of the recurrent infarcts and a substantial proportion of the deaths occur rather early in the postinfarc-

tion period, we decided to extend the administration of multidose subcutaneous insulin to ≥3 months. Intense insulin treatment may restore impaired platelet function (25), correct the disturbed lipoprotein pattern (67) and decrease plasma plasminogen activator inhibitor-1 activity, which is high in diabetic patients (27,68). Prolonged insulin treatment may also improve the metabolism in the noninfarcted areas, thereby reducing the gradual remodeling of the left ventricular myocardium (18,69). The compliance was good and after the 1-year visit 72% of patients in the infusion group were still receiving insulin. The extended insulin treatment, with its beneficial secondary metabolic effects, is one possible mechanism for the reduced long-term mortality in the infusion group. To our knowledge, there are no studies showing that good long-term metabolic control by means of intense insulin treatment reduces macroangiopathic complications in patients with diabetes mellitus. However, it was recently shown (70) that intense long-term metabolic control reduces microangiopathic complications.

Feasibility and safety. The number of hypoglycemic episodes was significantly higher in the infusion group (15%) than in the control group (0%). This finding was not unexpected. These episodes did not correlate with any increased morbidity or mortality and were often discovered as a low blood glucose level without any particular symptoms. There was no evidence that the insulin-glucose infusion followed by multidose insulin caused any harmful effects. A majority of patients in the infusion group were treated with multidose insulin during the follow-up period without problems. Only 10% had to stop insulin therapy because of episodes of hypoglycemia. Feasibility and safety aspects, together with descriptions of various protocols for insulin-glucose infusion, have been described in detail elsewhere (29).

Conclusions. The present data support the immediate use of insulin-glucose infusion followed by multidose insulin in diabetic patients with acute myocardial infarction. This treatment seems especially important in those not already receiving insulin. The insulin-glucose infusion used in this study did not have any untoward effects with the exception of an increased number of hypoglycemic episodes; however, these episodes did not aggravate signs of ischemia. Future studies should focus on specific pathophysiologic mechanisms behind the beneficial effects we have seen.

Appendix

The DIGAMI Study Group*

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*The numbers in brackets indicate number of patients. All cities are in Sweden.

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