Glycometabolic State at Admission: Important Risk Marker of Mortality in Conventionally Treated Patients With Diabetes Mellitus and Acute Myocardial Infarction

Long-Term Results From the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study

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Background—The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study addressed prognostic factors and the effects of concomitant treatment and glycometabolic control in diabetic patients with myocardial infarction (AMI).

Methods and Results—Of 620 diabetic patients with AMI, 306 were randomly assigned to a ≥24-hour insulin-glucose infusion followed by multidose subcutaneous insulin. Three hundred fourteen patients were randomized as controls, receiving routine antidiabetic therapy. Thrombolysis and β-blockers were administered when possible. Univariate and multivariate statistical analyses were applied to study predictors of long-term mortality. During an average follow-up of 3.4 years (range, 1.6 to 5.6 years), 102 patients (33%) in the intensive insulin group and 138 (44%) in the control group died ($P=0.011$). Old age, previous heart failure, diabetes duration, admission blood glucose, and admission Hb A_{Ic} were independent predictors of mortality in the total cohort, whereas previous AMI, hypertension, smoking, or female sex did not add independent predictive value. Metabolic control, mirrored by blood glucose and Hb A_{Ic}, improved significantly more in patients on intensive insulin treatment than in the control group. β-Blockers improved survival in control subjects, whereas thrombolysis was most efficient in the intensive insulin group.

Conclusions—Mortality in diabetic patients with AMI is predicted by age, previous heart failure, and severity of the glycometabolic state at admission but not by conventional risk factors or sex. Intensive insulin treatment reduced long-term mortality despite high admission blood glucose and Hb A_{Ic}. **(*Circulation*. 1999;99:2626-2632.)**

Key Words: myocardial infarction ■ diabetes mellitus ■ mortality ■ morbidity ■ glucose ■ insulin

Mortality among diabetic patients with acute myocardial infarction (AMI) remains high.[1–5] Many factors, such as severe coronary artery disease, diabetic cardiomyopathy, disturbed autonomic balance, and decreased fibrinolytic function, may contribute to the unfavorable outcome.[6] Other reasons relate to myocardial metabolism, characterized in diabetic patients by increased oxygen-consuming free fatty acid utilization rather than glucose oxidation.[6] In type 2 diabetes, metabolic control is a major risk factor for future coronary heart disease.[7–10] Furthermore, there is strong evidence that high blood glucose at admission predicts in-hospital mortality after AMI.[11–15]

In the recent Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, the long-term prognosis in diabetic patients with AMI was improved by strict metabolic care.[16–18] This report describes factors influencing the long-term prognosis and the effects of concomitant treatment by applying univariate and multivariate statistical analyses to the DIGAMI cohort. Besides giving mechanistic information on the beneficial effects behind improved insulin-glucose homeostasis, this study generated new hypotheses on the proper treatment of diabetic patients with AMI.

Methods

Definitions

Diabetes mellitus was considered present if a patient had been informed of this diagnosis and was on prescribed treatment (diet, tablets, or insulin). Patients without this diagnosis but with a blood glucose ≥11 mmol/L at admission were included as newly detected diabetes mellitus. Patients were categorized as non–insulin-dependent (NIDDM) or insulin-dependent diabetics by clinical history according to the National Diabetes Data Group. Accordingly, NIDDM patients were >40 years of age at diagnosis who did not need insulin for ≥2 years after the diagnosis and were not prone to ketoacidosis.

The diagnosis of definite AMI required that ≥2 of the following criteria were fulfilled: (1) chest pain of ≥15 minutes' duration; (2) ≥2 values of serum creatine kinase (S-CK) and serum creatine

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kinase isoenzyme B (S-CKB) or serum lactic dehydrogenase (S-LD) above the normal range (normal+2 SD), including an LD-isoenzyme pattern typical of myocardial damage; and (3) development of new Q waves in ≥2 standard ECG leads. The diagnosis of possible AMI was used if typical chest pain was accompanied by only 1 S-CK or S-LD value above the normal range and/or new Q waves in one ECG lead only. A reinfarction was defined as a new AMI (>72 hours after the index infarct).

Study Design

A detailed description of the DIGAMI study has been given elsewhere.[16] Briefly, it is a multicenter, randomized study of the effect of intensive insulin treatment on mortality and morbidity in patients with diabetes and AMI within the preceding 24 hours. Before randomization, the patients were stratified into 4 groups on the basis of risk classification and previous use of insulin. High-risk patients fulfilled ≥2 of the following criteria: age >70 years, history of previous AMI, history of congestive heart failure, or ongoing treatment with digitalis. The predefined strata were (1) no insulin and low risk, (2) no insulin and high risk, (3) insulin and low risk, and (4) insulin and high risk. Infusion was initiated as soon as possible (mean±SD, 13±7 hours) after the onset of symptoms and continued for ≥24 hours.

Patients randomized to the intensive insulin treatment received an insulin-glucose infusion followed by multidose subcutaneous insulin for ≥3 months; those assigned to the control group received conventional treatment at the discretion of the physician in charge. The subcutaneous insulin treatment was instituted at the cessation of the infusion. Concomitant medication was managed according to strict predefined criteria to establish treatment as uniform as possible in the 2 groups, except for the use of intensive insulin treatment. Thrombolysis, β-blockade, and aspirin were initiated as soon as possible in the absence of any contraindications. The study population was followed for 1 year, with outpatient visits scheduled 3 and 12 months after randomization. Subsequently, the patients were cared for by their usual physicians according to individual need. Information on the vital status of all patients (no losses to follow-up) was obtained July 31, 1995, from the physician in charge of DIGAMI at each participating center. The mean time of follow-up was 3.4 years (range, 1.6 to 5.6 years) and did not differ between patients within the 4 strata.

Informed consent was obtained from all patients. DIGAMI was approved by the local ethics committees at each participating hospital.

Statistical Analysis

Standard statistical methods were applied. The significance of differences between the 2 study groups was tested by Student's *t* test and Fisher's exact test. The Cox proportional hazards regression model was used to evaluate the relationship between risk factors and mortality.[19] Initially relative risks (RRs) and their CIs were estimated in a univariate model. To find variables independently contributive to mortality, significant variables from the univariate model were subsequently analyzed together with sex in a stepwise multivariate Cox model by means of the SAS statistical package version 6.12. A 2-tailed value of $P<0.05$ was accepted as statistically significant.

Results

Patients

Altogether, 1240 diabetic patients with suspected AMI were eligible for DIGAMI. Half were excluded, leaving 620 patients for randomization. Excluded subjects were logged and followed for 1 year in terms of mortality. They were somewhat older than the study cohort, with a higher proportion of women. In a Cox regression analysis, including correction for baseline dissimilarities, the mortality was almost the same in the excluded and study groups.[16]

TABLE 1. Patient Characteristics at Time of Randomization

Parameter	Patient Group: Control (n=314)	Patient Group: Infusion (n=306)	*P*
Age, y	68±9	67±9	NS
Sex, n (%)			
Male	197 (63)	191 (62)	NS
Female	117 (37)	115 (38)	NS
BMI, kg/m^2	27±4	27±4	NS
Previous disease, n (%)			
Myocardial infarction	117 (37)	121 (40)	NS
Angina pectoris	164 (52)	176 (58)	NS
Hypertension	154 (49)	143 (47)	NS
Congestive heart failure	70 (22)	69 (23)	NS
Type of diabetes mellitus, n (%)			
Type 2	265 (84)	251 (82)	NS
Type 1	49 (16)	55 (18)	NS
Previously unknown	47 (15)	31 (10)	NS
Diabetes duration, y	10±10	10±10	NS
Antidiabetic treatment, n (%)			
None	47 (15)	31 (10)	NS
Diet	39 (12)	33 (11)	NS
Tablets	115 (37)	140 (46)	NS
Insulin	113 (36)	102 (33)	NS
Blood glucose at randomization, mmol/L	15.7±4.2	15.4±4.1	NS
Hb A_{1c} at randomization, %	8.0±2.0	8.2±1.9	NS
Blood glucose 24 h after randomization, mmol/L	11.7±4.1	9.6±3.3	<0.0001
Blood glucose at hospital discharge, mmol/L	9.0±3.0	8.2±3.1	<0.01

BMI indicates body mass index. Values are mean±SD when appropriate.

Of the 620 study patients, 314 were allocated to the control and 306 to the intense insulin groups, respectively. The 2 groups were well balanced at the time of randomization (Table 1). A total of 78 subjects did not have previously known diabetes mellitus. Eight (5 with no evidence of ongoing antidiabetic treatment) died during the initial hospital phase. Seven of the hospital survivors were not considered to have diabetes and thus were discharged without antidiabetic treatment. Thus, the prevalence of previously undiagnosed diabetes mellitus was 11% (66 of the 620 patients) in the DIGAMI cohort, in which the selection was based on an admission blood glucose of >11 mmol/L.

In total, 270 (88%) of the patients in the insulin group and 264 (84%) in the control group had definite AMI; the number of possible AMIs was 9 (3%) and 23 (7%), respectively. Fewer than 2% of the patients lacked evidence of ischemic heart disease.

Treatment

Almost 50% of the patients were given thrombolysis. At the time of hospital discharge, 80% of all patients were on aspirin, 70% were on β-blockers, and 31% received ACE

TABLE 2. Univariate Associations Between Baseline Cardiovascular Risk Factors Recorded at Time of Randomization and Long-Term Mortality

	Patient Groups					
	All (240 of 620)		Control (138 of 314)		Intensive Insulin (102 of 306)	
Parameter	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Age (1 added y)	1.07 (1.05–1.10)	<0.001	1.07 (1.04–1.10)	<0.001	1.07 (1.05–1.10)	<0.001
Male sex	0.80 (0.61–1.03)	0.086	0.70 (0.50–0.98)	<0.05	0.94 (0.63–1.41)	0.77
Previous disease						
Myocardial infarction	1.64 (1.27–2.12)	<0.001	1.42 (1.01–1.99)	<0.05	2.01 (1.36–2.97)	<0.001
Congestive heart failure	2.59 (1.99–3.37)	<0.001	2.37 (1.67–3.38)	<0.001	2.90 (1.95–4.30)	<0.001
Hypertension	1.29 (1.01–1.67)	<0.05	1.45 (1.04–2.03)	<0.05	1.09 (0.74–1.61)	0.65
Diabetes duration (1 added y)	1.02 (1.01–1.03)	<0.01	1.01 (0.99–1.03)	0.078	1.02 (1.01–1.04)	<0.01
Smoker	0.56 (0.41–0.83)	<0.01	0.58 (0.37–0.92)	<0.05	0.60 (0.35–1.01)	0.054

Average long-term mortality was 3.4 y. Number of deaths divided by number of subjects at risk is presented above each column. RR with 95% confidence limits is given for 1 unit of risk factor.

inhibitors. Apart from antidiabetic treatment, the 2 groups did not differ significantly in terms of in-hospital or follow-up treatment. During the first year, PTCA was performed in 26 patients (n=13 in each group) and bypass surgery in 59 patients (intense insulin, n=30; control, n=29).

At hospital discharge, 249 patients (86%) in the intensive group were on insulin compared with 129 (44%) in the control group ($P<0.0001$). The corresponding proportions were 80% and 45% ($P<0.0001$) at the scheduled follow-up after 3 months and 72% and 49% after 1 year ($P<0.0001$). In stratum 1 (no prior insulin and low cardiovascular risk) comprising 272 patients, 81% of those randomized to the intensive insulin group were on insulin at hospital discharge compared with 15% of patients in the control group. The corresponding proportions were 66% and 24% after 1 year. This difference was also reflected by the more pronounced absolute reduction in Hb A_{Ic} in the intensive insulin group (−1.3%) than in control group (−0.4%, $P<0.001$).

Patients with previously unknown diabetes had significantly lower admission blood glucose and Hb A_{Ic} levels than those with established diabetes (14.3±3.4 versus 15.7±3.9 mmol/L, $P<0.01$, and 6.7±1.9% versus 8.3±1.9%, $P<0.001$).

Mortality

During the long-term follow-up, there were 240 deaths (39%), 138 in the control group (mortality, 44%) and 102 in the intensive group (mortality, 33%; $P=0.011$). This corresponds to a relative mortality reduction of 28% (95% CI, 8% to 45%) according to the Cox model. The most apparent effect was observed in patients without prior insulin treatment and with a low predicted cardiovascular risk (stratum 1, n=272). Subjects in this stratum had an absolute mortality reduction of 15%, from 44 deaths (33%) in the control group to 25 deaths (18%) in the intensive group. This corresponds to a relative reduction of 51% (19% to 70%, $P=0.004$). In this group, a mortality difference was already apparent at the time of hospital discharge.

Univariate Prediction

The univariate relationship between various risk factors recorded at the time of randomization and long-term mortality is reported in Table 2. In the complete patient cohort, age, previous myocardial infarction, previous congestive heart failure, hypertension, and long duration of diabetes mellitus were associated with an increased long-term mortality. Smokers had a significantly better 1-year prognosis than nonsmokers. There was no significant sex-related difference in mortality. Almost the same pattern was apparent in the intensive insulin and control groups separately.

The univariate associations between long-term mortality and baseline glucometabolic state, presence of congestive heart failure, and treatment during the hospital phase and at discharge are given in Table 3. Among all patients, the most powerful predictors of an unfavorable outcome were a high blood glucose level at admission and onset of heart failure during the hospital phase. Thrombolytic therapy and ongoing treatment with β-blockers at hospital discharge were associated with survival. ACE inhibitors, which were prescribed only for overt heart failure, were associated with increased mortality. A high level of Hb A_{Ic} at admission predicted long-term mortality in control patients but not in those given intensive insulin treatment.

As previously stated, admission blood glucose was 1 of the most powerful predictors of long-term mortality. Mortality in the different blood glucose tertiles is presented in the Figure. There was a close dose-response relationship between admission blood glucose and long-term mortality in control patients but not in the intensive insulin group.

Multivariate Analysis

Multivariate statistical analysis was applied to evaluate the independent associations of all baseline univariate predictors of long-term mortality (Table 4). In the complete study population, age, previous congestive heart failure, diabetes duration, blood glucose at admission, and Hb A_{Ic} (borderline significance) contributed to the prediction of fatal outcome during long-term follow-up. Such factors as sex, previous myocardial infarction, hypertension, and smoking did not remain independent predictors. Admission blood glucose and Hb A_{Ic} levels were powerful independent mortality predictors in the control group but did not reach statistical significance among intensive insulin patients. Because admission blood

TABLE 3. Univariate Associations Between Glucometabolic Parameters and In-Hospital Treatment With Long-Term Mortality

	Patient Groups					
	All (240 of 620)		Control (138 of 314)		Intensive Insulin (102 of 306)	
Parameter	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Blood glucose at admission, 1 mmol/L	1.08 (1.05–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.05 (1.01–1.11)	<0.05
Glucosylated hemoglobin, Hb A_{Ic}, 1%	1.07 (1.01–1.21)	<0.05	1.13 (1.04–1.25)	<0.01	1.01 (0.91–1.13)	0.813
Congestive heart failure during hospitalization	2.45 (1.88–3.20)	<0.001	2.59 (1.82–3.68)	<0.001	2.40 (1.59–3.62)	<0.001
Thrombolysis	0.57 (0.44–0.74)	<0.001	0.69 (0.49–0.97)	<0.05	0.44 (0.29–0.67)	<0.001
β-Blockers at discharge	0.56 (0.42–0.73)	<0.001	0.45 (0.31–0.65)	<0.001	0.69 (0.45–1.07)	0.097
ACE inhibitor at discharge	1.39 (1.04–1.86)	<0.05	1.46 (0.99–2.14)	0.053	1.35 (0.87–2.11)	0.179

See Table 2 for explanation.

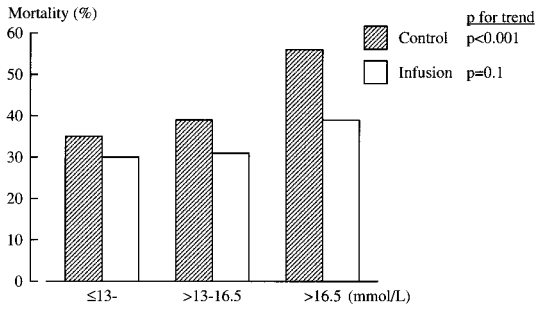
glucose was a significant predictor of mortality, attempts were made to identify clinical and biochemical parameters related to hyperglycemia. Hb A_{Ic} ($P<0.0001$), heart rate ($P<0.0001$), pulmonary rales ($P<0.01$), and body weight ($P<0.01$) at admission were independently linked to hyperglycemia in multivariate analysis.

Independent effects of concomitant treatment on long-term mortality after correction for age, sex, and congestive heart failure during the hospital period are presented in Table 5. Among all patients, thrombolysis and β-blockers at hospital discharge positively influenced long-term mortality. The effect of thrombolysis was most apparent in the intensive insulin group (mortality reduction, 55%), whereas β-blockers seemed efficient only in the control group (mortality reduction, 45%). ACE inhibitors, prescribed only for overt heart failure, remained linked to decreased survival.

Discussion

Diabetes mellitus is an independent marker of mortality after AMI.[1,2,4] In the DIGAMI study, the unfavorable long-term prognosis was improved by intensive insulin treatment, which tended to favorably influence all cardiovascular causes of death.[17,18]

Age and previous heart failure were the only conventional risk markers that independently predicted long-term mortality in the complete DIGAMI cohort. Previous myocardial infarction and hypertension, known risk factors in nondiabetic patients,[20] did not add prognostic power. Detailed information on infarct size was not available in DIGAMI. Maximum enzyme release did not differ between the 2 study groups.[16] With half the patients receiving thrombolytic therapy, enzyme release is only a rough measure of the infarct size. Glucometabolic state at admission, reflected by blood glucose, Hb A_{Ic}, and duration of diabetes, was an independent predictor of a poor outcome. This is in accordance with findings of Kuusito et al.[7]



Long-term (average time, 3.4 years; range, 1.6 to 5.6 years) mortality by admission blood glucose tertiles within 2 treatment groups.

Admission hyperglycemia is a predictor of poor in-hospital outcome after AMI according to several studies of diabetic and nondiabetic patients. Hyperglycemia has been linked to extensive myocardial damage causing heart failure and secondary stress.[11–15] In the DIGAMI control subjects, there was an almost linear relationship between blood glucose tertiles and long-term mortality. The most powerful predictor of blood glucose at admission was previous metabolic control (Hb A_{Ic}). This indicates that blood glucose at admission not only is a marker of acute stress but also reflects the present glucometabolic state. The relationship between a high admission blood glucose and poor long-term outcome did not reach statistical significance in the group on intensive insulin. Thus, the harmful effect of elevated blood glucose was attenuated. In the total DIGAMI cohort, baseline Hb A_{Ic} level tended to independently predict mortality in the control group but not in the group on intensive insulin. Thus, strict insulin treatment with improved metabolic control seems to reduce the adverse effect of an initially poor metabolic control.

Recent evidence suggests that metabolic control is an important determinant of future development of coronary heart disease among NIDDM patients.[7–10] Intensive treatment with insulin caused a 40% reduction in cardiovascular events in the Diabetes Control and Complications Trial.[21] This indicates that regardless of a causal relationship, improved metabolic care reduces the progression of the atherothrombotic process. During the first year of follow-up in the DIGAMI trial, a reduction in Hb A_{Ic} was most apparent in patients without previous insulin and at low cardiovascular risk. The most pronounced early and long-term mortality improvement was achieved in this group, supporting the assumption that glycemic control is mandatory for secondary

TABLE 4. Independent Associations Between Cardiovascular Risk Factors and Glucometabolic Markers With Long-Term Mortality by Multivariate Cox Regression Analysis

	Patient Groups					
	All (240 of 620)		Control (138 of 314)		Intensive Insulin (102 of 306)	
Parameter	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Age (1 added y)	1.08 (1.06–1.11)	<0.001	1.09 (1.06–1.12)	<0.001	1.08 (1.05–1.12)	<0.001
Male sex	1.12 (0.82–1.54)	0.46	0.97 (0.63–1.49)	0.88	1.44 (0.88–2.32)	0.15
Previous disease						
Myocardial infarction	1.22 (0.87–1.70)	0.25	1.10 (0.69–1.77)	0.68	1.40 (0.86–2.28)	0.16
Congestive heart failure	2.24 (1.60–3.14)	<0.001	2.37 (1.50–3.74)	<0.001	2.28 (1.33–3.73)	<0.01
Hypertension	1.01 (0.75–1.35)	0.96	1.15 (0.78–1.71)	0.48	0.86 (0.55–1.36)	0.52
Smoker	1.08 (0.69–1.68)	0.74	1.05 (0.57–1.93)	0.87	1.25 (0.62–2.52)	0.53
Diabetes duration (1 added y)	1.02 (1.01–1.03)	<0.01	1.01 (0.99–1.03)	0.21	1.03 (1.01–1.05)	<0.01
Admission						
Blood glucose, +1 mmol/L	1.06 (1.03–1.10)	<0.01	1.06 (1.01–1.11)	<0.05	1.05 (0.99–1.11)	0.065
Hb A_{1c}, +1%	1.09 (1.00–1.18)	0.054	1.15 (1.03–1.29)	<0.05	1.03 (0.90–1.17)	0.66

See Table 2 for explanation.

prevention of ischemic complications in diabetic patients, including NIDDM patients.

It is debatable whether improved metabolic control with insulin or decreased use of possibly harmful sulfonylureas caused the beneficial effects in DIGAMI. Data from the recently published UK Prospective Diabetes Study (UKPDS) of intensive blood glucose control by either sulfonylureas or insulin are of interest in this regard.[22] In UKPDS, there was a significant decrease in the risk of microvascular but not macrovascular disease in NIDDM patients regardless of the type of antidiabetic therapy. In any case, the reduction in myocardial infarctions reached borderline significance ($P=0.052$), indicating that the beneficial effect of intensive glucose control outweighed the theoretical risk of the antidiabetic agent and supporting the idea that improved metabolic control is of crucial importance.

Intensified insulin therapy in NIDDM patients is associated with a less atherogenic lipoprotein profile than treatment with oral antidiabetic drugs.[23,24] For methodological and logistic reasons, lipoprotein interactions were not addressed in DIGAMI. The study was started 4 years before availability of data from large-scale secondary preventive studies of the effects of lipid-lowering drugs, particularly the Scandinavian Survival Study.[25] In 1 center that recruited 44 DIGAMI patients, preparative ultracentrifugation revealed a trend toward lower triglyceride-rich lipoproteins in the intensive insulin group (data on file). It is unlikely that effects on lipoproteins would be a major factor behind the beneficial effects. The impact of lipid-lowering measures on cardiovascular events becomes apparent after 1 to 2 years. In the DIGAMI study, a mortality reduction was obvious much sooner, particularly in stratum 1.

Concerning other treatment modalities, thrombolysis independently improved survival, particularly in the intensive insulin group. Experimental studies revealed that glucose-insulin-potassium infusion is more protective in ischemia followed by reperfusion than during ischemia only.[26] In a randomized clinical study, Satler et al[27] reported an improved ejection fraction and less segmental wall motion abnormalities when glucose-insulin-potassium was infused with streptokinase in patients with anterior wall infarction. Metabolic support reduces complications during open-heart surgery.[28,29] A recent study reported a favorable mortality trend by glucose-insulin-potassium infusion in AMI patients given reperfusion therapy.[30] Together with the present data, this strengthens the hy-

TABLE 5. Independent Influence of Different Treatments on Long-Term Mortality by Multivariate Cox Regression Analysis Correcting for Age, Sex, and Congestive Heart Failure During Hospital Stay

	Patient Groups					
	All (240 of 620)		Control (138 of 314)		Intensive Insulin (102 of 306)	
Parameter	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Intensive insulin treatment	0.67 (0.51–0.88)	<0.01	. . .		. . .	
Thrombolysis	0.54 (0.41–0.72)	<0.001	0.63 (0.43–0.92)	<0.05	0.44 (0.28–0.72)	<0.001
β-Blockade at discharge	0.68 (0.50–0.88)	<0.01	0.55 (0.38–0.79)	<0.01	0.81 (0.52–1.27)	0.36
ACE inhibitor at discharge	1.36 (1.01–1.83)	<0.05	1.50 (1.04–2.30)	<0.05	1.20 (0.76–1.88)	0.45

See Table 2 for explanation.

pothesis that metabolic support may be of particular value in association with myocardial reperfusion.

The beneficial effect of β-blockade on survival fits with subgroup analyses from previous post–myocardial infarction trials. The explanation is presumably multifactorial. Experimentally, propranolol reduces myocardial oxygen consumption by reducing energy production via free fatty acids and the promotion of glucose use.[31] This may be important for diabetics who have increased levels of circulating free fatty acids.[32–36] Diabetic patients with AMI have a higher heart rate than nondiabetics, most likely because of cardiac autonomic neuropathy.[37,38] The mortality reduction in β-blocker treatment relates to the magnitude of heart rate reduction and is most pronounced in patients with high initial heart rates.[39–41] β-Blockade appeared to be of particular value in the control group, whereas it was not independently associated with survival in the intensive insulin group. This indicates that at least part of the beneficial mechanism of action of insulin and β-blockade in diabetics with AMI may be similar. A possible effect, common to both treatment modalities, may be a reduction in free fatty acid oxidation and promotion of glucose use.

ACE inhibitors, which were given only to patients with symptoms or signs of congestive heart failure, did not greatly improve survival. Analysis of ACE inhibitor trials in heart failure does not support a more pronounced effect among patients with diabetes,[42,43] except for GISSI-III.[44] In this post–myocardial infarction trial, early institution of lisinopril was followed by a somewhat reduced mortality in diabetic but not nondiabetic patients.[44]

Another interesting finding was the lack of sex differences in long-term outcome. When dissimilarities in baseline characteristics, particularly age, were taken into account, sex did not remain an independent predictor. This fits with findings by Bueno et al,[45] who suggested that previously reported increased mortality for women relates to risk factors rather than sex per se. This hypothesis gained support from the Danish TRACE study.[20]

In summary, long-term outcome in diabetic patients with myocardial infarction is predicted by age, previous myocardial damage, and not the least the actual glucometabolic state. Institution of intense insulin treatment reduces this risk considerably. β-Blockers also have a striking secondary preventive effect in diabetics with myocardial infarction.

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