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An Early Revascularization Strategy Is Associated with a Survival Benefit for Diabetic Patients in Cardiogenic Shock after Acute Myocardial Infarction

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Summary

Background: The role of diabetes mellitus (DM) in cardiogenic shock (CS) complicating an acute myocardial infarction (AMI) is not well understood. Previous studies have reported an in-hospital mortality rate for patients with DM and CS of about 60%.

Objectives: This study compares the 1-year mortality rates of patients with DM and those without (NDM) and evaluates early revascularization (ERV) compared with initial medical stabilization (IMS) in patients with DM and CS.

Methods: Baseline characteristics, clinical and hemodynamic measures, and management were compared for 90 patients (31%) with DM and 198 with NDM (69%) who were randomized to ERV or IMS in the SHOCK Trial.

Results: When compared with NDM, patients with DM were of similar age but had higher rates of prior MI (44.4 vs. 27.8%, p = 0.007) and hypertension (56.2 vs. 42.5%, p = 0.04). The DM group had a lower rate of fibrinolytic therapy (44.4 vs. 60.1%, p = 0.02). In patients randomized to ERV, patients with DM had a higher rate of coronary artery bypass grafting (CABG) (50.0 vs. 30.9%, p = 0.03) despite similar rates of triple-vessel disease. The 1-year mortality rates in both groups were equivalent (58.9%). One-year mortality was not associated with diabetes (hazard ratio [HR] 1.02, 95% CI, 0.73–1.42, p = 0.91). The benefit of an ERV strategy was similar (HR [DM] 0.62; HR [NDM] 0.75, p = 0.58). Even after adjusting for the imbalance in CABG rates, 1-year mortality was not associated with DM.

Conclusion: Diabetes mellitus is not a predictor of 1-year mortality in CS after AMI. The benefit from an ERV strategy is similar for DM and NDM. The management strategies and influence of DM on mortality in CS deserve further evaluation.

Key words: cardiogenic shock, acute myocardial infarction, outcomes, diabetes, mortality

Introduction

The role of diabetes mellitus (DM) in cardiogenic shock (CS) complicating acute myocardial infarction (MI) is not well understood. Impaired fasting glucose has been shown to be an independent predictor for developing CS after acute MI.[1] Data from the National Registry of Myocardial Infarction suggest that the incidence of CS after acute MI is stable despite higher utilization of primary percutaneous coronary interventions (PCI).[2] Patients with diabetes and CS have a higher mortality compared with patients without diabetes (NDM), with an in-hospital mortality rate of > 60% in previous reports.[3, 4] Significant differences between analyses of trial and registry data have emerged after the Bypass Angioplasty Revascularization Investigation (BARI) program and underscore the challenges in generalizing findings from clinical trials into real world practice.

In the large trials of reperfusion therapy in acute MI, patients with DM have experienced relative risk reductions in mortality similar to those of NDM patients. In fact, the absolute risk reductions for thrombolytic therapy and PCI are high-

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er in the diabetic subgroup.[5] We analyzed patients enrolled in the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) trial to determine the impact of an early revascularization strategy (ERV) compared with initial medical stabilization (IMS) on outcomes for patients with DM and CS complicating an acute MI and to evaluate the relative efficacy of PCI versus coronary artery bypass graft (CABG) among those treated aggressively.

Methods

The design of the SHOCK trial has been reported previously.[6] Patients were enrolled at 30 sites from April 1993 to November 1998. In the trial, 302 patients post MI with CS were randomly assigned to either a strategy of ERV or IMS. All patients were recommended to have intra-aortic balloon counterpulsation (IABC). In the ERV group, PCI or CABG surgery had to be performed as soon as possible and within 6 h of randomization (within 18 h of MI onset). In the IMS group, the use of fibrinolytic therapy was permitted in patients without an absolute contraindication in addition to the usual medical care, and delayed revascularization was permitted at a minimum of 54 h after randomization. In SHOCK overall, six patients in the IMS group (2.7%) violated protocol and crossed over to revascularization within 54 h. Delayed revascularization was attempted in 32 medical patients (21%) at a median of 103 h after randomization. In the ERV group, 20 patients had no revascularization and an additional 10 patients had no early revascularization.

Patients were eligible for the SHOCK trial if they had electrocardiographic evidence for acute MI including at least one of the following: ST-segment elevation, new Q waves, posterior infarction with anterior ST-segment depression, or new left bundle-branch block. The diagnosis of cardiogenic shock was based on a combination of clinical evidence of end-organ hypoperfusion with strict hemodynamic criteria consisting of a systolic hypotension (blood pressure < 90 mmHg or the requirement of supportive measures to maintain systolic blood pressure ≥ 90 mmHg), pulmonary capillary wedge pressure ≥ 15 mmHg, and a cardiac index of ≤ 2.2l/min/m^2. Major exclusion criteria included severe systemic illness, predominantly non-left ventricular (LV) failure causes of CS, and unsuitability for revascularization.

Patients were classified as having diabetes at enrollment using a case report form completed by local coordinators by abstracting data from patient records. The types of antidiabetic medications on entry and during hospitalization as well as measurements of hemoglobin A1C levels were not recorded.

All baseline coronary angiograms and two-dimensional echocardiograms were interpreted by the Angiographic and Echocardiographic Core Laboratories using prespecified methods and definitions.[7] All core laboratory staff were blinded to the patients' clinical details and randomization assignments in the SHOCK trial.

Vital status at both 30 days and 1 year were determined using telephone contact with patients discharged alive.

Statistical Analysis

The primary outcome measure for this analysis was 1-year mortality; the secondary endpoint was 30-day mortality. Descriptive statistics are presented as means ± standard deviation (median and quartiles for skewed variables) for continuous data, or as percentages for categorical data. P values < 0.05 were considered statistically significant. Differences in DM and NDM in baseline patient and hemodynamic characteristics were compared using Student's *t*-test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables, and Fisher's exact test for categorical variables. Thirty-day mortality was analyzed by logistic regression and Kaplan-Meier curves were generated to demonstrate the survival differences. Cox proportional hazards regression was also used to analyze 1-year survival. Analyses were conducted with the Statistical Analysis System (SAS, Inc., Cary, N.C., USA, version 9.1) and S-Plus (Insightful Corporation, Seattle, Wash., USA, version 6.0.3) software.

Results

Of the 302 patients randomized in the SHOCK trial, complete data on diabetes status were ascertained in 288 (95%). Left ventricular failure was the predominant etiology for CS. Ninety patients (31%) were classified as having diabetes (Fig. 1). Of the 85 patients with diabetic treatment status known, 77% (n = 66 ps) were treated with oral hypoglycemics and/or insulin.

The baseline characteristics and important clinical presentation findings of the cohort divided into patients with and without diabetes are shown in Table I. In general, patients with DM and NDM were similar with regard to age, gender, history of prior revascularization, and history of congestive heart failure (CHF). Patients with DM were less likely to be Caucasian (62.2 vs. 80.8%, p = 0.01), and had a higher rate of hypertension (56.2 vs. 42.5%, p = 0.04), peripheral vascular disease (24.1 vs. 11.4%, p = 0.03), and prior MI (44.4 vs. 27.8%, p = 0.007).

There were no significant differences in MI location, lowest systolic blood pressure, LV ejection fraction, and cardiac index between the patients with DM and NDM. Similar rates of coronary angiography were observed in the DM and NDM groups (83.3 vs. 81.3%, p = 0.743). Diabetes was not associated with the presence of triple-vessel disease. However, patients with DM were more likely to have more severe coronary disease when the proportion of patients with multiple non-infarct-related arteries with > 90% stenoses was considered (p = 0.029).

Similarly, Table II demonstrates the in-hospital management of CS for patients with DM and NDM. Although the two groups were equally likely to be randomized to an ERV strategy, the patients with DM were more likely to undergo CABG surgery as their mode of early revascularization (50.0 vs. 30.9%, p = 0.030). Fibrinolytic therapy was less likely in

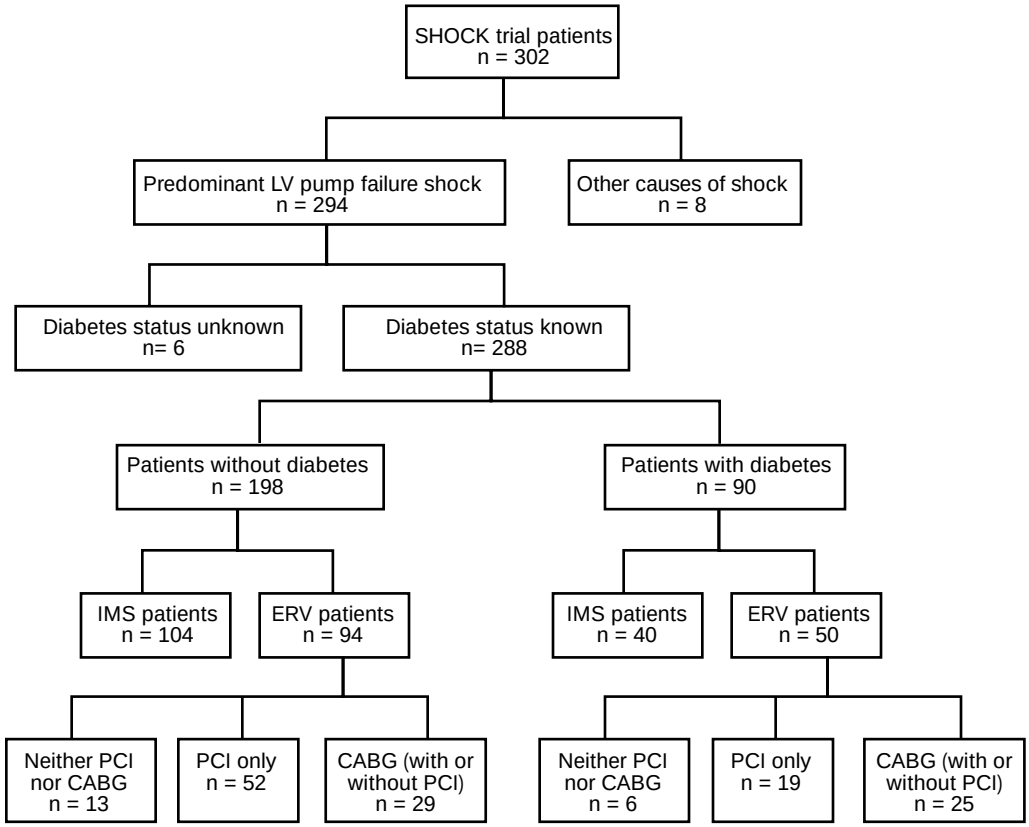

FIG. 1 Flowchart of patient sample. LV = left ventricular, IMS = initial medical stabilization, ERV = early revascularization, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

patients with DM (44.4 vs. 60.1%, p = 0.015), despite similar proportions of patients with DM and NDM being assigned to ERV.

As shown in Table III and Figure 2, the 1-year mortality rate was not higher for the patients with DM (58.8 vs. 58.9%, p = 1.000). After adjusting for age, gender, and LV function, diabetes was not an independent predictor of 30-day mortality. The association between DM and 30-day mortality was also examined within subgroups defined by CABG and fibrinolytic therapy (Table IV). There was no significant difference in mortality between patients with DM and NDM within any subgroup. This remained unchanged when adjusted for a history of hypertension.

When the 44 patients with DM randomized to the ERV strategy were analyzed according to their modes of revascularization (Table V), patients treated with PCI alone versus CABG with or without PCI were similar with regard to baseline characteristics, clinical presentation, and in-hospital treatment.[8] Of the 25 patients undergoing CABG, 2 had both PCI and CABG. Most important, the 30-day and 1-year mortality rates were not significantly different between the PCI and CABG ERV-treated groups; however, there was a trend toward better survival for patients treated with ERV-PCI, followed by treatment with ERV-CABG and then followed by IMS (Table VI).

Using Cox proportional hazards regression in Table VII, DM was not associated with excess risk of 1-year mortality (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.73–1.42; p = 0.91). The magnitude of the benefit of an ERV strategy was similar (p = 0.58) in the DM and NDM groups (HR [DM] 0.62, 95% CI, 0.36–1.08; HR [NDM] 0.75, 95% CI, 0.52–1.09).

Discussion

Although patients with DM are at an increased risk of developing CS complicating acute MI, they did not appear in the SHOCK trial to have excess mortality once shock develops.[3] The benefits of an ERV-based strategy in the diabetic subgroup of the SHOCK trial at 30 days and 1 year are comparable with those experienced by the overall population.[8] In general, patients with DM are similar to patients with NDM and CS with regard to baseline characteristics and clinical presentation. In the SHOCK trial, patients with DM and CS were more likely to have prior MI and hypertension and less likely to be Caucasian.

The rate of fibrinolytic therapy use in acute MI complicated by CS has previously been shown to be lower in patients with DM even though they have the potential to experience a

TABLE I Clinical characteristics of patients with and without diabetes (n = 288) with cardiogenic shock due to predominantly left ventricular failure

	Without diabetes n = 198	With diabetes n = 90	p Value
Age (years)	65.8 ± 11.1	65.7 ± 9.1	0.901
Female gender (%)	28.8	37.8	0.135
Race white non-Hispanic (%)	80.8	62.2	0.001
Anterior index myocardial infarction (%)	58.3	65.2	0.230
Prior myocardial infarction (%)	27.8	44.4	0.007
Prior coronary bypass surgery (%)	6.6	5.6	1
Prior percutaneous coronary intervention (%)	7.6	8.0	1
History of congestive heart failure (%)	5.1	6.7	0.585
History of hypertension (%)	42.5	56.2	0.04
History of cigarette smoking (%)	57.5	45.2	0.095
Elevated lipids (n = 146) (%)	34.3	47.7	0.141
Peripheral vascular disease (n = 198) (%)	11.4	24.1	0.03
≥ 2 ECG leads with ST elevation (%)	91.9	92.2	1
New Q waves in ≥ 2 leads (%)	43.9	56.7	0.056
New LBBB (%)	9.6	12.4	0.533
Median highest total creatine kinase (Q_1, Q_3)	3832 (1621, 6331)	2142 (951, 4461)	0.977
Median time from myocardial infarction to shock (h) (Q_1, Q_3)	5.6 (2.3, 14.0)	6.2 (2.5, 15.5)	0.71
Lowest systolic blood pressure (mmHg) (n = 206) [a]	68.7 ± 12.1	66.1 ± 14.8	0.175
PCWP (mmHg) [a]	23.9 ± 7.3	25.5 ± 6.8	0.095
Cardiac index (l/min/m^2) [a]	1.8 ± 0.7	1.8 ± 0.4	0.676
CPi (watts/m^2) (n = 241) [a]	0.3 ± 0.01	0.3 ± 0.1	0.999
LV ejection fraction (%) (n = 164)	30.8 ± 11.8	29.1 ± 12.1	0.832
Median creatinine clearance (ml/min) (Q_1, Q_3) (n = 238)	55.8 (39.7, 79.8)	55.0 (37.3, 75.7)	0.527
Creatinine clearance < 60 ml/min (%) (n = 238)	53.6	55.6	0.889
Triple-vessel disease (%) (n = 228)	61.5	73.6	0.100
Severe disease: Non-infarct-related arteries with >90% occlusion and infarct artery (%)			
1	72.7	58.9	0.029
2	18.7	27.8	
3	8.6	13.3	0.029

Values in parentheses indicate the interquartile range.

[a] Obtained while on support measures.

Abbreviations: ECG = electrocardiogram, LBBB = left bundle-branch block, PCWP = pulmonary capillary wedge pressure, CPi = cardiac power index, LV = left ventricular.

TABLE II In-hospital treatments of patients with and without diabetes (n = 288)

	Without diabetes n = 198	With diabetes n = 90	p Value
Pulmonary artery catheterization (%)	97.5	88.9	0.007
Fibrinolytic therapy (%)	60.1	44.4	0.015
Intra-aortic balloon pump (%)	84.9	90.0	0.270
Coronary angiography (%)	81.3	83.3	0.743
PCI (no coronary bypass) (%)	33.8	26.7	0.274
Coronary bypass (with or without PCI) (%)	21.7	30.0	0.140
Revascularization (PCI or coronary bypass) (%)	55.6	56.7	0.899
Randomization to ERV (%)	47.5	55.6	0.253
Type of revascularization for ERV patients (n = 144)			
PCI (no coronary bypass) (%)	55.3	38.0	0.055
Coronary bypass with or without PCI (%)	30.9	50.0	0.030
No revascularization (nonsignificant disease or death prior to revascularization) (%)	13.8	12.0	1.000

Abbreviations: ERV = early revascularization, PCI = percutaneous coronary intervention.

TABLE III Mortality rates of patients with and without diabetes (n = 288)

	Without diabetes n = 198	With diabetes n = 90	p Value
30-Day mortality (%)	51	48.9	0.800
History of hypertension (n = 132)	50	50	1.000
No history of hypertension (n = 150)	50.5	48.7	1.000
1-Year mortality (%)	58.9	58.9	1.000
History of hypertension (n = 132)	59.3	60	1.000
No history of hypertension (n = 150)	57.7	56.4	1.000

Diabetes and hypertension interaction p = 0.9 for both time points.

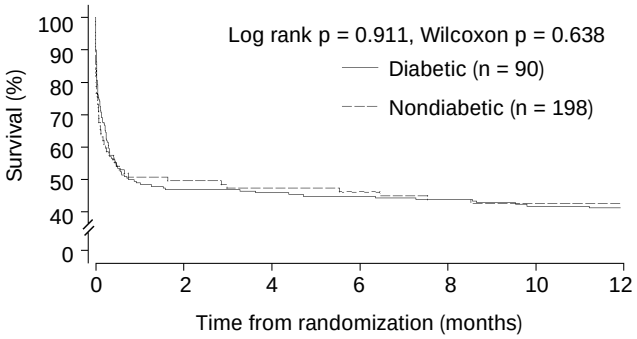

FIG. 2 One-year survival for diabetic and nondiabetic patients (n = 288).

greater absolute risk reduction.[4] Given the fact that trials powered to demonstrate differences in the diabetes population have not been conducted, it is possible that clinicians are hesitant to administer these types of therapies to patients at high risk. The results of our analysis suggest that a more aggressive approach to CS in patients with DM appears to be effective.

Numerous secondary analyses from large randomized trials have demonstrated that diabetes is consistently a strong predictor of short- and long-term mortality.[4, 9, 10] This has long been attributed to diabetes-related thrombosis and progression of underlying atherosclerotic heart disease.

For patients in CS, multiple registries have demonstrated higher mortality in those with diabetes. In the Olmsted County registry of 73 patients that included 16 patients with DM, diabetes conferred a three-fold increase in the risk of adjusted in-hospital mortality and a two-fold increase in the risk of 5-year mortality.[8] Diabetes was independently associated with hospital mortality. In the SHOCK Registry, which included patients with DM, diabetes was independently associated with in-hospital mortality with an adjusted odds ratio of 1.5.

There are several explanations for the lack of association of diabetes and mortality in CS between the SHOCK trial and previous studies. The use of cointerventions may account for much of this difference. The use of IABC therapy was protocol recommended and almost twice as likely in the diabetic group of the SHOCK trial (90%) as in the registries.[4, 8] The American College of Cardiology (ACC) and the American Heart Association (AHA) recommendations on the use of IABC in patients with shock refractory to pharmacologic therapy is based on small studies, observations from subgroup analyses of large randomized studies (GUSTO I /III), and community registries.[9, 11–14] Similarly, the rate of angiography in patients with DM was considerably higher (83.3%) in the SHOCK trial. In addition, overall rates of CABG surgery among patients with DM was twice as likely in the SHOCK trial as in the registries, with rates increased almost three fold in the subgroup randomized to an ERV strategy.[4, 8] Other therapies, such as the medical management of patients with diabetes, which were not record-

TABLE IV Logistic regression models for 30-day mortality (n = 288)

	p Value	Odds ratio	95% CI
Model 1 (n = 288)			
Interaction of diabetes and coronary bypass	0.562		
Coronary bypass: Diabetes vs. no diabetes		0.74	(0.28, 2.00)
No coronary bypass: Diabetes vs. no diabetes		1.04	(0.58, 1.88)
Model 2 (n = 288)			
Interaction of diabetes and fibrinolytic therapy	0.919		
Fibrinolytic therapy			
Diabetes vs. no diabetes		0.86	(0.42, 1.77)
No fibrinolytic therapy			
Diabetes vs. no diabetes		0.91	(0.45, 1.84)
Model 3 (n = 288)			
Interaction of diabetes and assignment to ERV	0.555		
Diabetes: ERV vs. IMS		0.73	(0.42, 1.27)
No diabetes: ERV vs. IMS		0.54	(0.23, 1.24)

Abbreviations: CI = confidence interval, ERV = early revascularization, IMS = initial medical stabilization.

TABLE V Characteristics of patients with diabetes randomized to early revascularization and treated with percutaneous coronary intervention or coronary bypass (n = 44)

	PCI only n = 19	CABG with or without PCI n = 25	p Value
Age (years)	64.9 ± 8.8	62.4 ± 9.8	0.399
Female (%)	36.8	28.0	0.745
White non-Hispanic (%)	57.9	60.0	1.000
Anterior index MI (%)	84.2	56.0	0.058
Prior MI (%)	42.1	40.0	1.000
History of hypertension (%)	57.9	70.8	0.521
PVD (%) (n = 32)	15.4	36.8	0.249
IABP (%)	89.5	100	0.181
Pulmonary artery catheterization (%)	89.5	92.0	1.000
Left main disease (%)	16.7	29.2	0.473
Triple-vessel disease (%)	72.2	80.0	0.717

Abbreviations: MI = myocardial infarction, PVD = peripheral vascular disease, IABP = intra-aortic balloon pump, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

TABLE VI Mortality rates of patients with diabetes randomized to early revascularization and treated with percutaneous coronary intervention or coronary bypass (n = 44)

	PCI only n = 19	CABG with or without PCI n = 25	p Value
30-Day mortality (%)	36.8	40.0	1.000
1-Year mortality (%)	47.4	52.0	1.000

TABLE VII Cox proportional hazards models for 1-year survival for patients with and without diabetes (n = 288)

	p Value	Hazard ratio	95% CI for the hazard ratio
Model 1 (n = 288)			
Diabetes	0.911	1.02	(0.73, 1.42)
Model 2 (n = 288)			
Interaction of Diabetes and assignment to ERV	0.578		
Diabetes: ERV vs. IMS		0.62	(0.36, 1.08)
No diabetes: ERV vs. IMS		0.75	(0.52, 1.09)

Abbreviations as in Table IV.

ed, may have been different in the SHOCK trial and may have played a role in the outcomes observed.

The observations from our analysis may be interpreted as evidence for treating the diabetic population with CS as aggressively as possible. The greater use of IABC and coronary angiography may be responsible for making up the differences with the NDM group. The other hypothesis is that once CS occurs after acute MI, DM no longer exerts an independent effect on short- and long-term mortality.

It is very interesting to explore the differences in outcomes between the diabetic subgroup in the SHOCK trial and Registry in which patients are enrolled in the same centers during the same time period. The patients with DM were much more likely to have a history of CHF in the registry (30 vs. 15%, $p < 0.001$) than the patients with NDM.[4] The SHOCK trial, however, excluded patients with a history of CHF due to cardiomyopathy. The length of follow-up in the SHOCK Registry was limited to an in-hospital period as opposed to the 1-year period in the trial.

In patients assigned to ERV in the SHOCK trial, there was no significant difference in survival at 1 year between those patients with DM who were selected to undergo PCI alone vs. CABG. Evidence from the large BARI trial had demonstrated a long-term superiority of CABG over PCI in patients with DM with multivessel disease who were not in cardiogenic shock, and one of our hypotheses was that this trend would also emerge in the SHOCK trial.[15] This analysis, however, is consistent with the BARI trial registry, in which the outcomes of patients with DM were not different between PCI and CABG when the decision as to how to revascularize was left to the discretion of the attending physician.[16]

Limitations of the Study

There are several limitations to the present analysis. Patients with DM enrolled in the SHOCK trial may not represent the overall DM population in CS after acute MI. Differences between the patients with DM in the SHOCK trial and in the Registry are not dramatic, but the possibility of selection bias was likely and should be acknowledged. The diagnosis of diabetes was based upon history and is likely underestimated. There are no data abstracted evaluating glycemic control and no documentation of antidiabetic therapy administered. Elevated plasma glucose levels in the intensive care unit setting

correlate highly with poor outcomes in patients with NDM and may, in part, explain our study findings. Plasma glucose levels were not collected during the SHOCK trial. In general, the odds ratio expressed in this analysis have wide CIs and should be interpreted with caution. A limitation of the PCI versus CABG comparison in patients with DM undergoing ERV is the small sample size (a total of 44 patients) and the influence of bias in how patients were selected for the type of revascularization procedure performed.

Recently, use of an insulin infusion has been shown to reduce mortality in the intensive care unit.[17] It is possible that the diabetic subgroup in the SHOCK trial was treated with more aggressive antidiabetic strategies than those observed in the nonrandomized studies. These analyses are underpowered despite the high event rate. Therefore, in our current analysis, we cannot exclude small mortality differences between the DM and NDM subgroups.

Conclusion

In the SHOCK trial, DM is not a predictor of 1-year mortality in CS after AMI. The magnitude of benefit from an ERV strategy at 30 days and 1 year is similar for DM and NDM. Newer treatment modalities, including the effect of intensive insulin to normalize elevated serum glucose associated with CS in both DM and NDM deserves further prospective evaluation.

Acknowledgments

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