Original articles

Clinical characteristics and outcome of diabetic patients with acute myocardial infarction. Data from the BLITZ-1 study

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Diabetes mellitus; Management in cardiology; Myocardial infarction; Prognosis.

Background. **The determinants of a worse outcome in diabetic patients after an acute myocardial infarction (AMI) are controversial. They include delayed hospital admission, worse clinical presentation and lesser efficacy of accepted therapeutic interventions. Therefore, to improve our knowledge, we aimed to describe the clinical characteristics, treatment options and short-term outcomes of diabetic patients in a survey of consecutive AMI subjects admitted to the Italian coronary care unit (CCU) network in the current era of reperfusion.**

Methods. **The BLITZ study prospectively enrolled patients with AMI, within 48 hours of symptom onset, admitted to 296 out of the 341 existing Italian CCUs from October 15 to 29, 2001. Diabetic status was recorded by collecting clinical history. In-hospital and post-discharge management and outcomes were collected up to 30 days from admission.**

Results. **Overall, 434 of 1959 enrolled patients (22%) had a clinical diagnosis of diabetes. Diabetic patients were older, more frequently women, had a worse coronary risk profile, and an unfavorable clinical presentation compared to non-diabetics. Among 1275 patients with ST-elevation AMI, diabetics (20%) received a similar proportion of any reperfusion therapy (61 vs 66%, p = 0.10), but significantly less primary percutaneous coronary angioplasty (9 vs 16%, p = 0.003). Diabetic patients were treated less often with oral beta-blockers than non-diabetics both during hospitalization (56 vs 64%, p = 0.003) and at discharge (54 vs 61%, p = 0.01). In contrast, in-hospital use of angiotensin-converting enzyme inhibitors (76 vs 67%, p = 0.0003), digitalis (10 vs 5%, p = 0.0005), and diuretics (54 vs 36%, p < 0.0001) was more frequent among diabetics. During their index admission, subjects with diabetes had higher in-hospital mortality (11 vs 6%, p = 0.0004), as well as higher rates of reinfarction (6 vs 2%, p = 0.0003), new congestive heart failure (28 vs 14%, p < 0.0001), cardiogenic shock (10 vs 5%, p = 0.0005) or recurrent angina (22 vs 16%, p = 0.0034). A similar pattern was observed at 30-day follow-up. At multivariate analysis, diabetic status was not confirmed to be an independent predictor of 30-day mortality.**

Conclusions. **Although diabetic patients with AMI admitted to the Italian CCU network have a higher in-hospital and 30-day morbidity and mortality rates compared to non-diabetics, a clinical diagnosis of diabetes has no independent predictive value on short-term outcome.**

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Introduction

After an acute myocardial infarction (AMI), patients with diabetes have higher mortality and morbidity rates than non-diabetics[1-3]. This increased risk persists even after implementation of modern revascularization and pharmacological treatment strategies[4,5]. Whether this finding is due to metabolic factors[6], a diabetic cardiomyopathy[7] or to a less aggressive treatment[8] is still an issue. In fact, from a pathophysiological standpoint, it is well known that diabetics have more severe and diffuse coronary artery disease compared to non-diabetics[4,5] and may have a subclinical myocardial dysfunction as well[7]. As far as treatment is concerned, the effect of specific metabolic therapy is still controversial. In fact, although intensified insulin treatment appeared to be beneficial in the DIGAMI trial[9], this strategy did not improve short-term outcome[10] nor has been proven by larger studies so far. Notably, very effective evi-

dence-based treatments, like thrombolytic agents and beta-blockers, are often withheld in diabetic patients with AMI due to unverified worries[11,12]. At present, most information on AMI in diabetics derive from small studies in highly selected, medium-to-low-risk populations, and results are often conflicting[3,13-15]. Therefore, the BLITZ-1 study[16], which enrolled a consecutive series of patients with a broad spectrum of AMI admitted to the majority of the Italian coronary care units (CCUs), offers the opportunity to investigate the clinical profile, the therapeutic strategies and the short-term outcome of contemporary patients with AMI with or without a clinical diagnosis of diabetes.

Methods

Study organization. A detailed description of methods and patients has been published elsewhere[16]. Briefly, the BLITZ-1 study was designed by the Italian Association of Hospital Cardiologists (ANMCO) as a nationwide survey of patients admitted to the CCUs for an AMI either with (STEMI) or without (NSTEMI) ST-segment elevation, along a 15-day period (October 15 to 29, 2001). The survey collected data from the pre-hospital phase to 30-day follow-up afterward. Each center agreed to enroll all consecutive patients admitted with AMI, within 48 hours of symptom onset. No other exclusion criteria were considered. Data on clinical variables, procedures, and events were collected prospectively using standardized forms during hospitalization. The 30-day follow-up was conducted by hospital visits and recorded any major cardiac events occurred from hospital discharge to the follow-up visit (death, non-fatal reinfarction, new hospitalizations for angina or heart failure, as well as revascularization procedures). Extensive quality-control efforts were made to ensure completeness and accuracy of data. Follow-up data were completed in 99.1% of the patients at 30 days. Informed consent was obtained from each patient.

Definitions. Diabetes mellitus was defined as a known history of diabetes treated with diet, oral antidiabetic agents or insulin. Criteria for diagnosing an AMI were suggested, including both the classical[17] and new disease definitions[18]. STEMI was defined by the presence of ST-segment elevation ≥ 1 mm (≥ 2 mm in V_1 to V_3) in two or more contiguous leads. NSTEMI was defined by the presence of ST-segment depression, T-wave inversion, or non-significant ST-T changes. Patients with complete left bundle branch block, paced rhythm or other abnormalities that made it impossible to analyze the ST segment were defined as having an AMI with undetermined ECG location. Pre-hospital delay was defined as the time interval between symptom onset and the first in-hospital ECG. Delay of reperfusion treatment was defined as the time interval between symptom onset and start of thrombolysis or primary percutaneous coronary intervention (PCI). Stroke was identified by a clinical diagnosis (with or without confirmation by computed tomography scan or magnetic resonance imaging) and symptoms persisting > 24 hours. Major bleeding was defined as a bleed considered fatal or life-threatening, an overt bleeding requiring transfusion of > 2 units of packed red blood cells (or equivalent), or a bleed requiring surgical intervention. Heart failure was identified through a clinical diagnosis of new-onset congestive heart failure with: a) radiological evidence to support this diagnosis or b) a depressed ejection fraction (≤ 45% detected by echocardiography, angiography or radionuclide assessment). A patient was considered to have a previous known cardiovascular disease if previous myocardial infarction, stroke, congestive heart failure, PCI, or coronary artery bypass graft (CABG) had been reported.

Statistical analysis. Baseline historical data, in-hospital management, and in-hospital or short-term outcome rates of all diabetic and non-diabetic patients enrolled in the registry were summarized. Continuous data are reported as means and SD, with intergroup comparisons performed by Student's t-test. Categorical data are reported as counts and proportions, with intergroup comparisons by the χ^2 or Fisher's exact test. Time intervals are presented as median times (and interquartile ranges - IQR). Kaplan-Meier event curves for diabetic and non-diabetic patients were constructed for total mortality. These curves were compared by the log-rank test. Multivariable models (Cox proportional hazards regression model) were constructed to detect which variables were predictive of 30-day mortality in the 1943 subjects with 30-day follow-up completed. The models were constructed with all variables that had univariate predictive values ($p < 0.05$). The variables included were: gender, age > 75 years, previous history of heart failure, myocardial infarction, diabetes, peripheral vascular disease or stroke, smoking status, cholesterol level > 200 mg/dl, systolic blood pressure ≤ 90 mmHg, heart rate > 100 b/min, Killip class III-IV on admission, creatine phosphokinase and troponin levels (in quartiles) and medication used during hospitalization (aspirin, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors and statins). The odds ratios and the relative risk with 95% confidence intervals were calculated. A p value < 0.05 was considered as statistically significant. All statistical analyses were done with the use of the SAS system software (SAS Institute Inc., Cary, NC, USA).

Results

The study included 1959 patients, of whom 434 (22%) had a clinical diagnosis of diabetes. Before admission, most diabetics were treated with oral antidia-

betic agents alone (182, 42%) or insulin (76, 17%), whereas 176 (41%) were untreated. Ten out of the 76 patients on insulin received it in association with oral antidiabetic agents. Table I shows the baseline characteristics of diabetic and non-diabetic patients. Diabetics had a worse coronary risk profile compared to non-diabetics and were treated more frequently with aspirin, beta-blockers, calcium-channel blockers, ACE-inhibitors, statins or digitalis before admission. In particular, a higher proportion of diabetic patients received a preventive treatment with ACE-inhibitors, aspirin or statins before admission (53 vs 39%, $p < 0.0001$).

The proportion of women vs men and the gender relation with age are shown in figure 1.

Admission phase. The clinical findings on admission are summarized in table II. Diabetic patients were more often admitted without symptoms (37 vs 29%, $p = 0.005$), or with undetermined myocardial infarction location on the qualifying ECG.

They also had higher heart rate, systolic blood pressure and Killip class as compared to non-diabetics. Among the 1275 patients with STEMI, the pre-hospital delay was likely to be longer in diabetics than in non-diabetics (196 vs 175 min, IQR 107-473 vs 90-430 min).

In-hospital treatment and evaluation. Among the 1275 patients with STEMI, 828 (65%) received a reper-

Table I. Baseline characteristics of the study population.

Variable	Diabetes (n=434)	No diabetes (n=1525)	p
Age (years)	70 ± 10	66 ± 13	< 0.0001
Female gender	177 (41%)	419 (27%)	< 0.0001
Previous history			
Myocardial infarction	113 (26%)	273 (18%)	0.0002
Congestive heart failure	65 (15%)	64 (4%)	< 0.0001
Angina	121 (28%)	280 (18%)	< 0.0001
Stroke	47 (11%)	105 (7%)	0.0067
Peripheral vascular disease	81 (19%)	129 (8%)	< 0.0001
PCI*	22 (5%)	63 (4%)	0.39
CABG*	31 (7%)	54 (3%)	0.0012
Hypercholesterolemia**	156 (46%)	639 (52%)	0.06
Hypertension	297 (68%)	790 (52%)	< 0.0001
Present or past smoker	199 (46%)	937 (61%)	< 0.0001
Previous treatment			
Beta-blockers	65 (15%)	157 (10%)	0.0066
Antiplatelet agents	137 (32%)	340 (22%)	< 0.0001
ACE-inhibitors	145 (33%)	322 (21%)	< 0.0001
Digitalis	27 (6%)	54 (3%)	0.0133
Calcium channel blockers	85 (20%)	184 (13%)	< 0.0001
Statins	54 (12%)	103 (7%)	0.0001

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention. * counts and proportions calculated for the 1958 patients with available data (434 diabetics, 1524 non-diabetics); ** counts and proportions calculated for the 1571 patients with available data (338 diabetics, 1233 non-diabetics).

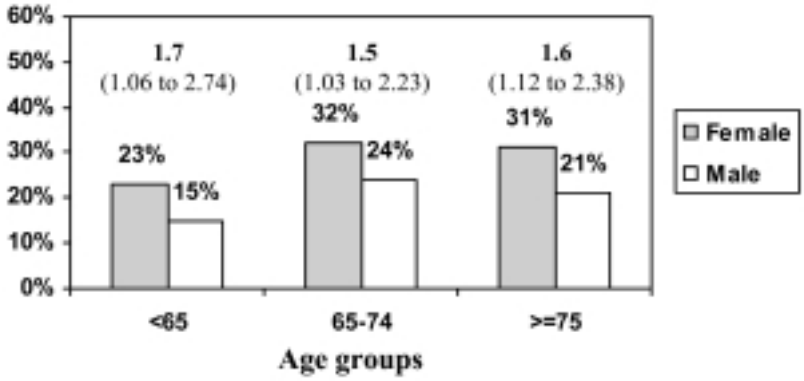

Figure 1. *Proportion of patients with diabetes in three age groups (< 65, 65-74, ≥ 75 years). The total prevalence of diabetics was 22%. Female-related odds ratio (with 95% confidence intervals) for prevalence of diabetes in the different age groups are reported above the bars.*

Table II. Clinical findings on admission.

	Diabetes (n=434)	No diabetes (n=1525)	p
Typical chest pain	241 (55%)	963 (63%)	0.005
Heart rate* (b/min)	85 ± 21	77 ± 20	< 0.0001
Heart rate > 100 b/min*	80 (18%)	139 (9%)	0.0001
Systolic blood pressure** (mmHg)	143 ± 29	134 ± 26	< 0.0001
Systolic blood pressure ≤ 90 mmHg**	16 (4%)	65 (4%)	0.6
Killip class III-IV	49 (11%)	77 (5%)	< 0.0001
Admission ECG			
ST-elevation AMI	253 (58%)	1022 (67%)	< 0.0001
Non-ST-elevation AMI	141 (32%)	439 (29%)	
Undetermined location	40 (10%)	64 (4%)	

AMI = acute myocardial infarction. * means (± SD) and proportions calculated for the 1957 patients with available data (433 diabetics, 1524 non-diabetics); ** means (± SD) and proportions calculated for the 1955 patients with available data (432 diabetics, 1523 non-diabetics).

fusion treatment: 642 (50%) were treated with thrombolysis and 186 (15%) with primary PCI, respectively. As outlined in table III, primary PCI was used more frequently in non-diabetics, though the rate of thrombolytic treatment did not differ between the groups. Therefore, reperfusion therapy was more often withheld in patients with diabetes. The delay of reperfusion was longer for diabetics (175 vs 165 min, IQR 120-315 vs 105-250 min, p = 0.04). Interestingly, the use of reperfusion therapy in diabetic or non-diabetic patients did not differ between Northern, Central or Southern Italy. In addition, when demographic and clinical features of the study population were analyzed according to diabetic status and reperfusion treatment (Table IV), diabetic patients showed a worse risk profile and clinical presentation than non-diabetics, even when reperfusion was used.

With respect to adjunctive therapy (Table V), diabetic patients were less likely to be treated with intravenous or oral beta-blockers, but more likely to receive ACE-inhibitors, digitalis, diuretics, calcium channel blockers, intravenous nitrates or amiodarone during hospitalization. The same underuse of beta-blockers as opposed to a higher rate of ACE-inhibitors, digitalis, or nitrates in diabetics was still observed at discharge.

Concerning antidiabetic therapy, the proportion of diabetics treated with insulin raised up to 48% during hospitalization, while the number of subjects receiving only oral antidiabetic agents fell to 26%. The proportions of patients discharged on insulin, oral antidiabetic agents alone or left pharmacologically untreated were 29, 43 and 28%, respectively.

Diabetic patients underwent exercise testing less often than non-diabetics during hospitalization. The rate of in-hospital cardiac catheterization was much lower in diabetics as compared to non-diabetics. However, this underuse of coronary angiography in diabetics did not translate into a substantial difference in elective PCI or CABG rates (Table V).

In-hospital outcome and 30-day follow-up. During the index admission, patients with diabetes had significantly higher rates of mortality, non-fatal reinfarction, congestive heart failure, cardiogenic shock, and recurrent angina than their non-diabetic counterparts (Table VI). However, no differences were observed in the rates of stroke or bleeding.

At 30 days after admission, the rates of elective PCI were similar between diabetic and non-diabetic patients, whereas more diabetics underwent CABG surgery (Table VI). Patients with diabetes had significantly higher rate of death, congestive heart failure, and non-fatal reinfarction than non-diabetics, whereas the incidence of stroke and recurrent angina after hospitalization did not differ according to diabetic status.

Table III. Reperfusion therapy for the 1275 patients with ST-elevation myocardial infarction.

	Diabetes (n=253)	No diabetes (n=1022)	p
Thrombolysis	131 (52%)	511 (50%)	0.6
Primary PCI*	22 (9%)	164 (16%)	0.003
No reperfusion therapy	100 (39%)	347 (34%)	0.10
Delay of reperfusion (min, IQR)	175	165	
(symptoms-to-treatment)	(120-315)	(105-270)	0.04

IQR = interquartile range; PCI = percutaneous coronary intervention. * primary PCI was defined as primary or facilitated PCI.

Table IV. Demographic and clinical characteristics of the ST-elevation myocardial infarction population according to the diabetes status and reperfusion treatment.

Variable	Reperfusion therapy		No reperfusion therapy	
	Diabetes (n=153)	No diabetes (n=675)	Diabetes (n=100)	No diabetes (n=347)
Age (years)	66 ± 9	62 ± 12	73 ± 10	69 ± 14
Female gender	49 (32%)	144 (21%)	48 (48%)	132 (38%)
Previous history				
Myocardial infarction	18 (12%)	93 (14%)	23 (23%)	56 (16%)
Congestive heart failure	9 (6%)	7 (1%)	12 (12%)	17 (5%)
Peripheral vascular disease	19 (12%)	43 (6%)	20 (20%)	41 (12%)
Hypertension	91 (59%)	293 (43%)	75 (75%)	197 (57%)
Previous treatment				
Beta-blockers	19 (12%)	54 (8%)	12 (12%)	29 (8%)
Antiplatelet agents	35 (23%)	137 (20%)	27 (27%)	66 (19%)
ACE-inhibitors	31 (20%)	104 (15%)	34 (34%)	73 (21%)
Statins	9 (6%)	43 (6%)	9 (9%)	13 (4%)
Clinical findings on admission				
Heart rate (b/min)	82 ± 22	75 ± 17	84 ± 22	78 ± 21
Systolic blood pressure (mmHg)	137 ± 26	134 ± 27	143 ± 29	134 ± 26
Killip class III-IV	11 (7%)	16 (2%)	11 (11%)	19 (5%)

ACE = angiotensin-converting enzyme.

Table V. In-hospital or discharge treatment and procedures.

	Diabetes (n=434)	No diabetes (n=1525)	p
In-hospital treatment			
Oral antiplatelet agents	382 (88%)	1388 (91%)	0.06
GP IIb/IIIa inhibitors	72 (16%)	288 (19%)	0.27
Intravenous heparin	283 (65%)	1040 (68%)	0.24
LMWH	163 (38%)	525 (34%)	0.22
Intravenous beta-blockers	72 (16%)	320 (21%)	0.04
Oral beta-blockers	242 (56%)	969 (64%)	0.003
ACE-inhibitors	331 (76%)	1025 (67%)	0.0003
Intravenous nitrates	367 (85%)	1211 (79%)	0.02
Digitalis	44 (10%)	83 (5%)	0.0005
Diuretics	235 (54%)	548 (36%)	< 0.0001
Amiodarone	57 (13%)	125 (8%)	0.0018
Calcium channel blockers	74 (17%)	195 (13%)	0.02
Statins	184 (42%)	660 (43%)	0.74
In-hospital procedures			
Exercise testing	64 (15%)	318 (21%)	0.0046
Echocardiography	417 (96%)	1459 (96%)	0.7
Coronary angiography	165 (38%)	726 (48%)	< 0.0001
Elective PCI	36 (8%)	176 (11%)	0.06
CABG	6 (1.4%)	21 (1.4%)	0.99
Treatment at discharge	(n=385)	(n=1430)	
Aspirin	313 (81%)	1184 (83%)	0.49
Beta-blockers	209 (54%)	879 (61%)	0.01
ACE-inhibitors	292 (76%)	938 (66%)	0.0001
Digitalis	22 (6%)	44 (3%)	0.01
Nitrates	281 (73%)	854 (60%)	< 0.0001
Calcium channel blockers	61 (16%)	191 (13%)	0.21
Statins	182 (47%)	693 (48%)	0.67

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; GP = glycoprotein; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention.

Table VI. In-hospital and short-term follow-up cardiac events.

	Diabetes (n=434)	No diabetes (n=1525)	p
In-hospital cardiac events			
All-cause death	49 (11%)	95 (6%)	0.0004
Non-fatal reinfarction	25 (6%)	36 (2%)	0.0003
Cardiogenic shock	43 (10%)	81 (5%)	0.0005
Congestive heart failure	123 (28%)	207 (14%)	< 0.0001
Recurrent angina	94 (22%)	239 (16%)	0.0034
Exercise-induced ischemia	39 (9%)	104 (7%)	0.12
Stroke	7 (2%)	19 (1%)	0.55
Major bleeding	7 (2%)	31 (2%)	0.57
From discharge to 30-day follow-up	(n=378)	(n=1412)	
All-cause death	17 (5%)	21 (2%)	0.0003
Non-fatal reinfarction	8 (2%)	12 (1%)	0.04
Congestive heart failure	18 (5%)	30 (2%)	0.0048
Recurrent angina	26 (7%)	79 (6%)	0.34
Stroke	3 (1%)	4 (0.3%)	0.15
PCI	41 (11%)	138 (10%)	0.53
CABG	45 (12%)	83 (6%)	< 0.0001

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

Absolute mortality clearly increased with age and diabetics fared worse in all age groups (Fig. 2). Moreover, the 30-day mortality was higher in women compared to men (14.5 vs 7.1%, $p < 0.0001$) and the higher risk among women persisted after adjusting for diabetic status according to the Cochran-Mantel-Haenszel evaluation (Fig. 3).

Since diabetics were more likely to have had a prior myocardial infarction, we performed survival analyses stratified according to prior AMI and reported diabetes status. The 30-day mortality rates in diabetic patients were 24.1% for those with and 12.2% for those without a prior AMI, respectively. For non-diabetic patients, the corresponding figures were 7.0 and 7.8% as well (log-rank test for global comparisons, $p < 0.0001$). Therefore, a history of diabetes was associated with increased mortality both in patients with and without a previous AMI; in the former case the short-term prognosis was ominous.

In addition, survival analyses stratified according to reperfusion treatment and diabetes in patients with STEMI demonstrated that mortality rates were higher in patients not treated with reperfusion, whether or not they were diabetics (Fig. 4). However, in the former case the short-term prognosis was severe.

Interestingly, short-term survival in diabetic patients was not influenced by the antidiabetic therapy (insulin or oral antidiabetic agents) used both during hospitalization or at discharge.

Independent predictors of short-term prognosis. Diabetic status did not result as an independent predictor of 30-day mortality. The variables independently associated with 30-day mortality were age > 75 years, sys-

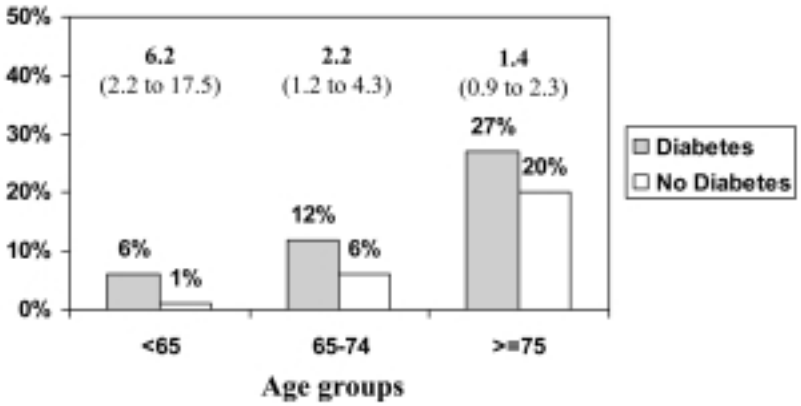

Figure 2. *Thirty-day cumulative mortality in three different age groups. Values above bars are odds ratios and 95% confidence intervals. Diabetic patients demonstrate a higher mortality in all age groups.*

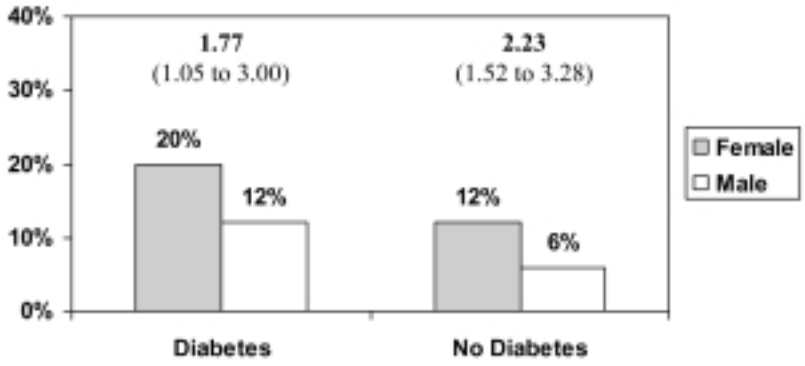

Figure 3. *Thirty-day cumulative mortality in the study population stratified for gender and diabetes status. Values above bars are odds ratios and 95% confidence intervals.*

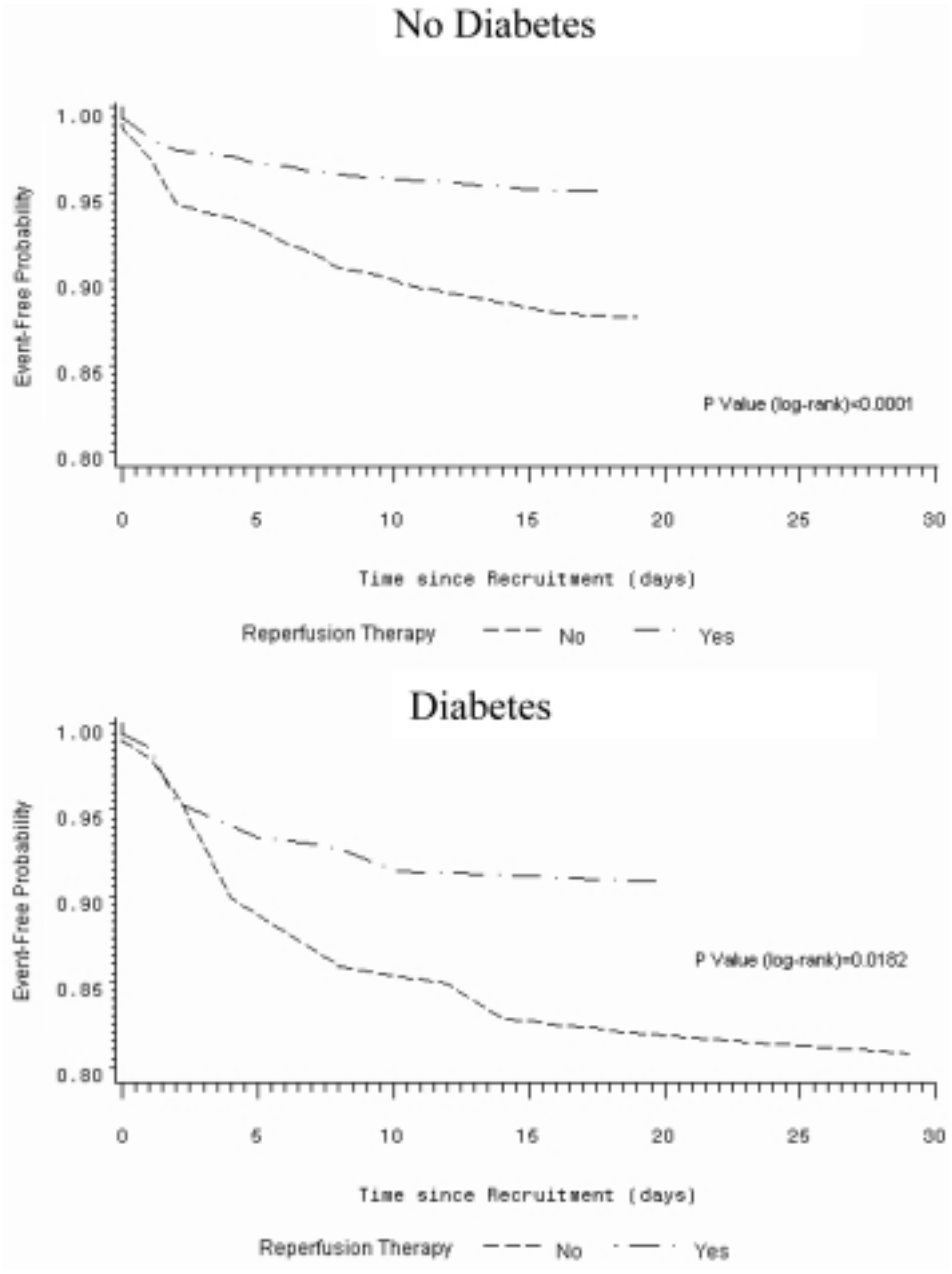

Figure 4. *Kaplan-Meier estimates of short-term survival after acute myocardial infarction according to reperfusion therapy and diabetes in the 1275 patients with ST-elevation myocardial infarction. Mortality rates were higher in patients not treated with reperfusion, whether* (lower panel) *or not* (upper panel) *they were diabetics. However, in the former case the short-term prognosis was more severe.*

tolic blood pressure ≤ 90 mmHg, heart rate > 100 b/min, Killip class III-IV on admission, previous history of heart failure, stroke, peripheral vascular disease (Table VII). The results were not substantially different when patients with or without previous AMI were compared.

Discussion

The present study confirms that a clinical diagnosis of diabetes is common across the whole spectrum of AMI, and shows a higher prevalence among women. However, although in the present survey the diabetic status was associated with a worse outcome in all age groups, it had no independent predictive value after correction for other powerful variables derived from the medical history and clinical presentation, most of which may be considered as the cardiovascular correlates of diabetes itself.

Unfavorable short-term prognosis of diabetes following acute myocardial infarction. Diabetes is a well documented risk factor for coronary artery disease and its prevalence is expected to double by the year 2025 as the population ages and becomes more sedentary and obese[19]. Among consecutive patients admitted to CCUs for AMI, the diabetes prevalence of 22%, observed in our study, compares well with those reported in other registries[13,20,21], although some randomized trials reported lower rates[22,23]. Several studies have shown increased short- and long-term morbidity and mortality after an AMI[1-3] in diabetic patients. In the GISSI-2 study, the in-hospital mortality was 7.2% among patients without diabetes and 12.4% among those with diabetes[24]. In a pooled analysis of several large fibrinolytic trials, the 30-day mortality was 1.7 times higher among diabetics compared to non-diabetics[25]. However, in other studies[2,13] as well as in the present one, diabetes was not found to be an independent predictor of increased in-hospital mortality in AMI. According to our data, a partial explanation for such a discrepancy could be identified in the higher prevalence of other important components of the coronary dysmetabolic syndrome (hypertension, obesity and hyperlipidemia), a more extensive and long-lasting coronary artery disease, older age, and higher prevalence of female gender among diabetics[26]. In addition, myocardial dysfunction, as shown by the higher prevalence of clinical signs of heart failure and cardiogenic shock, may contribute to a higher mortality in diabetics[4,5,25]. Therefore, the worse outcome of diabetic patients after AMI could be explained by the higher prevalence of several risk factors and clinical features that are strongly correlated with or even belong to the diabetic status itself. We refer to markers of diffuse atherosclerosis, endothelial dysfunction, hypertension, renal insufficiency and dyslipidemia[27]. On the other hand, a recent retrospective analysis of the FRISC II database[5] revealed that diabetes is an independent predictor of outcome even after adjustment for all baseline differences including the extent of coronary artery disease, myocardial damage and revascularization. Such a finding, derived from a study population of NSTEMI acute coronary syndromes would suggest that the diabetic status by itself is important for the final outcome and call for more aggressive diabetic-specific treatments as well[9]. In fact, different metabolic dysfunctions have been advocated for the increased number of adverse outcomes in diabetics. These mechanisms include an abnormal metabolic response to ischemia with inefficient energy use and accumulation of deleterious oxygen-free radicals, greater endothelial dysfunction, and abnormalities of thrombosis and fibrinolysis as well.

Therefore, through a variety of direct and indirect pathophysiological mechanisms, patients with diabetes are associated with a substantially worse outcome after AMI. Such a finding is confirmed by the present study across all age groups, even in the current era of reperfusion.

Underutilization of evidence-based treatments in diabetics with acute myocardial infarction. Almost all large-scale trials in AMI, including those with thrombolytic agents, beta-blockers, ACE-inhibitors, statins and coronary interventions, demonstrated a

Table VII. Independent predictors of 30-day mortality by the Cox proportional hazards model.

	HR (95% CI)	χ^2	p
Age > 75 years	3.28 (2.29-4.68)	42.49	< 0.0001
Systolic blood pressure ≤ 90 mmHg on admission	2.96 (1.90-4.61)	22.91	< 0.0001
Previous heart failure	2.26 (1.47-3.46)	13.91	0.0002
Killip class III-IV on admission	2.03 (1.37-3.00)	12.40	0.0004
Peripheral vascular disease	1.85 (1.27-2.70)	10.11	0.0015
Elevated CPK/CK-MB (highest quartiles)	1.84 (1.21-2.80)	8.00	0.005
STEMI	1.79 (1.23-2.60)	9.27	0.0023
Previous stroke	1.68 (1.13-2.49)	6.59	0.01
Heart rate > 100 b/min on admission	1.49 (1.03-2.16)	4.43	0.03

Included parameters are ordered by their contribution to the model. CI = confidence interval; CK = creatine kinase; CPK = creatine phosphokinase; HR = hazard ratio; STEMI = ST-elevation myocardial infarction.

similar or even higher protective effect of each treatment in diabetic as compared to non-diabetic patients[25,28]. However, as confirmed by our study, some of these evidence-based therapies are often underused in diabetics[11,12]. The OASIS[14] and RIKS-HIA[20] registries evaluated patients with acute coronary syndromes or AMI. These studies clearly showed that, even in contemporary care, diabetics were less likely to receive reperfusion therapy, heparins, beta-blockers, statins and early revascularization than non-diabetic patients. In addition, other studies reported less favorable results of invasive procedures in diabetic patients with AMI and have speculated that this may be a reason for a worse prognosis[8,29]. Emerging data support exactly the contrary[25,30]. Notably, in our study, an underuse of reperfusion therapy as well as beta-blockers was observed in diabetics. On the other hand, diabetic patients had more preventive treatments before admission and received more often ACE-inhibitors either during hospitalization or at discharge. Therefore, whether underuse of some effective treatments may have contributed to a worse outcome or was at least partially counterbalanced by a higher use of other therapies cannot be clarified by our data.

Study limitations. This study represents a retrospective analysis of a prospective, nationwide survey reflecting contemporary care and outcome of AMI in the Italian CCU network[16], and may not apply to other AMI patients admitted to cardiology wards, or non-cardiology units. Furthermore, a possible limitation of our study could be inaccuracy of identification of diabetes. We relied on clinical diagnoses, made by the treating physicians, which might have misclassified patients with undiagnosed diabetes. Nevertheless, such misclassification is rather likely to have minimized any negative effect of diabetes, resulting in a rather conservative relative risk. Moreover, due to the time-dependent influence of diabetes on mortality following AMI[31], the follow-up period for this study was too short to address the issue of long-term outcome in such patients. In addition, because information on hypoglycemic agents or insulin treatment was not systematically available, the potential deleterious effects of sulphonylureas or the positive effects of intensive insulin treatment during the infarction could not be assessed. Lastly, but most relevant, it is extremely difficult to assess the independent prognostic significance of diabetes in AMI due to its tight relation with other significant variables. For example, it is hard to establish whether the development of acute heart failure after AMI is independent of or rather dependent on diabetic status. Consequently, although we adopted a well-established methodology for our multivariable analysis, it may have been difficult to separate the independent effects of variables that are closely correlated each other. In fact, the precision of the adjusted estimates of effect declines as the degree of correlation between the variables increases[32].

In conclusion, this study demonstrates that diabetes in patients with AMI is common in the real world and that patients with diabetes have a substantially worse outcome even in the current era of reperfusion. This negative outcome may depend directly on the diabetic status or, most probably, may be an indirect consequence of a worse coronary risk profile and clinical presentation of diabetic patients. However, this worse prognosis might be adversely affected by a lesser utilization of evidence-based treatments as well. Given these findings, diabetics should be always regarded and treated as very high-risk patients. In addition, more knowledge and education regarding specific care and treatment in this fast growing patient population is urgently needed.

Appendix

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