The impact of diabetes mellitus on survival after myocardial infarction: can it be modified by drug treatment?

Results of a population-based myocardial infarction register follow-up study

H. Löwel[1], **W. Koenig**[2], **S. Engel**[3], **A. Hörmann**[4], **and U. Keil**[5]

[1] GSF-Institute of Epidemiology, Neuherberg, Germany
[2] Department of Internal Medicine II-Cardiology, University of Ulm, Ulm, Germany
[3] Central Hospital of Augsburg, Augsburg, Germany
[4] GSF-Medis-Institute, Neuherberg, Germany
[5] Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany

Abstract

Aims/hypothesis. Mortality of diabetic patients after myocardial infarction remains high despite recent improvement in their management. This study population-based evaluates the impact of cardiovascular drug therapy on mortality within 28 days and during 5-year follow-up in diabetic compared with non-diabetic patients.

Methods. Using the MONICA Augsburg register from 1985 to 1992, 2210 inpatients with incident Q-wave myocardial infarction aged 25–74 years were included, of whom 468 had diabetes. Primary end point was mortality within 28 days and over 5 years. General linear model procedures were used for age-adjustment, controlling for sex, and testing significance; hazard risk ratios were calculated using multivariable Cox proportional hazards model procedures.

Results. During the 5-year follow-up, 598 subjects died (396 diabetic, 202 non-diabetic). The mortality rate within 28 days was 12.6 % in diabetic patients (women 18.0 %, men 9.9 %) and 7.3 % in non-diabetic patients ($p = 0.001$). Mortality in diabetic patients over 5 years was increased by 64 % (95 % confidence interval 1.39–1.95) compared with non-diabetic patients. This was considerably reduced ($p < 0.001$) in patients treated with thrombolytic drugs (risk ratio: diabetes 0.57, no diabetes 0.65) and with beta blockers (0.62 and 0.64) and antiplatelets (0.76 and 0.74) at hospital discharge. Mortality of diabetic patients treated with these drugs was reduced to that of non-diabetic patients without such treatment (risk ratio 1.01 to 1.27; $p > 0.1$).

Conclusion/interpretation. Diabetic patients after myocardial infarction are at particularly high risk of dying, but benefit clearly from treatment with thrombolytics, beta blockers and antiplatelets. This study does not, however, allow any inferences to be drawn for treatment with angiotensin converting enzyme inhibitors or the impact of left ventricular function. [Diabetologia (2000) 43: 218–226]

Keywords Diabetes mellitus, acute myocardial infarction, 28-day mortality, long-term survival, population-based register, secondary prevention.

Large cohort studies [1–4] and two European MONICA (monitoring of trends and determinants in cardiovascular disease) centres [5, 6] have published a threefold (men) to sixfold (women) increased incidence of myocardial infarction (MI) in subjects with diabetes mellitus. It is also well established that even newly diagnosed diabetic subjects have an increased atherogenic cardiovascular risk profile such as increased concentrations of total and LDL cholesterol, of triglycerides, glucose, insulin, raised blood pressure, and lower concentrations of HDL cholesterol [7–10]. Recently, results of a population-based cohort

study from Finland with a 7-year follow-up have suggested that diabetic patients without previous MI (incidence 20%) have as high a risk for MI as non-diabetic subjects with previous MI (incidence 19%; [11]). Furthermore, it has often been reported from large hospital-based studies [12–18] and recently from two population-based MONICA registers [19, 20] that diabetic patients have a worse short-term and long-term prognosis after acute MI compared with non-diabetic patients.

Subgroup analyses from randomized clinical trials have suggested that the modern treatment strategies (thrombolytic agents, beta blockers, antiplatelets, angiotensin converting enzyme (ACE) inhibitors) were not able to reduce the differences in survival after MI between diabetic and non-diabetic patients [21–24]. From the population-based MONICA Augsburg register 1985/1990 a statistically significant increase in 5-year survival after incident Q-wave MI was reported for non-diabetic patients treated with thrombolytic drugs, beta blockers and antiplatelets but no effect for calcium antagonists [25]. There is no population-based data on treatment and long-term survival in diabetic patients who have had a myocardial infarction.

This paper focuses on the impact of diabetes on mortality within 28 days and over 5 years of follow-up in relation to clinical characteristics and cardiovascular drug treatment. The subjects were inpatients with incident Q-wave MI from the MONICA Augsburg MI Register for the years 1985 to 1992.

Subjects and methods

The population-based Augsburg MI Register was part of the international World Health Organization (WHO) MONICA Project [26], which has focused on premature MI with traditional cardiovascular risk factors. All the inhabitants of Augsburg (study population 1985: 156 000 men, 171 000 women; 1992: 186 000 men, 191 000 women; aged 25 to 74 years) who had an acute non-fatal or fatal MI including sudden coronary death (SCD) were registered according to the WHO MONICA protocol [27]. Methods of case finding and data quality control have been described elsewhere [28]. Briefly, diagnostic criteria for MI were chest pain lasting 20 min or more (not relieved by rest or nitrates), electrocardiographic changes suggestive of an evolving MI according to Minnesota codes including ST elevations [29] and a subsequent increase in the concentration of at least one of three cardiac enzymes [creatinine phosphokinase (CPK), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH)] to more than twice the upper limit of normal. Data on medical history including diabetes mellitus were gathered in a standardized interview by trained nurses after discharge from coronary

care units and completed or validated or both by chart review; 70% of the patients admitted to 17 hospitals of the study region were interviewed at a mean time of 12.4 days after onset of acute symptoms. Laboratory data, vital signs, clinical complications and medication during their stay in hospital as well as at discharge were abstracted from the medical records. Information on drug compliance during long-term follow-up was not available. Data from questionnaires completed by the patients themselves 1 year after the event were used to determine a low degree of switching.

A total of 5502 patients without a known history of previous MI were registered between 1985 and 1992. To obtain a homogenous cohort, only inpatients surviving the first 24 hours ($n = 2232$) with incident Q-wave MI were included in our analysis. Of the 3270 patients who died within 24 h (SCD) before ($n = 2200$) or after admission to hospital ($n = 1070$) were excluded because of lack of sufficient information on ECG and other diagnostic criteria. Of them, 824 (25%) had a known history of diabetes and for 655 deceased (12%) no information on history of diabetes could be obtained. Of those who survived 24 h, 22 with missing data on previously diagnosed diabetes were excluded from the analyses. At discharge, 45 patients (11%) received insulin only, 32 patients (8%) received insulin in combination with other antidiabetic drugs, 176 patients (44%) received mostly sulphonylurea drugs and for 150 patients (37%) no antidiabetic medication was recommended by hospital physicians; it can therefore be assumed that the majority of these patients had Type II (non-insulin-dependent) diabetes mellitus [30].

Information about the vital status of each registered patient was obtained by address search and contacting the regional registration offices; there were 66 patients with a follow-up time less than 5 years (mean observation time 4.2 years). The cause of death was taken from the original death certificates and validated by a questionnaire mailed to the coroner or the last treating physician or both. Four main groups of causes of death were summarized: coronary heart disease [international classification of diseases (ICD) 410–414], other cardiovascular diseases (ICD 390–409, 415–459), cancer (ICD 140–208) and the remaining causes.

For medical care consequences, two criteria for survival after MI were defined: a survival of 28 days for inpatients (acute phase of MI, WHO phase I) and of up to 5 years for those who survived 28 days (secondary prevention, WHO phase II).

Statistical analysis. All analyses were done separately for diabetic and non-diabetic patients by sex using the SAS statistical package (Version 6.12, SAS Institute Inc., Cary N.C., USA). All characteristics of diabetic and non-diabetic patients including those who died within 28 days were age-adjusted by the general linear

Table 1. Number of inpatients with an incident Q-wave myocardial infarction (MI; $n = 2210$), number of deaths within 28 days ($n = 186$) and within 5 years after 28-day survival ($n = 412$). Augsburg Myocardial Infarction Register 1985–1992, 5-year mortality follow-up 1997

Age groups (years)	Number of MI patients $n = 100\%$	Number of deaths	
		≤ 28 days n (%)	> 28 days to 5 years n (%)
Diabetic men	287	31 (10.8)	79 (27.5)
25–54	67	2 (3.0)	9 (13.4)
55–64	105	10 (9.5)	26 (27.6)
65–74	115	19 (16.5)	44 (38.2)
Non-diabetic men	1358	92 (6.8)	203 (14.9)
25–54	490	17 (3.5)	32 (6.5)
55–64	490	36 (7.3)	82 (16.7)
65–74	378	39 (10.3)	89 (23.5)
All men	1645	123 (7.5)	282 (17.1)
Diabetic women	181	34 (18.8)	58 (32.0)
25–54	10	–	4 (40.0)
55–64	40	6 (15.0)	14 (35.0)
65–74	131	28 (21.4)	40 (30.5)
Non-diabetic women	384	29 (7.6)	72 (18.8)
25–54	61	4 (6.6)	4 (6.6)
55–64	127	7 (5.5)	21 (16.5)
65–74	196	18 (9.2)	47 (24.0)
All women	565	63 (11.2)	130 (23.0)
All men and women	2210	186 (8.4)	412 (18.6)

model procedure (GLM); a p value less than 0.05 was considered significant. Hazard risk ratios (RR) with 95% confidence intervals (CI) describing the risk of death in diabetic compared with non-diabetic 28-day survivors were calculated using the multivariable Cox proportional hazards model (PHREG procedure in SAS [31]); statistical significance was given, if "1" was not included. Actuarial survival curves were produced by the SAS-LIFETEST procedure [32].

Results

Between 1985 and 1992, a total of 2210 patients aged 25–74 years whose history or lack of history of diabetes was known (1645 men, 565 women) were admitted to hospital with an incident Q-wave MI. Table 1 shows the number of patients by sex, age groups, history of diabetes and the number of deaths within 28 days (123 men, 63 women) and during the following 5 years (282 men, 130 women). At baseline, 468 patients (21%; men 17%, women 32%) were diabetic and 65 (13.9%; men 10.8% and women 18.8%) of them died within 28 days and another 137 (29.3%; men 27.5 and women 32.0) died during the following 5 years. The corresponding crude case fatalities for the 1742 non-diabetic patients were 6.9% (121 deaths) and 15.8% (275 deaths). Main causes of death (not shown in Table 1 were coronary heart disease among diabetic (79%) and non-diabetic (75%) deaths; causes of death of the remainder were other cardiovascular disease (diabetes 7%, no dia-

betes 8%) and cancer (diabetes 8%, no diabetes 8%) and other causes (diabetes 6%, no diabetes 9%). Table 2 compares the age-adjusted baseline characteristics in diabetic (287 men, 181 women) and non-diabetic patients (1358 men, 384 women). Compared with non-diabetic patients, those with diabetes in general were older (men: 61 vs 58 years and women 67 vs 64 years, respectively), were more often female (35% vs 23%) more frequently had a history of hypertension (men 56 vs 44%, women 73 vs 60%) and were less frequently cigarette smokers (men 39 vs 50%, women 22 vs 30%; all differences $p < 0.001$). Compared with non-diabetic patients and diabetic men, diabetic women were characterized further by the longest prehospital delay, the lowest percentage of thrombolysis (13% vs 27 to 32%; $p = 0.0001$), the lowest rates of coronary angiography (27% vs 42 to 55%; $p = 0.0003$) and exercise stress testing (23% vs 37 to 45%; $p = 0.001$). In both sexes, coronary angioplasty and coronary bypass grafting played a minor part at the time of the study in this population. There were significant differences in drug prescriptions: during the acute phase, diabetic patients received beta blockers less often (men 54 vs 65%, women 46 vs 61%; $p < 0.001$) and antiarrhythmic drugs (men 37% vs 44%, women 30 vs 42%; $p < 0.05$) compared with non-diabetic patients. Calcium-channel blockers and diuretics were more often prescribed in diabetic compared with non-diabetic men and women, whereas ACE-inhibitors were prescribed in about 20% of diabetic patients and non-diabetic women but only in 12% of non-diabetic men ($p = 0.0002$).

Table 2. Age-adjusted baseline characteristics of inpatients with incident Q-wave myocardial infarction ($n = 2210$) by history of diabetes mellitus and sex: Augsburg Myocardial Infarction Register 1985–1992

Baseline characteristics	Men		Women	
	Diabetes	No diabetes	Diabetes	No diabetes
Mean age	61.0	58.0[b]	67.0	63.5[b]
(95 % CI; years)	(60.0; 62.1)	(57.5; 58.5)	(66.2; 67.9)	(62.1; 63.7)
History of:				
– Cigarette smoking (%)	39.4	49.6[b]	22.1	29.7[a]
– Hypertension (%)	55.9	43.6[b]	73.0	59.8[b]
– Anterior MI (%)	45.8	41.8[c]	54.0	50.1[c]
Prehospital time < 4 hours (%)	51.8	55.3[c]	44.9	59.3[b]
Therapeutic procedures during hospital stay (%):				
– Thrombolysis	27.0	32.3[c]	12.6	28.1[b]
– CABG	6.1	5.1[c]	1.4	2.6[c]
– PTCA	7.8	8.4[c]	6.1	8.3[c]
Diagnostic procedures during hospital stay (%):				
– Coronary angiography	51.6	55.4[c]	27.4	42.1[b]
– Echocardiography	44.0	43.1[c]	37.7	49.7[b]
– RNV	51.4	51.8[c]	47.1	54.6[c]
– Tl 201-szintigraphy	5.3	8.5[c]	3.5	5.1[c]
– Exercise stress test	40.2	45.4[c]	23.0	36.7[b]
– None	15.6	15.0[c]	27.8	18.4[a]

Diabetes vs no diabetes: [a] *p* value < 0.01, [b] *p* value < 0.05, [c] NS. RNV, Radionuclide ventriculography; CABG, coronary artery bypass grafting; PTCA, percutane transluminal coronary angioplasty

Table 3. Age-adjusted percentages of drug treatment of patients with incident Q-wave myocardial infarction during their hospital stay ($n = 2210$) and at discharge from hospital ($n = 2024$) by history of diabetes and sex: Augsburg Myocardial Infarction Register 1985–1992

Medication	During hospital stay		At discharge	
	Diabetes	No diabetes	Diabetes	No diabetes
Men	*n* = 287	*n* = 1358	*n* = 256	*n* = 1266
Nitrates	97.5	97.4[c]	78.6	77.2[c]
Antiplatelet drugs	77.4	78.7[c]	68.8	70.7[c]
Ca-channel blockers	76.4	71.4[c]	52.9	50.4[c]
Diuretics	67.2	62.9[c]	43.7	31.8[a]
Beta blockers	54.3	65.3[a]	41.2	55.4[a]
ACE-inhibitors	20.8	12.4[a]	15.0	9.1[b]
Anticoagulants	97.9	98.3[c]	9.8	10.8[c]
Antiarrhythmic drugs	37.0	44.4[b]	9.6	7.2[c]
Lipid lowering drugs	4.6	3.6[c]	12.3	10.5[c]
Women	*n* = 181	*n* = 384	*n* = 147	*n* = 355
Nitrates	95.3	96.2[c]	79.8	81.2[c]
Antiplatelet drugs	69.4	78.6[c]	67.4	68.6[c]
Ca-channel blockers	82.5	73.3[b]	65.1	49.1[a]
Diuretics	83.5	73.3[a]	53.8	45.2[c]
Beta blockers	45.7	61.3[a]	37.7	47.8[b]
ACE-inhibitors	20.9	19.6[c]	14.5	14.0[c]
Anticoagulants	98.5	99.7[c]	6.5	8.4[c]
Antiarrhythmic drugs	30.4	42.4[a]	4.3	5.4[c]
Lipid lowering drugs	4.8	6.1[c]	16.0	15.7[c]

Diabetes vs no diabetes: [a] *p* < 0.01, [b] *p* < 0.05, [c] NS

No treatment differences were observed for nitrates, antiplatelet drugs, anticoagulants and lipid lowering drugs. At discharge, diabetic men and women were less likely to receive a beta blocker than non-diabetic men (*p* < 0.05). Diabetic women showed the highest prescription rate of Calcium-channel blockers (65 % vs 49 to 53 %; *p* = 0.001) and non-diabetic men were treated less often with ACE-inhibitors compared with the other three patient groups (9 % vs 14 to 15 %, *p* = 0.004).

Table 4 summarizes selected patient characteristics of potential relevance for long-term survival by history of diabetes and sex. Mean peaks of enzyme values were significantly lower among diabetic com-

Table 4. Age-adjusted biochemical and clinical characteristics in 25 to 74-year-old inpatients with incident Q-wave myocardial infarction ($n = 2210$) by sex and history of diabetes: Augsburg Myocardial Infarction Register 1985–1992

Clinical characteristics	Men		Women	
	Diabetes	No diabetes	Diabetes	No diabetes
Peak CPK mean (μ/l, 95% CI)	786 (668; 904)	831 (790; 873)	590 (519; 660)	818 (732; 904)
Peak CK-MB mean (μ/l, 95% CI)	61 (55; 67)	75 (72; 78)	57 (51; 64)	86 (78; 93)
Systolic BP < 100 mm Hg (%)				
On admission	6.5	8.5[c]	8.1	8.9[c]
At discharge	15.3	20.3[c]	8.0	17.8[b]
Heart rate > 100/min (%)				
On admission	27.1	17.6[b]	38.9	25.3[b]
At discharge	5.9	1.4[b]	5.4	2.4[c]
During hospital stay:				
Recurrent MI (%)	5.6	6.6[c]	8.0	6.7
Cardiogenic shock (%)	10.1	5.9[a]	16.0	9.0[a]
Pulmonary oedema (%)	6.9	2.8[b]	4.8	3.5[c]
Cardiac arrest (%)				
Before hospital stay	1.5	2.5[c]	3.9	2.1[c]
After hospital stay	13.6	13.5[c]	20.9	13.9[a]
Death within 28 days	9.9	7.0[c]	18.0	8.0[b]

Diabetes vs no diabetes: [a] *p* value > = 0.05, [b] *p* value < = 0.01, [c] NS

pared with non-diabetic patients. Cardiogenic shock and pulmonary oedema were higher in diabetic than non-diabetic patients whereas no differences in pre-hospital cardiac arrest were observed between the four patient groups. After admission to hospital cardiac arrest (21% vs 14%; *p* = 0.04) and death within 28 days (18% vs 7–10%; *p* = 0.001) were increased in diabetic women compared with diabetic men and the non-diabetic patients.

Figure 1 presents the observed survival curves for the 5-year follow-up period separately for diabetic and non-diabetic patients adjusted for age, sex and medication; 71% of the diabetic and 83% of the non-diabetic patients were still alive 5 years after their incident Q-wave MI (RR 1.64 95% CI 1.39–1.95; Table 5). The impact of diabetes was highest in the age group 25–54 years (RR 2.29–2.45), decreased with increasing age (RR 65–74 years: RR 1.60–1.78) and varied only little after controlling for confounders. No significant differences were found in long-term survival between male and female diabetic and non-diabetic patients who survived more than 28 days.

Table 6 presents 5-year mortality risk ratios calculated by multivariable Cox proportional hazards model for diabetic and non-diabetic patients separately by age, sex, thrombolysis and medication at discharge. Patients treated with thrombolytic drugs (diabetes RR 0.58; no diabetes RR 0.65), beta blockers (diabetes RR 0.62; no diabetes 0.64) and antiplatelets (diabetes RR 0.76; no diabetes 0.74) showed significant reductions in mortality during the 5-year follow-up after adjustment for potential confounders. Those diabetic patients who received thrombolytic therapy and were prescribed beta blockers or antiplatelets at discharge showed no differences in mortality rate during the 5-year follow-up compared with non-diabetic patients after controlling for confounders (Table 7). In contrast, treatment with Calcium-channel blockers had no influence on the excess diabetes-related mortality. Treatment with ACE-inhibitors of the subgroup of patients with chronic heart failure at the time of the study was only included in the statistical models as a confounder variable.

Discussion

These data from a southern German population show an increase in mortality within 28 days of 81% and within 5 years of follow-up of 64% in patients with compared with those without diabetes and thus confirm results of previous studies [13–22, 33]. Although increase in mortality in diabetic women within 28 days was clearly related to a more unfavourable treatment profile, no sex differences in long-term mortality were observed. Coronary heart disease was the main cause of death in 79% of all diabetic and 75% of all non-diabetic patients after incident Q-wave MI; similar data have been reported from the Minnesota Heart Survey [34] and recently from FINMONICA [22]. The latter study has published similar data for death within 28 days and mortality rates within 1 year for 28-day survivors and the MONICA register in New South Wales [19] also found the highest rates of death within 28 days were in diabetic women.

Table 5. The 5-year mortality risk ratios with 95 % CI for diabetic patients with a non-fatal incident Q-wave myocardial infarction ($n = 403$) relative to non-diabetic patients ($n = 1621$) adjusted for age, sex, thrombolytic treatment after hospital stay, and drug treatment at discharge using the multivariate Cox proportional hazards model: Augsburg Myocardial Infarction Register 1985–1992, mortality follow-up 1997

Age groups (years)	Controlling for		
	Sex	Sex, hypertension, anterior MI smoking	Sex, thrombolysis; medication at discharge (antiplatelets, beta blockers, Ca-channel blockers, ACE-inhibitors)
25–54	2.45 (1.56; 3.85)	2.31 (1.45; 3.68)	2.29 (1.44; 3.64)
55–64	1.81 (1.35; 2.42)	1.77 (1.31; 2.40)	1.57 (1.16; 2.11)
65–74	1.76 (1.40; 2.20)	1.78 (1.39; 2.28)	1.60 (1.26; 2.03)
All (adjusted for age)	1.83 (1.55; 2.17)	1.85 (1.55; 2.22)	1.64 (1.39; 1.95)

Table 6. Relative risk of 5-year mortality with 95 % CI of diabetic ($n = 403$) and non-diabetic patients ($n = 1621$) with a 28-day survived incident Q-wave myocardial infarction by treatment with thrombolytic drugs after hospital stay and discharge treatment with beta blockers, antiplatelets, antidiabetic drugs vs no such treatment, adjusted for age, sex, and the above mentioned medications, calculated by Cox proportional hazards model: Augsburg Myocardial Infarction Register 1985–1992, mortality follow-up 1997

|	Diabetes RR (95 % CI)	No diabetes RR (95 % CI)
Age (years)		
25–54	1.00	1.00
55–64	1.42 (0.88–2.30)	2.07 (1.57–2.72)
65–74	1.70 (1.06–2.73)	2.65 (2.01–3.49)
Thrombolytic drugs	0.58 (0.37–0.90)	0.65 (0.51–0.81)
Treatment at discharge		
Beta blockers	0.62 (0.45–0.85)	0.64 (0.52–0.78)
Antiplatelets	0.76 (0.57–1.01)	0.74 (0.61–0.90)
Ca-channel blockers	0.95 (0.72–1.27)	1.12 (0.93–1.36)
ACE-inhibitors	1.15 (0.79–1.66)	1.52 (1.15–2.01)
Sulphonylurea drugs	0.95 (0.72–1.26)	–
Insulin	1.63 (1.18–2.25)	–
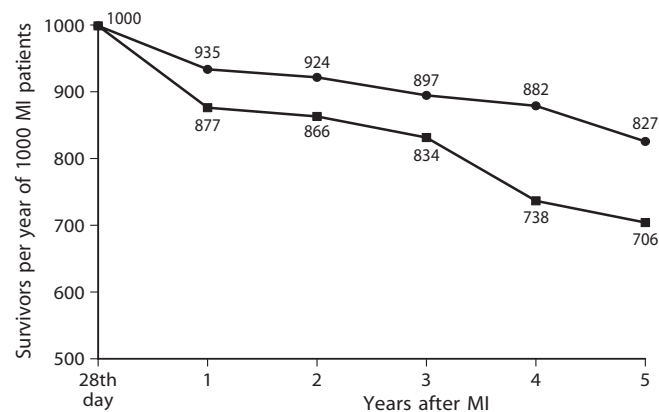
Fig. 1. Observed 5-year survival curves in 28-day survivors after incident Q-wave myocardial infarction by history of diabetes adjusted for age, sex and cardiovascular drug medication. MONICA Augsburg myocardial infarction register 1985–1992, mortality follow-up 1997 –●– Non-diabetic subjects –■– Diabetic subjects

The GUSTO-I-Trial [24], tested the effect of various thrombolytic drugs in acute MI (34 888 non-diabetic patients and 4301 Type II diabetic patients; first and recurrent MI with ST elevations) and found a mortality rate within 1 year of those who survived 30 days of $14.5 \pm 0.5\%$ in diabetic and $8.9 \pm 0.2\%$ ($p = 0.0001$) in non-diabetic patients. This is nearly identical to that in the population-based Augsburg cohort (Fig. 1) despite the lower percentage of thrombolysis in Augsburg (diabetes 22 %, non-diabetes 31 %; GUSTO-I 100 %).

In the Augsburg study, no data could be obtained on results of invasive diagnostic procedures. Based on coronary angiography, the GUSTO-I-Trial reported a more diffuse coronary heart disease in diabetic patients (32 % with two-vessel and 31 % with three-vessel disease; no diabetes 28 % and 21 %, respectively). Data from the Corpus Christi Heart Project [35] have suggested that the increased long-term mortality in diabetic patients was largely independent of the severity of MI and thus might reflect the more rapid progression of coronary heart disease and the more frequent occurrence of cardiac failure in diabetic patients. In this study, the peak of cardiac enzyme values for CPK and creatinine phosphokinase – M (muscle) B (brain) were significantly lower in diabetic than in non-diabetic patients – which was also reported for peak creatinine phosphokinase from the GUSTO-I trial and from FINMONICA [20] – and this also argues against a more severe presentation of the MI in diabetic patients as the reason for their improved prognosis.

As an important result of our population-based observational study over 5 years of a real life situation a remarkable reduction was observed in the mortality rate for diabetic and non-diabetic patients treated with thrombolytic drugs (diabetes –42 %, no diabetes –35 %), beta blockers (–38 % respectively –36 %), and antiplatelets (–24 % respectively –26 %). Effects of thrombolysis and treatment with beta blockers were larger than expected on the basis of randomized clinical trial results [21, 22, 24, 33, 36]. The effect of an-

Table 7. Relative risk ratios with 95 % CI of diabetic patients with thrombolysis, discharge medication with beta blockers, antiplatelets or Ca-channel blockers compared with non-diabetic patients without such drug treatment controlled for age, sex, the above mentioned drugs, and ACE-inhibitors[a] at discharge: Augsburg Myocardial Infarction Register 1985–1992, mortality follow-up 1997

	Treated diabetic patients		Non-treated non-diabetic patients		RR (95 % CI)
	Crude % of deaths (n)	Person years (n)	Crude % of deaths (n)	Person years (n)	
Thrombolytic therapy	4.9 (18)	367 (86)	4.3 (208)	4818 (1085)	1.01 (0.67; 1.53)
Beta blockers	5.2 (34)	651 (148)	5.2 (166)	3202 (732)	1.07 (0.79; 1.44)
Antiplatelets	7.3 (84)	1143 (272)	4.5 (94)	2085 (477)	1.22 (0.96; 1.55)
Ca-channel blockers	8.3 (79)	955 (233)	3.3 (120)	3676 (805)	1.78 (1.40; 2.27)

[a] indicating the subgroup of chronic heart failure, ACE-inhibitors (62 diabetic and 161 non-diabetic patients) that had not yet been established for secondary prevention of CHD at the time of the study were used only as confounder

tiplatelets was a 24 % (diabetes) to 26 % (no diabetes) reduction as has been reported by the Anti platelet Trialists for secondary prevention [37]. Data on the benefit of treatment with beta blockers in diabetic patients after an acute MI is scarce [38]. Although the controversial debate on their metabolic side effects potentially outweighing their therapeutic efficacy in diabetics has been settled in the literature [39], there are still some restraints to prescribing beta blockers in diabetic patients in clinical practice (Table 4).

In non-diabetic patients on long-term treatment with ACE-inhibitors (12 %) an increased mortality of 52 % during 5-year follow-up compared with those without such therapy was observed. Before 1992 the use of ACE-inhibitors after an acute MI, for secondary prevention was, however, not well established. Thus, patients on an ACE-inhibitor, registered before 1992 were only those with severe, symptomatic congestive heart failure carrying an extremely bad prognosis. Therefore, the Augsburg results are not comparable with observations from the GISSI-3 trial [40], where no 6-month survival differences were observed in non-diabetic MI patients treated with an ACE inhibitor compared with the control group and a benefit was suggested for diabetic patients (mortality 12.9 % in the treated vs 16.1 % in the control group; odds ratio 0.77 95 % CI 0.62 to 0.95).

Similarly, beta blockers might have been mainly prescribed to low risk patients (excluding those with chronic obstructive pulmonary disease, heart failure or impaired left ventricular function; [39]). Due to the limitations of the study design we cannot prove whether the observed low mortality can be attributed to the suggested drug effect or is a consequence of treatment assignment. Only a randomized clinical trial could solve this issue.

A further important observation is that diabetic patients with thrombolysis, beta blocker or antiplatelet therapy showed a clearly improved long-term survival; diabetes-related mortality risks were reduced to the level of non-diabetic patients without such medication (non-significant RR between 1.01 and 1.22; Table 7). For the above mentioned reasons, we

were, however, not able to reliably assess the effect of ACE inhibitor use or the impact of impaired left ventricular function on survival. Despite this, our results underscore the importance of optimal treatment in both diabetic and non-diabetic patients in the acute phase and during secondary prevention.

In practice, the importance of rigorously intervening in all patients with diabetes to control glycaemia, lower blood pressure and blood lipids should be emphasized [35, 36, 41–43]. Data from the 4S-study and the CARE-study have clearly shown that long-term treatment with lipid lowering drugs, like simvastatin or pravastatin, provide an effective strategy to improve survival in diabetic and non-diabetic patients who have had a MI and have a normal or moderately high serum cholesterol [44, 45].

Despite the observational nature of the Augsburg study and its inherent limitations, diabetes remains an important predictor of short-term and long-term mortality after MI even in the thrombolytic era. Finally, as surveys like EUROASPIRE [46] have shown, the evidence from clinical trials needs to be taken into account in clinical practice. This seems to be even more important in patients with than in those without diabetes [47].

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