Reduced Cardio-Renal Function Accounts for Most of the In-Hospital Morbidity and Mortality Risk Among Patients With Type 2 Diabetes Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

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OBJECTIVE

ST-segment elevation myocardial infarction (STEMI) patients with type 2 diabetes mellitus (DM) have higher in-hospital mortality than those without. Since cardiac and renal functions are the main variables associated with outcome in STEMI, we hypothesized that this prognostic disparity may depend on a higher rate of cardiac and renal dysfunction in DM patients.

RESEARCH DESIGN AND METHODS

We retrospectively analyzed 5,152 STEMI patients treated with primary angioplasty. Left ventricular ejection fraction (LVEF) and estimated glomerular filtration rate (eGFR) were evaluated at hospital admission. The primary end point was in-hospital mortality. A composite of in-hospital mortality, cardiogenic shock, and acute kidney injury was the secondary end point.

RESULTS

There were 879 patients (17%) with DM. The incidence of LVEF ≤40% (30% vs. 22%), eGFR ≤60 mL/min/1.73 m^2 (27% vs. 18%), or both (12% vs. 6%) was higher ($P < 0.001$ for all comparisons) in DM patients. In-hospital mortality was higher in DM patients than in non-DM patients (6.1% vs. 3.5%; $P = 0.002$), with an unadjusted odds ratio (OR) of 1.81 (95% CI 1.31–2.49; $P < 0.001$). However, DM was no longer associated with an increased mortality risk after adjustment for cardiac and renal function (OR 1.03, 95% CI 0.68–1.56; $P = 0.89$). A similar behavior was observed for the secondary end point, with an unadjusted OR for DM of 1.52 (95% CI 1.25–1.85; $P < 0.001$) and an OR after adjustment for cardiac and renal function of 1.07 (95% CI 0.85–1.36; $P = 0.53$).

CONCLUSIONS

The study indicates that the increased in-hospital mortality and morbidity of DM patients with STEMI is mainly driven by their underlying cardio-renal dysfunction.

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The outcome of patients with ST-segment elevation myocardial infarction (STEMI) has significantly improved over the years with the introduction of primary percutaneous coronary intervention (pPCI) and evidence-based medical therapies (1,2). However, some STEMI patient subgroups still have a less favorable outcome (3). Notably, STEMI patients with type 2 diabetes mellitus (DM) are at higher risk of in-hospital morbidity and mortality than those without DM, irrespective of therapeutic strategies (4–9).

Excess mortality in DM patients was initially observed in several thrombolysis trials and registries (4,6). In the more recent pPCI era, a post hoc analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial also confirmed that patients with DM have a twofold higher 30-day mortality rate than those without DM (4.6% vs. 2.1%) (7). Consistently with previous reports, the increased mortality of DM patients in the HORIZONS-AMI did not relate to failed reperfusion or suboptimal medical therapy (8). The harmful effects of DM were further confirmed in a systematic review of 139 studies performed between 1970 and 2011 that enrolled myocardial infarction patients treated with different therapeutic strategies (9). They found that DM patients had a 66% higher early mortality than their counterparts without DM.

Several factors may explain the worse long-term outcome of STEMI patients with DM, including higher coronary atherosclerotic burden, more vulnerable plaques, and enhanced platelet reactivity (4,10,11). However, the mechanisms underlying their higher in-hospital mortality risk remain largely unclear. Since cardiac and renal dysfunctions are the main clinical variables associated with the in-hospital mortality of STEMI patients (12–14), we hypothesized that the prognostic gap still existing between patients with and without DM might be due to a higher rate of cardiac and renal impairment in patients with DM resulting in a reduced cardio-renal functional reserve.

Thus, the aim of the current study was to assess whether cardiac and renal function at hospital admission differs between DM and non-DM STEMI patients undergoing pPCI and to investigate whether this may affect in-hospital morbidity and mortality.

RESEARCH DESIGN AND METHODS

Study Population

The data analyzed in this retrospective study were obtained from consecutive STEMI patients who underwent pPCI at Centro Cardiologico Monzino in Milan, University of Milan, Italy, between 1 January 2005 and 1 August 2017, and at Policlinico San Matteo of Pavia, Italy, between 1 January 2005 and 25 September 2017. Patients underwent pPCI if they had typical chest pain initiated within 12 h (24 h for those with cardiogenic shock) and at least 1-mm ST-segment elevation in two or more contiguous leads or a new left bundle branch block. We excluded patients in chronic peritoneal or hemodialysis treatment and those experiencing STEMI during elective PCI (type 4a myocardial infarction). The Ethics Committee (no. R520-CCM549) approved the study as a retrospective cohort study.

Study Protocol

Demographic, clinical, biochemical, and echocardiographic data were obtained in all patients. An echocardiogram was performed in all patients within 24 h from hospital admission. Left ventricular ejection fraction (LVEF) was calculated by Simpson's rule (15), and left ventricular systolic dysfunction was defined as an LVEF of ≤40% (16,17). Serum creatinine concentration was measured by means of the Jaffe method at hospital admission (before pPCI) and every day for the following 72 h in all patients. The total coefficients of variation for serum creatinine determinations were no greater

Table 1—Baseline characteristics and in-hospital outcomes of the study patients according to the presence of DM

	DM		
Variable	No (n = 4,273)	Yes (n = 879)	P value
Age (year)	63 ± 13	67 ± 11	<0.001
Men	3,331 (78)	677 (77)	0.54
Body weight (kg)	76 ± 15	79 ± 16	<0.001
Hypertension	2,179 (51)	615 (70)	<0.001
Smoking	2,594 (61)	462 (53)	<0.001
Dyslipidemia	1,700 (40)	388 (44)	0.01
Anterior MI	2,041 (48)	376 (43)	0.007
Prior MI	540 (13)	216 (25)	<0.001
Prior CABG	113 (3)	56 (6)	<0.001
Index PCI vessel			<0.001
LAD	2051 (48%)	369 (42)	
RCA	1,410 (33)	343 (39)	
LCX	726 (17)	132 (15)	
Bypass graft	43 (1)	26 (3)	
LM	43 (1)	9 (1)	
LVEF (%)	47 ± 11	44 ± 11	<0.001
Serum creatinine (mg/dL)	1.03 ± 0.4	1.13 ± 0.6	<0.001
eGFR (mL/min/1.73 m^2)	81 ± 26	76 ± 29	<0.001
CK-MB peak (ng/mL)	148 (58–293)	140 (60–267)	0.27#
In-hospital outcomes			
Death	149 (3.5)	54 (6.1)	<0.001
Cardiogenic shock	355 (8)	91 (10)	0.01
AKI	256 (6)	88 (10)	<0.001
Combined end point*	542 (13)	159 (18)	<0.001
APE	358 (8)	118 (13)	<0.001
Atrial fibrillation	447 (10)	124 (14)	0.001
VT/VF	507 (12)	75 (8)	0.005
Blood transfusions	129 (3)	53 (6)	<0.001
CCU LOS (days)	4 (3–6)	4 (3–7)	0.04#

Data are presented as the mean ± SD, median (interquartile range), or as n (%). APE, acute pulmonary edema; CABG, coronary artery bypass graft surgery; CCU LOS, coronary care unit length of stay; CK-MB, creatine kinase-MB isoenzyme; LAD, left anterior descending, LCX, left circumflex; LM, left main; MI, myocardial infarction; RCA, right coronary artery; VT/VF, ventricular tachycardia/ventricular fibrillation. *Combined end point of death, cardiogenic shock, and AKI. #By Wilcoxon rank sum test.

than 3%. Estimated glomerular filtration rate (eGFR) was estimated by applying the abbreviated MDRD equation (18), and renal insufficiency at admission was defined as eGFR ≤60 mL/min/1.73 m^2 (16,17). A diagnosis of DM was made if this disease and/or antidiabetic treatment, including oral agents or insulin, were recorded in the medical history.

PCI Procedure

The pPCI was performed by 24-h on-call interventional teams according to standard clinical practice. Standard guide catheters (6F), guidewires, balloon catheters, and coronary stents were used via a radial or femoral approach. Pharmacology therapy and poststenting antithrombotic treatment were administered according to institutional protocols and guideline recommendations.

Study End Points

The primary study end point was in-hospital mortality. A composite of in-hospital mortality, cardiogenic shock, and acute kidney injury (AKI) was considered as a secondary end point. We used this combined end point because cardiogenic shock and AKI are the complications most closely associated with mortality in STEMI (19) and are the clinical manifestations of reduced cardiac and renal function, respectively. Cardiogenic shock was defined as prolonged hypotension (systolic blood pressure ≤85 mmHg) with evidence of decreased organ perfusion resulting from severe left ventricular dysfunction, right ventricular infarction, or mechanical complications of infarction requiring an intra-aortic balloon pump and/or inotropic agents. AKI was defined as an absolute ≥0.5 mg/dL increase in the serum creatinine concentration between baseline (hospital admission) and the first 72 h (20). Other in-hospital major adverse clinical events were also evaluated as secondary end points.

Statistical Analysis

A sample size of 5,000 patients was calculated under the following assumptions: 4% overall incidence of in-hospital mortality (21), 20% prevalence of DM patients (5), and an expected increased risk (odds ratio [OR]) of 1.6 in DM patients compared with non-DM patients (9). This sample size allowed 80% statistical power in assessing a significant difference (α error of 0.05) of in-hospital mortality between the two groups.

Continuous variables are presented as mean ± SD and were compared using the *t* test for independent samples. Nonnormally distributed variables are presented as median and interquartile ranges and were compared with the Wilcoxon rank sum test. Categorical data were compared using χ^2 test or the Fisher exact test, as appropriate. The correlation between LVEF and eGFR was determined using the Spearman test. The association between DM status and the study end points was assessed by logistic regression, using different models unadjusted and adjusted for *1*) baseline characteristics found to be associated with DM at univariate analysis ($P < 0.05$), *2*) LVEF alone, *3*) eGFR alone, and *4*) the combination of LVEF and eGFR. Results are presented as ORs with 95% CIs.

We also performed a subgroup analysis by DM status. In particular, we evaluated the association between LVEF ≤40% and/or eGFR ≤60 mL/min/1.73 m^2 and the study end points, and we calculated the interaction between DM status and cardio-renal dysfunction by logistic regression. Finally, the "attenuation effect," defined as the residual effect of DM on the study end points after adjustment for baseline characteristics, LVEF alone, eGFR alone, and for the combination of LVEF and eGFR, was computed as described by Kershaw et al. (22) as the logistic regression coefficient for DM in each incremental model divided by the coefficient in the unadjusted model, -1×100.

All tests were two-tailed, and $P < 0.05$ was required for statistical significance. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

The study included 5,152 STEMI patients (4,008 men) who underwent pPCI (mean age 63 ± 12 years) and 879 patients (17%) with DM. The baseline clinical characteristics and in-hospital outcomes of patients with and without DM are reported in Table 1. As expected, patients with DM were older and more likely to have comorbidities and prior cardiovascular events than those without DM. The infarct size, estimated by the creatine kinase-MB isoenzyme peak value, was similar in the two patient groups. Patients with DM had a more complicated in-hospital clinical course and a longer hospital stay. In-hospital mortality in the overall population was 3.9% (*n* = 203) and was significantly higher in patients with DM. The incidence of the combined end point was also significantly higher in DM than in non-DM patients.

At hospital admission, the rate of cardiac dysfunction, renal insufficiency, or both, was significantly higher in

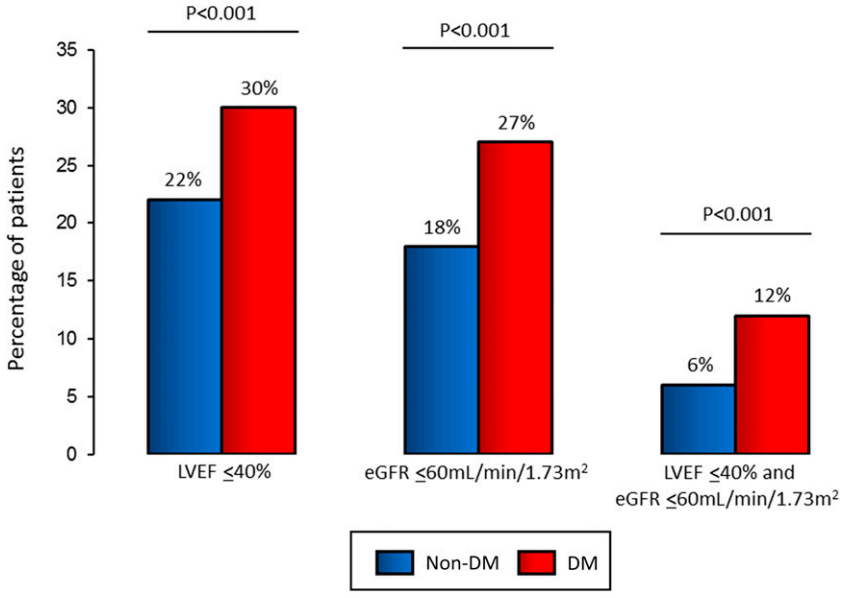

Figure 1—Percentage of patients with and without diabetes with STEMI presenting cardiac and/or renal dysfunction at hospital admission.

patients with DM than in those without DM (Fig. 1). Supplementary Table 1 reports the incidence of the study end points in patients with and without cardiac and/or renal dysfunction, according to DM status.

Figure 2*A* shows the unadjusted OR for in-hospital mortality of patients with DM and the OR adjusted for baseline clinical characteristics, LVEF, and/or eGFR. In particular, after adjustment for cardiac and renal function, DM was no longer an independent predictor of in-hospital mortality. The attenuation of the relation between DM and in-hospital mortality, resulting from the adjustment for baseline characteristics, LVEF, and/or eGFR, is depicted in Fig. 2*B*. Remarkably, after adjustment for both LVEF and eGFR, the residual effect of DM was as low as 5% of the unadjusted effect. A similar behavior was found when the combined clinical end point was considered: unadjusted OR, 1.52 (95% CI 1.25–1.85; $P < 0.001$); OR adjusted for baseline clinical characteristics, 1.33 (95% CI 1.08–1.66; $P = 0.009$); OR adjusted for LVEF alone, 1.23 (95% CI 0.99–1.54; $P = 0.06$); OR adjusted for eGFR alone, 1.25 (95% CI 1.02–1.53; $P = 0.03$); and OR adjusted for LVEF and eGFR, 1.07 (95% CI 0.85–1.36; $P = 0.53$). At attenuation analysis, only 17% of the effect of DM was maintained for the combined end point after adjustment for LVEF and eGFR.

A significant relationship between LVEF and eGFR was observed in both DM ($R = 0.17$; $P < 0.0001$) and non-DM ($R = 0.11$; $P < 0.0001$) patients.

Figure 3 shows the ORs for in-hospital mortality and the combined clinical end point of reduced LVEF and/or eGFR in patients with and without DM. The risk was similar for the two end points in all considered subgroups, and no interaction was observed between DM status and cardio-renal function.

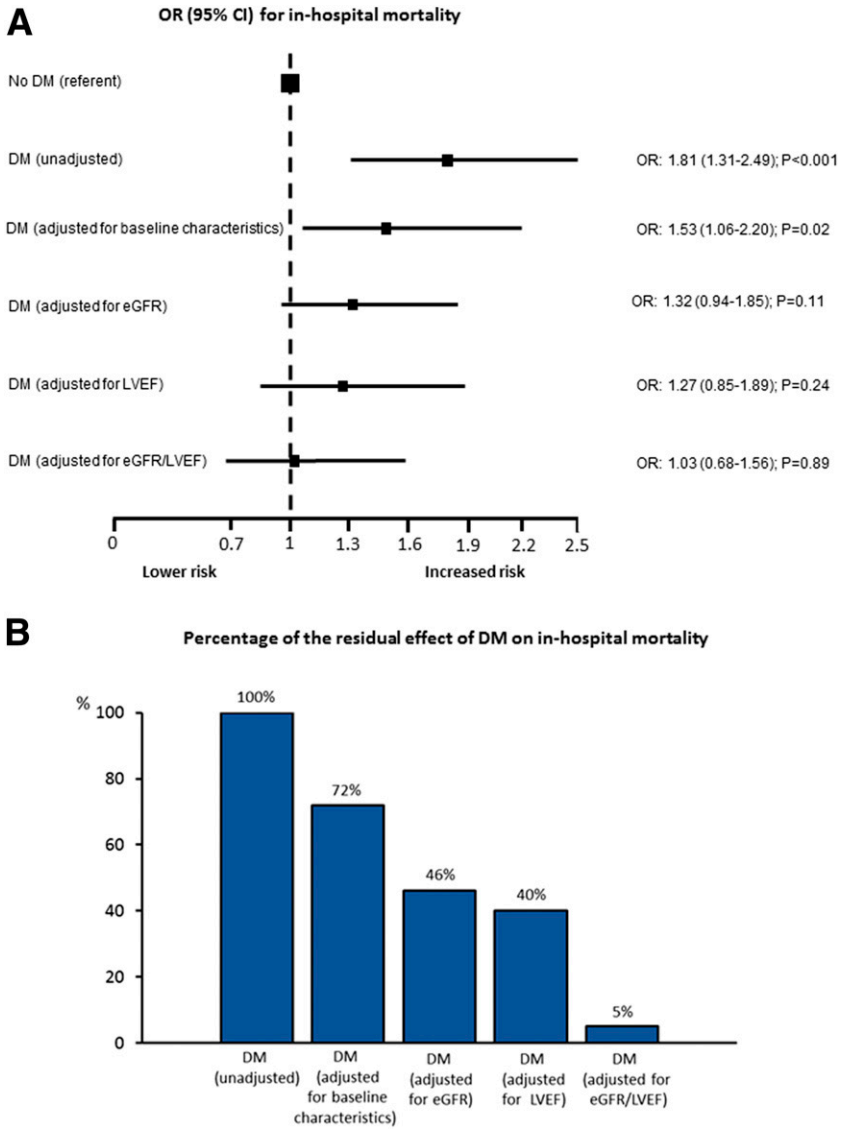

Figure 2—*A*: Unadjusted and adjusted ORs and 95% CIs for the primary end point (in-hospital mortality) of DM. *B*: Residual effect (%) of DM on in-hospital mortality. ORs were adjusted for baseline clinical characteristics (age, body weight, hypertension, smoking, dyslipidemia, myocardial infarction location, prior myocardial infarction, prior coronary artery bypass, and coronary culprit vessel), for LVEF alone, eGFR alone, and for the combination of LVEF and eGFR.

CONCLUSIONS

The main finding of the current study is that the worse in-hospital morbidity and mortality of DM patients are mainly mediated by their greater degree of cardio-renal impairment. Indeed, the in-hospital prognostic power of DM status in STEMI patients undergoing pPCI loses significance after adjustment for cardiac and renal function.

Patients with DM presenting with STEMI have a substantially greater incidence of early and late death than those without DM, despite similar therapeutic strategies (6,23–25). In the thrombolytic era, a subgroup analysis of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trial demonstrated significantly higher 30-day mortality in STEMI patients with DM compared with that of non-DM patients (10% vs. 6%) (6). More recently, the Global Registry of Acute Coronary Events (GRACE) showed that the in-hospital death incidence of patients with DM and STEMI was almost twice as high as that observed in patients without DM (26). Furthermore, among 93,569 STEMI patients from the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network-Get with the Guidelines (ACTION Registry-GWTG), 80% of whom underwent pPCI, there was an increased risk of in-hospital mortality associated with DM, even after multivariable adjustment (5). Although most studies suggest a significant unfavorable role of DM in the in-hospital outcome of STEMI patients (4–9), few studies failed to find an independent association between DM and short-term outcome (27). The reasons for these controversial

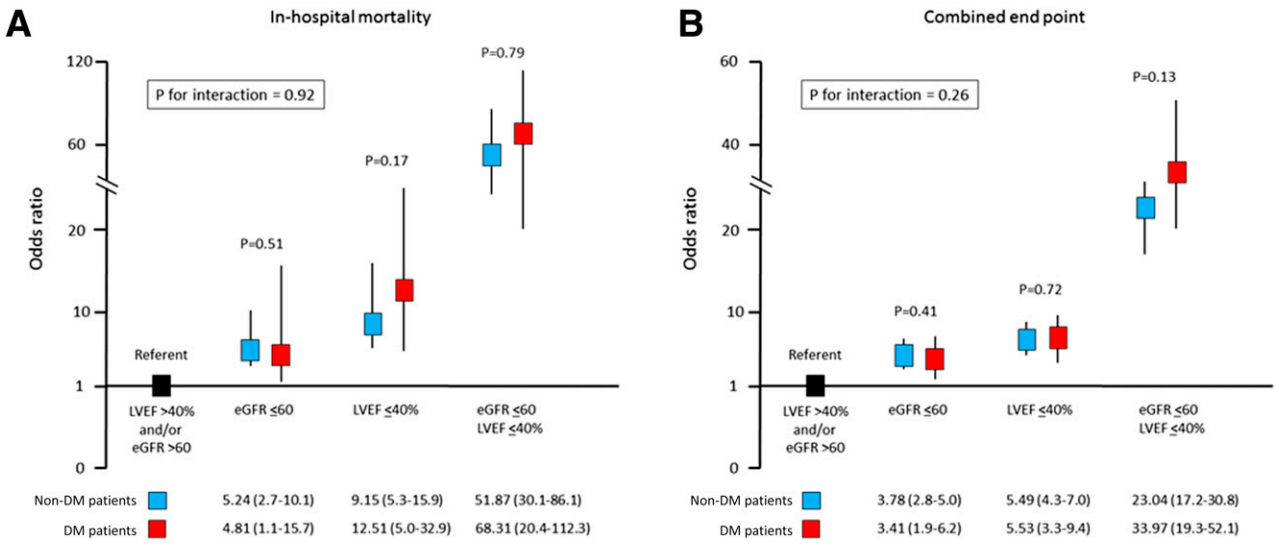

Figure 3—*A*: ORs and 95% CIs for in-hospital mortality, grouped according to cardiac and/or renal dysfunction in patients with and without DM. *B*: ORs and 95% CIs for the combined clinical end point (composite of in-hospital mortality, cardiogenic shock, and AKI), grouped according to cardiac and/or renal dysfunction in patients with and without DM.

findings are unclear, and the true impact of DM on in-hospital mortality during STEMI remains to be established.

In our study, we evaluated the independent effect of DM on in-hospital mortality in a large cohort of consecutive STEMI patients treated with pPCI at two Italian tertiary care centers. The prevalence of DM in our study was ~20%, which is comparable with previously reported rates (5,25). Moreover, and similar to previous studies, we found that DM patients were older and had more cardiovascular risk factors (4,25,26). Our analysis also confirmed that DM is more likely associated with cardiac and/or renal dysfunction (4,25,26). As a result, the rate of in-hospital complications, including mortality, was higher than that of patients without DM. However, the prognostic power of DM was no longer confirmed after adjustment for cardiac and renal function. This finding is not surprising, since cardiac and renal functions are the two most important predictors of in-hospital outcomes in STEMI (16,17,20). To the best of our knowledge, this is the first study that specifically investigated the impact of LVEF and eGFR when assessing the prognostic implications of DM in STEMI. Notably, the evaluation of cardiac function at hospital admission, usually by means of LVEF assessment, incorporates several types of clinical information, including preexisting cardiac dysfunction, extent of the ongoing ischemic process, and the related hemodynamic effects. Similarly, the evaluation of renal function by eGFR provides acute (hemodynamic impairment) and chronic (underlying comorbidities) information. Thus, our data further support the well-known unfavorable effect associated with DM in the early phase of STEMI and demonstrate that the worse outcome observed in DM patients may in large part be explained by cardiac and renal dysfunction.

Our data do not allow clarifying whether and to what extent the lower LVEF and eGFR observed in DM patients at hospital admission are due to a preexisting dysfunction or whether they are the acute consequences of a more severe STEMI. However, the risk associated with DM remained higher even after adjustment for more relevant comorbidities, in particular age, hypertension, and prior cardiovascular events, that may all chronically impair cardiac and renal function. Moreover, the infarct size estimated by the enzymatic peak value was similar in both groups. Taken together, these findings seem indicative of an acute impairment of heart and kidney, likely facilitated by their greater vulnerability in DM patients during a critical cardiac event. This is further supported by the correlation found between LVEF and eGFR that may reflect a concomitant DM-related frailty of the two organs. However, further studies are needed to confirm this cardio-renal hypothesis and to investigate the underlying pathophysiological mechanisms.

Our study may have some potential clinical implications. All STEMI patients, and particularly those with DM, should undergo early LVEF and eGFR assessment to identify high-risk patients. Moreover, a reduction of risk in STEMI patients with DM may be achieved not only by good glycemic control but also through cardio- and renal-protective therapies. For example, glucagon-like peptide 1 receptor agonists improved glycemic control and myocardial function after myocardial infarction (28). More recently, sodium–glucose cotransporter 2 inhibitors, which promote urinary glucose excretion and improve glycemic status without inducing hypoglycemia, were shown to provide cardiovascular protection and to prevent kidney function deterioration (29). Whether these effects might be of benefit also during the acute phase of STEMI needs to be investigated in DM patients (30).

The strengths of our study include a large and well-characterized population, adjustment for several risk factors, prospective assessment of cardiac and renal function in all patients, and a special focus on in-hospital mortality. However, some limitations need to be mentioned. Firstly, because we used data from a prospectively collected database, our results should be considered exploratory and hypothesis generating only. Secondly, all STEMI patients underwent

pPCI. Thus, this may have influenced the study results, and the overall applicability to all acute myocardial infarction patients needs to be clarified. Thirdly, the impact on outcomes of in-hospital and prior glycemic control, DM duration, unknown DM, stress hyperglycemia, and chronic antidiabetic medications was not investigated, and this should be taken into account as a possible bias. Fourthly, although the LVEF is easily detectable and strongly associated with prognosis in STEMI, we cannot exclude that other parameters may better reflect cardiac function. In particular, the possible presence of diastolic dysfunction, more likely in patients with DM, of acute mitral valve regurgitation and/or left ventricular compensatory hyperkinesia may have influenced the LVEF value in our study. Finally, clinical events were assessed during hospital stay only, not allowing any inference from our data on long-term outcomes.

In conclusion, the higher in-hospital morbidity and mortality rate of STEMI patients with DM is mainly driven by their more frequent cardio-renal dysfunction. Whether the disparity in mortality between DM and non-DM patients with STEMI may be reduced by therapeutic strategies that combine acute glycemic control with cardio- and renal-protective effects should be the focus of future investigations.

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