

# Intensification of Therapeutic Approaches Reduces Mortality in Diabetic Patients With Acute Myocardial Infarction

## The Munich registry

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**OBJECTIVE** — The myocardial infarction (MI) registry of the Academic Schwabing Hospital, Munich, investigates the hospital course of diabetic and nondiabetic patients with acute MI. The aim of this study was to improve quality care management and to compare hospital mortality and therapeutic approaches (i.e., PTCA, stenting, GPIIb/IIIa receptor antagonists, glucose-insulin infusion).

**RESEARCH DESIGN AND METHODS** — Data of diabetic patients and nondiabetic patients were analyzed. All diabetic and nondiabetic subjects who were admitted in 1999 and 2001 were included: 1999, 126 (38%) diabetic and 204 (62%) nondiabetic patients; 2001, 91 (31%) diabetic and 205 (59%) nondiabetic patients.

**RESULTS** — In 1999, coronary angiography ( $P < 0.01$ ), percutaneous transluminal coronary angioplasty (PTCA) ( $P < 0.001$ ), and stenting ( $P < 0.001$ ) were performed less frequently in diabetic than in nondiabetic patients. During this period, total hospital mortality (29 vs. 16%,  $P < 0.01$ ) and mortality within 24 h after admission (14 vs. 5%,  $P = 0.01$ ) were higher in diabetic than in nondiabetic patients. In 2001, frequencies of coronary angiography, PTCA, and stenting were increased in diabetic patients ( $P < 0.001$  vs. 1999), and the interventions were comparable with those performed in nondiabetic patients. Furthermore, glucose-insulin infusion was administered in 46% of diabetic subjects. In 2001, total hospital mortality decreased to 17% in diabetic subjects ( $P = 0.028$  vs. 1999) and mortality within 24 h after admission declined to 4% ( $P = 0.027$  vs. 1999). Logistic regression analysis revealed that an increase in the number of therapeutic approaches (also when adjusted for clinical variables) is associated with a reduction in mortality of diabetic patients with acute MI (adjusted odds ratio 0.14,  $P < 0.0001$ ).

**CONCLUSIONS** — Intensification of multiple advanced therapeutic strategies in diabetic patients with acute MI enables a substantial reduction in hospital mortality. The enforcement leads to rates of hospital mortality that are comparable to those of nondiabetic patients.

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**D** iabetes is associated with a high risk for the development of coronary artery disease (1,2). It represents a risk for cardiac mortality of 20% over 7 years, which is equal to the risk of nondi-

abetic patients after myocardial infarction (MI) (3). As evidenced by the Monitoring Trends and determinants of Cardiovascular disease (MONICA) Augsburg study, mortality of diabetic patients after acute

MI is substantially enhanced (4). A two-fold increased in-hospital mortality has been reported in diabetic patients (5,6). Furthermore, the risk for cardiovascular mortality in diabetic patients with acute MI over a time period of 7 years has been observed to be 45% (3).

Although the mortality-reducing effects of evidence-based treatments such as reperfusion are equally beneficial in patients with and without diabetes, evidence-based treatment has been demonstrated to be less used in diabetic patients (4,7). This resistance to utilize treatment options has been suggested to partially contribute to the poorer outcome in diabetic compared with nondiabetic patients (4,7). Furthermore, the need of optimized glycemic control in the critical phase of disease has been underestimated (8). Emphasizing the importance of metabolic control, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study reported a reduction of in-hospital mortality in diabetic patients who obtained a glucose-insulin infusion followed by an intensified therapy of diabetes (9).

The MI registry of the Academic Schwabing Hospital, Munich, analyzes both therapeutic approaches and hospital mortality in diabetic and nondiabetic patients. The aim of the present study was to improve quality care management in general. Results of the registry of 1999 were analyzed with regard to hospital treatment and outcome of diabetic and nondiabetic patients. In 2001, treatment approaches of diabetic patients were intensified and results of hospital outcome of diabetic and nondiabetic patients were analyzed.

## RESEARCH DESIGN AND METHODS

— The data of the Munich MI registry of 1999 was analyzed with regard to mortality and therapeutic approaches. It was then the aim to intensify treatment in diabetic patients. In 2001,

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**Abbreviations:** CRP, C-reactive protein; DIGAMI, Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; MI, myocardial infarction; MONICA, Monitoring Trends and determinants of Cardiovascular disease; PTCA, percutaneous transluminal coronary angioplasty.

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the goal was to apply strategies at comparable levels between diabetic and nondiabetic patients. Furthermore, in view of the results of the DIGAMI study (10), glucose-insulin infusion was administered in diabetic patients. The results of hospital outcome were compared.

The diagnosis of diabetes in the registry was based on the following criteria. The presence of diabetes was defined if the patient had been informed of this diagnosis or was on prescribed antidiabetic treatment (diet, tablets, or insulin). Patients without the diagnosis but with a blood glucose  $\geq 200$  mg/dl (hexokinase reaction) were also classified as having diabetes.

Acute MI was diagnosed in the presence of two or more of the following criteria (9): persistent angina pectoris for  $\geq 15$  min, ST segment elevation in at least two contiguous standard leads of  $\geq 1$  mm and  $\geq 2$  mm in precordial leads, respectively, and elevation of serum creatinine kinase above the normal range of 70 units/l. Patients were classified according to the recommendations of the European Society of Cardiology and the American College of Cardiology (11).

Patients with acute MI were treated according to the guidelines of the American College of Cardiology and the American Heart Association (12). Fibrinolytic therapy with alteplase or acute percutaneous intervention were applied as reperfusion strategies. In Germany, the use of thrombolysis in diabetic patients is not limited by local restrictions. Early percutaneous transluminal coronary angioplasty (PTCA) was defined as performance of PTCA within 6 h after admission.

In 2001, diabetic patients with acute MI and who were aged  $<75$  years obtained a glucose-insulin infusion for a minimum of 24 h. The scheme of insulin infusion was a modification of the protocol of the DIGAMI study (10): 10% glucose was infused at 30 ml/h. Regular insulin (50 IU) was dissolved in 50 ml of 0.9% NaCl. Insulin was infused according to the blood glucose level:  $>250$  mg/dl (13.9 mmol/l), 3 IU/h; 200–249 mg/dl (11.1–13.8 mmol/l), 2.5 IU/h; 150–199 mg/dl (8.3–11.0 mmol/l), 1.5 IU/h; 100–149 mg/dl (5.6–8.2 mmol/l), 1.0 IU/h; and  $<100$  mg/dl (5.6 mmol/l), insulin infusion ceased. Insulin was applied separately from glucose solution and was administered with an external pump (Perfusor FM; B. Braun Melsungen,

Melsungen, Germany). Blood glucose was tested every 2 h (Glucometer Elite; Bayer Vital, Leverkusen, Germany). Administration of glucose-insulin infusion was succeeded by an intensive insulin therapy that comprised four to six injections of regular insulin and two injections of basal insulin.

Discharge from the intensive care unit was determined by the decline of serum creatinine kinase to the near-normal range and was succeeded by admittance to the general ward of the Department of Cardiology.

Plasma glucose, HBA<sub>1c</sub> (normal range  $<6.2\%$ ), creatinine kinase, electrolytes, blood count, lipids, and C-reactive protein (CRP) were analyzed. Albuminuria was defined as  $>300$  mg/l. Hypertension was defined according to World Health Organization criteria, which include multiple measurements of blood pressure of  $\geq 140/90$  mmHg (13). The history of peripheral artery disease was assessed in all patients. Resuscitation was defined as a cardiopulmonary resuscitation, which included cardiac massage, use of a heart defibrillator, and/or artificial respiration.

If not otherwise specified, the results are reported as means  $\pm$  SD. Group comparisons were performed by the Mann-Whitney test for continuous variables and  $\chi^2$  test for categorical variables. Logistic regression analyses were used to identify the influence of clinical variables (age, sex, BMI, heart rate, blood glucose on admission, total cholesterol, triglycerides, creatinine, CRP, maximal value of creatinine kinase, hypertension, and previous coronary artery disease) and the number of treatment approaches performed in the patients (coronary angiography, PTCA, stenting, GbIIb/IIIa, fibrinolysis, coronary artery bypass grafting, and glucose-insulin infusion). Crude odds ratios (ORs) and CIs were calculated. They were adjusted for age, sex, and clinical variables (adjusted OR). The statistical analyses were performed with SAS version 8.2.

**RESULTS**—Clinical characteristics of diabetic and nondiabetic patients with acute MI who were admitted in 1999 and 2001 are presented in Table 1. In diabetic patients, age, sex, and smoking distribution, BMI, heart rate on admission, duration of diabetes, glycemic control, lipid profile, kidney function, CRP, and maximal value of creatinine kinase were comparable between 1999 and 2001. All

characteristics, except sex distribution and age, were comparable in nondiabetic patients.

Therapeutic approaches changed between 1999 and 2001 (Table 2). In 1999, coronary angiography ( $P < 0.01$ ), PTCA ( $P < 0.001$ ), and stenting ( $P < 0.001$ ) were performed less frequently in diabetic patients than in nondiabetic patients. In 2001, performance of these therapeutic options was substantially increased ( $P < 0.001$  vs. 1999) to levels comparable with those of nondiabetic patients. Also, GbIIb/IIIa was administered more frequently in 2001 than in 1999 ( $P < 0.001$ ).

In nondiabetic patients, early PTCA ( $P < 0.01$ ), stenting ( $P < 0.05$ ), and GbIIb/IIIa ( $P < 0.001$ ) were applied more frequently in 2001 than in 1999. In both diabetic and nondiabetic patients, the application of fibrinolysis decreased ( $P < 0.05$ ). Performance of coronary artery bypass grafting did not change significantly in the groups.

The mortality rates were consistently higher in diabetic patients than in nondiabetic patients. In 1999, total hospital mortality of diabetic patients was nearly twofold increased compared with nondiabetic patients (29 vs. 16%,  $P < 0.01$ ). In 2001, total hospital mortality was 17% in diabetic patients and 14% in nondiabetic patients ( $P = \text{NS}$ ). In 1999, hospital mortality was nearly threefold higher within the first 24 h after admission ( $P = 0.01$ ) (Fig. 1), whereas subsequent in-hospital mortality was not significantly different between the two groups (Fig. 1).

In 2001, mortality within 24 h after admission and subsequent in-hospital mortality did not differ significantly between diabetic and nondiabetic patients (Fig. 1). In diabetic patients, total hospital mortality was reduced by 44% ( $P = 0.028$ , 2001 vs. 1999), and 24-h mortality decreased by 67% ( $P = 0.027$ , 2001 vs. 1999). Hospital mortality among nondiabetic subjects, however, did not change significantly between 1999 and 2001 (Fig. 1).

The outcome of the logistic regression analysis in diabetic patients (1999 and 2001) is presented in Table 3. It reveals that an increase in the number of therapeutic approaches in diabetic patients with acute MI (also when adjusted for age, sex, and other clinical variables) is associated with a reduction in mortality.

Blood glucose on admission of dia-

Table 1—Clinical characteristics and serum parameters in diabetic and nondiabetic patients with acute MI: 1999 vs. 2001

	1999 vs. 2001		1999 vs. 2001	
	Diabetic patients	Diabetic patients	Nondiabetic patients	Nondiabetic patients
n	126	91	204	205
Age (years)	73 ± 11	71 ± 13	65 ± 14*	67 ± 14
Female	43	40	26*	36†
Smoker	27	23	46‡	33
BMI (kg/m <sup>2</sup> )	27.3 ± 4.6	27.3 ± 5.1	26.0 ± 3.7	26.1 ± 4.2
Heart rate (bpm)	91 ± 27	85 ± 23	82 ± 23*	79 ± 22§
Hypertension	63	57	45	46
Blood glucose [mg/dl (mmol/l)]	225 ± 99 (12.5 ± 5.4)	231 ± 88 (12.8 ± 4.9)	115 ± 26 (6.4 ± 1.4)	142 ± 32 (7.8 ± 1.8)¶
HbA <sub>1c</sub> (%)	7.3 ± 1.9	7.7 ± 1.6	5.3 ± 0.6	5.6 ± 0.4¶
Total cholesterol (mg/dl)	194 ± 61	185 ± 50	206 ± 51	184 ± 42
HDL (mg/dl)	42 ± 12	42 ± 24	43 ± 13	44 ± 13
LDL (mg/dl)	157 ± 57	127 ± 34	153 ± 49	120 ± 31
Triglycerides (mg/dl)	152 ± 78	157 ± 51	142 ± 72	125 ± 84#
Creatinine (mg/dl)	1.52 ± 1.01	1.32 ± 0.81	1.15 ± 0.48*	1.24 ± 0.86#
Albuminuria	18	16	9‡	7#
CRP (mg/l)	58 ± 70	29 ± 54	47 ± 72	27 ± 56
Maximal value of creatinine kinase (units/l)	627 ± 772	599 ± 729	432 ± 1,383	517 ± 659

Data are means ± SD or percent. \**P* = 0.01 vs. diabetic 1999; †*P* < 0.05 vs. nondiabetic 1999; ‡*P* < 0.05 vs. diabetic 1999; §*P* < 0.01 vs. diabetic 2001; ||*P* < 0.001 vs. diabetic 1999; ¶*P* < 0.001 vs. diabetic 2001; #*P* < 0.05 vs. diabetic 2001.

betic and nondiabetic patients was comparable between 1999 and 2001 (Table 1). In 2001, nearly one-half of diabetic patients received a glucose-insulin infusion at  $1.6 \pm 2.2$  IU/h for  $33 \pm 13$  h. This substantiated in a decrease of blood glucose levels from  $234 \pm 88$  mg/dl ( $13.0 \pm 4.9$  mmol/l) to  $152 \pm 52$  mg/dl ( $8.4 \pm 2.9$  mmol/l) (*P* < 0.001) within 12 h. Severe hypoglycemia did not occur in the course.

In 1999, lengths of hospitalization at the intensive care unit was  $5.8 \pm 5.5$  days in diabetic patients and  $5.5 \pm 5.1$  day in

nondiabetic patients. Also, lengths of entire hospitalization were comparable between diabetic and nondiabetic patients:  $14.1 \pm 9.5$  vs.  $14.5 \pm 9.0$  days. In 2001, hospitalization at the intensive care unit was longer in diabetic patients ( $4.1 \pm 2.4$  days) than in nondiabetic patients ( $3.6 \pm 2.5$  days, *P* < 0.05), whereas the entire hospitalization was not significantly different ( $13.2 \pm 9.0$  vs.  $12.1 \pm 7.6$  days). Differences between 1999 and 2001 were not statistically significant.

Total mortality in patients with and

without previous coronary artery disease was as follows: 1999: diabetic patients 32 vs. 26%, nondiabetic patients 19 vs. 13%; 2001: diabetic patients 21 vs. 14%, nondiabetic patients 15 vs. 13%. Differences between diabetic and nondiabetic patients were not significantly different.

In the diabetic patients, previous antidiabetic medication (insulin and/or oral antidiabetic agents) did not influence the hospital outcome.

In both 1999 and 2001, heart rate on admission was higher in diabetic patients than in nondiabetic patients. Also, creatinine levels were increased and albuminuria was more frequently detected in diabetic patients (Table 1).

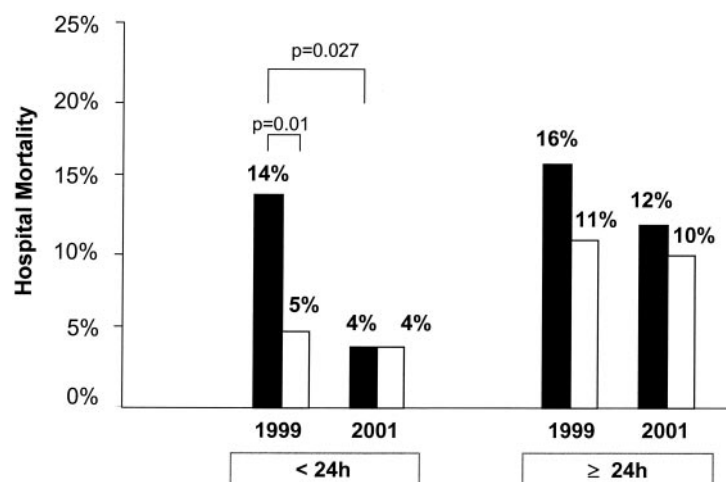
In 1999 and 2001, blood glucose on admission of the entire group of patients was higher in those who died during hospitalization than in those who survived: 1999,  $191 \pm 95$  mg/dl ( $10.6 \pm 5.2$  mmol/l) vs.  $158 \pm 85$  mg/dl ( $8.8 \pm 4.7$  mmol/l) (*P* < 0.001); 2001,  $209 \pm 91$  mg/dl ( $11.1 \pm 5.0$  mmol/l) vs.  $163 \pm 72$  mg/dl ( $9.0 \pm 4.0$  mmol/l) (*P* < 0.001).

In 1999, resuscitation was performed more frequently in diabetic patients than in nondiabetic patients (24 vs. 11%, *P* < 0.01). In 2001, it decreased significantly to 9% (*P* < 0.01) in diabetic patients. The frequency of resuscitation in diabetic patients was comparable with that of nondi-

Table 2—Therapeutic approaches in diabetic and nondiabetic patients with acute MI: 1999 vs. 2001

	1999 vs. 2001		1999 vs. 2001	
	Diabetic patients	Diabetic patients	Nondiabetic patients	Nondiabetic patients
n	126	91	204	205
Coronary angiography	51	73*	75†	79
Acute PTCA	21	50*	38	51‡
PTCA	38	52*	63§	61
Stenting	27	52*	44§	54
GbIIb/IIIa	8	52*	17#	57¶
Fibrinolysis	13	4#	13	6
CABG	4	4	4	8
Glucose-insulin infusion	—	46	—	—

Data are percent. \**P* < 0.001 vs. diabetic 1999; †*P* < 0.01 vs. diabetic 1999; ‡*P* < 0.01 vs. nondiabetic 1999; §*P* < 0.001 vs. diabetic 1999; ||*P* < 0.05 vs. nondiabetic 1999; ¶*P* < 0.001 vs. nondiabetic 1999; #*P* < 0.05 vs. diabetic 1999. CABG, coronary artery bypass graft.



**Figure 1**—Early hospital mortality and subsequent hospital mortality of diabetic (■) and non-diabetic (□) patients with acute MI in 1999 and 2001.

abetic patients. In 1999, catecholamines were infused more frequently in diabetic than in nondiabetic patients (29 vs. 12%,  $P < 0.01$ ). In 2001, differences between the groups were not significantly different (12 vs. 14%).

In 1999, arterial hypertension was reported in 61% of diabetic and 44% nondiabetic patients ( $P < 0.01$ ) compared with 57 and 46% in 2001 ( $P < 0.05$ ). Frequencies of known coronary artery disease did not change significantly between 1999 and 2001 (diabetic patients 49% vs. 37 and 45% and 33% in nondiabetic patients).

Initially, aspirin and clopidogrel were recommended less frequently as discharge medication in diabetic than in nondiabetic patients. ACE inhibitors and diuretic agents were administered more frequently (Table 4). In 2001, the recommendation of aspirin, clopidogrel, and ACE inhibitors was enforced and levels were comparable to those of nondiabetic patients (Table 4). In nondiabetic patients, only the increase in recommendation of ACE inhibitors was significant.

**CONCLUSIONS**— This study demonstrates that the reenforcement of early

therapeutic approaches (revascularization procedures and glucose-insulin infusion) in diabetic patients with acute MI is accompanied by a substantial reduction in hospital mortality. In 2001, the decrease resulted in a mortality rate of diabetic patients that was comparable with that of nondiabetic patients. It is interesting to note that frequencies of both diagnostic and therapeutic interventions were comparable between diabetic and nondiabetic patients. Furthermore, glucose-insulin infusion was successfully introduced as a new treatment strategy for diabetic patients.

The analysis of both years confirms the high prevalence of diabetes among patients with acute MI. Recently, 20.3% of patients with acute MI who were <80 years of age were reported to be diabetic patients (7). The Augsburg MONICA registry observed a prevalence of diabetes in 21% of patients with acute MI who were admitted to the hospital (4).

In 1999, early hospital mortality of diabetic patients was nearly threefold higher in diabetic patients than in nondiabetic patients. This substantial increase was reduced by 67% in 2001. An early hospital mortality rate of 4%, which was comparable to the rate of nondiabetic pa-

tients, was achieved. Since patients who died in the first 24 h were excluded from the Augsburg MONICA registry, data of early mortality are not available in the publication (4).

The study emphasizes the necessity to reduce hospital mortality in diabetic patients and highlights that the goal is achievable in the clinical setting. It demonstrates that early hospital mortality, which is pivotal for the future prognosis, can be successfully targeted. A more extensive application of established treatment has a potential to ameliorate the poor prognosis in diabetic patients with acute MI and is therefore supported.

The data of the Munich registry of 1999 reveals a reduced utilization of several diagnostic and therapeutic approaches in diabetic patients. This has recently been reported for the Swedish registry (RIKS-HIA [Register of Information and Knowledge about Swedish Heart Intensive Care Admission]), which included patients with MI who were admitted between 1995 and 1998 (7). The Augsburg MONICA registry, which investigated patients from 1985 to 1992, also observed an underutilization of treatment strategies (4).

As in RIKS-HIA, reperfusion strategies were initially performed less frequently in diabetic patients (7). In our registry, the gap of diagnostic procedures and therapeutic interventions between diabetic and nondiabetic patients was closed in 2001.

Admission plasma glucose levels have been previously shown to be a predictor of mortality of MI (9,14,15). Patients who died during hospitalization demonstrated higher blood glucose levels on admission than those who survived. Therefore, the importance of admission plasma glucose levels on hospital outcome in patients with MI is reemphasized.

It has been demonstrated that glucose metabolism is altered in a large proportion of patients with acute MI and no previous diagnosis of diabetes (16). Of

**Table 3**—Adjusted and crude ORs for 24-h hospital mortality of diabetic patients in 1999 and 2001

	Adjusted OR	95% CI	P	Crude OR	95% CI	P
Age	1.36	0.57–3.21	0.49	2.33	1.1–4.89	0.03
Sex	0.89	0.43–1.84	0.75	0.74	0.39–1.41	0.36
Clinical variables	3.21	1.45–7.12	<0.01	3.77	1.80–7.90	<0.001
Number of therapeutic approaches	0.14	0.06–0.32	<0.0001	0.12	0.05–0.26	<0.0001



**Table 4—Discharge medication of diabetic and nondiabetic patients with acute MI: 1999 vs. 2001**

	1999 vs. 2001		1999 vs. 2001	
	Diabetic patients	Diabetic patients	Nondiabetic patients	Nondiabetic patients
n	126	91	204	205
Aspirin	80	92*	90†	90
Clopidogrel	49	69*	64†	71
ACE inhibitors	74	92‡	61†	82§
Diuretic agents	68	55	42	44
β-Blockers	83	85	87	80
Statins	61	67	68	59

Data are percent. \* $P < 0.05$  vs. diabetic 1999; † $P < 0.05$  vs. diabetic 1999; ‡ $P < 0.01$  vs. diabetic 1999; § $P < 0.05$  vs. nondiabetic 1999; || $P < 0.01$  vs. diabetic 1999.

patients, 35 and 40% presented with impaired glucose tolerance at discharge and after 3 months, respectively, and 31 and 25% had undiagnosed diabetes (16).

A limitation of the present analysis is that patients who qualified as nondiabetic patients might have had unknown diabetes. The study emphasizes the need for standardized oral glucose tolerance tests in the postinfarction period to detect previously unknown abnormalities of glucose metabolism. Also, larger studies are required to separately analyze the effects of therapeutic approaches in patients.

Glucose-insulin infusion as an adjunct to reperfusion after acute myocardial ischemia has become an effective strategy in the salvage of ischemic myocardium (17–19). Insulin has not only been suggested to act via modulation of cardiac and circulating metabolites but also to promote tolerance against ischemic cell death via activation of cell-survival pathways of the heart (18). There is evidence that early hospital mortality can be reduced by optimization of blood glucose control. The DIGAMI study, which assessed the effect of glucose-insulin infusion during 24 h after admission followed by an intensified therapy of diabetes for 3 months, reported a reduction of both early and long-term mortality in diabetic patients (9,12). Glucose-insulin infusion was applied to a large proportion of diabetic patients who were admitted with an acute MI in 2001. Since a reduction of mortality was mainly seen within the first 24 h after admission, a contribution of glucose-insulin infusion is suggested.

Autonomic incompetence plays a key role in the disturbed performance of the

diabetic heart (1,20–22). Increased heart rate has also been suggested to be an indicator of cardiac incompetence (1). This observation also supports the use of β-blockers, which have been reported to be underused in diabetic patients with MI (23).

The present study demonstrates that a combination of multiple advanced treatment strategies in diabetic patients with acute MI enables a substantial reduction of hospital mortality in the patients. The analysis emphasizes the need for early intervention that targets both arterial occlusion and metabolic disturbances in an appropriate hospital setting. Resistance to early diagnostic and therapeutic interventions in diabetic patients should be abandoned.

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