Impact of Diabetes on Mortality in Patients With Myocardial Infarction and Left Ventricular Dysfunction

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Background: Diabetes is a major risk factor for developing coronary heart disease. In patients with diabetes who survived myocardial infarction (MI), less is known about subsequent morbidity and mortality. We evaluated the effects of diabetes in post-MI patients with left ventricular dysfunction on cardiovascular events and death.

Methods: The Survival and Ventricular Enlargement, a randomized, double-blind, placebo-controlled multicenter trial, evaluated the efficacy of captopril vs placebo in 2231 patients following acute MI with left ventricular dysfunction defined as an ejection fraction less than or equal to 40%. Patients were randomly assigned to captopril or placebo 3 to 16 days following MI and were followed up for 2 to 5 years (mean, 3.5 years).

Results: Among the 2231, 496 (22.2%) were patients with a history of diabetes, of which 168 (33.9%) were treated with insulin. Patients with diabetes were significantly older; more likely to be women; have a history of prior MI or hypertension; be obese or manifest Killip class II or greater; and have higher systolic blood pressure, pulse pressure, and heart rate, as well as lower ejection fraction. During follow-up, 31.3% of patients with diabetes and 20.1% of nondiabetic patients died ($P<.001$). Furthermore, 50% of the patients with diabetes had at least 1 major cardiovascular event compared with 32.3% among the nondiabetic patients ($P<.001$). In multivariate analysis that adjusted for all significant differences in baseline characteristics, patients with diabetes had a 39% higher total mortality ($P=.001$) and 49% more cardiovascular events ($P=.001$). Among the patients with diabetes, baseline insulin treatment was associated with a greater risk of death (41.1% vs 26.2%; $P=.001$) and cardiovascular events (58.3% vs 45.7%; $P=.008$).

Conclusions: In patients who survived MI with left ventricular dysfunction, diabetes increased risk of death from all causes even after controlling for differences in other risk factors. Patients with diabetes treated with insulin have a particularly higher mortality risk. Patients with diabetes who survived MI with left ventricular dysfunction, in particular those receiving insulin, are at high risk of subsequent mortality and cardiovascular events and thus require intensive risk factor modification, as well as evaluation for novel therapies.

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D I A B E T E S M E L L I T U S IS A MAJOR risk factor for cardiovascular disease in general and for coronary heart disease in particular. In the thrombotic era, descriptive and analytic epidemiologic studies, including randomized trials, demonstrate that in-hospital mortality remains 1.5 to 2 times higher among patients with diabetes. This may be due, at least in part, to their higher rates of reinfarction and congestive heart failure. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-1 Study, patients with diabetes who survived acute MI had a worse prognosis than nondiabetic patients at 1 year. In the Secondary Prevention Israeli Nifedipine Trial, patients with diabetes had a higher mortality rate in later years, which was pri-
SAVE was a randomized, double-blind, placebo-controlled, multicenter trial that tested whether angiotensin-converting enzyme inhibitor therapy with captopril decreases morbidity and mortality in survivors of acute MI. SAVE enrolled 2231 patients between January 27, 1987, and January 29, 1990. Patients were 21 to 80 years old and had a radio nuclide left ventricular ejection fraction (LVEF) less than or equal to 40% (mean, 31%). Symptomatic heart failure requiring angiotensin-converting-enzyme inhibitors was an exclusion criterion, as was clinically evident ischemia or a positive exercise test result after the presenting MI, unless addressed by a revascularization procedure. A patient was defined as having diabetes if a history of diabetes was present and/or insulin treatment was given within 24 hours of randomization. Randomization to captopril or placebo occurred 3 to 16 days after a documented acute MI. About 84% of patients presented with acute ST elevation MI with 55% involving the anterolateral wall, 17% involving the inferior wall, and 12% involving both the anterolateral and the inferior walls. Among the remaining 16%, 10% were non-Q wave MIs. About 35% of patients had a prior MI. Patients were treated and followed up for 2 to 5 years (mean of 3.5 years). Prospectively defined end points included all-cause mortality, cardiovascular mortality, and cardiovascular morbidity defined as the development of congestive heart failure (hospitalization for this condition or the administration of an open-label angiotensin-converting enzyme inhibitor), recurrent MI, and a composite end point of cardiovascular mortality and morbidity. All analyses of morbidity end points were time to first event. Further details of SAVE are reported elsewhere.29,30 Differences in baseline characteristics were assessed by χ² test for categorical variables and the t test for continuous variables. To determine whether diabetes in general and insulin treatment in particular were independent predictors of all-cause mortality and cardiovascular mortality and morbidity, Cox proportional-hazards ratio models were used to control for potential confounding variables as well as to test the effect of captopril in patients with or without diabetes. Survival curves were generated by the Kaplan-Meier method.32

### RESULTS

#### BASELINE CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETES

Of 2231 patients, 496 (22.2%) were reported as having diabetes. Among the patients with diabetes, 168 (33.9%) were receiving insulin at the time of randomization; were older and more likely to be women and obese; and had a higher prevalence of prior MI and hypertension. In addition, patients with diabetes were less likely to have received thrombolytic therapy as well as to have undergone cardiac catheterization or percutaneous transluminal angioplasty for their index MI (Table 1).

The peak serum creatine kinase measured at the time of MI was lower in patients with diabetes (1913 vs 2790

### METHODS

**SAVE** was a randomized, double-blind, placebo-controlled, multicenter trial that tested whether angiotensin-converting enzyme inhibitor therapy with captopril decreases morbidity and mortality in survivors of acute MI. SAVE enrolled 2231 patients between January 27, 1987, and January 29, 1990. Patients were 21 to 80 years old and had a radio nuclide left ventricular ejection fraction (LVEF) less than or equal to 40% (mean, 31%). Symptomatic heart failure requiring angiotensin-converting-enzyme inhibitors was an exclusion criterion, as was clinically evident ischemia or a positive exercise test result after the presenting MI, unless addressed by a revascularization procedure. A patient was defined as having diabetes if a history of diabetes was present and/or insulin treatment was given within 24 hours of randomization. Randomization to captopril or placebo occurred 3 to 16 days after a documented acute MI. About 84% of patients presented with acute ST elevation MI with 55% involving the anterolateral wall, 17% involving the inferior wall, and 12% involving both the anterolateral and the inferior walls. Among the remaining 16%, 10% were non-Q wave MIs. About 35% of patients had a prior MI. Patients were treated and followed up for 2 to 5 years (mean of 3.5 years). Prospectively defined end points included all-cause mortality, cardiovascular mortality, and cardiovascular morbidity defined as the development of congestive heart failure (hospitalization for this condition or the administration of an open-label angiotensin-converting enzyme inhibitor), recurrent MI, and a composite end point of cardiovascular mortality and morbidity. All analyses of morbidity end points were time to first event. Further details of SAVE are reported elsewhere.29,30 Differences in baseline characteristics were assessed by χ² test for categorical variables and the t test for continuous variables. To determine whether diabetes in general and insulin treatment in particular were independent predictors of all-cause mortality and cardiovascular mortality and morbidity, Cox proportional-hazards ratio models were used to control for potential confounding variables as well as to test the effect of captopril in patients with or without diabetes. Survival curves were generated by the Kaplan-Meier method.32

### Table 1. Baseline Characteristics in Diabetic and Nondiabetic Post-MI Patients With LV Dysfunction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Without Diabetes (n = 1735)</th>
<th>Patients With Diabetes (n = 496)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>58.7 ± 10.9</td>
<td>61.7 ± 9.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1471 (84.8)</td>
<td>370 (74.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>26.6 ± 4.6</td>
<td>27.9 ± 5.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obesity (BMI &gt;/= 30)</td>
<td>314 (18.3)</td>
<td>133 (27.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical history at presentation with MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>590 (34.0)</td>
<td>202 (40.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>651 (37.5)</td>
<td>279 (56.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>774 (41.8)</td>
<td>151 (30.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Events between MI and randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest serum creatine kinase, U/L</td>
<td>2790 ± 2472</td>
<td>1913 ± 1756</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class ≥ II</td>
<td>652 (37.6)</td>
<td>231 (40.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>623 (36.2)</td>
<td>108 (21.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>989 (57.2)</td>
<td>240 (48.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PTCA</td>
<td>321 (18.6)</td>
<td>58 (11.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>150 (8.7)</td>
<td>52 (10.5)</td>
<td>.011</td>
</tr>
<tr>
<td>ASA use</td>
<td>1052 (60.6)</td>
<td>256 (52.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blocker use</td>
<td>622 (35.9)</td>
<td>167 (33.7)</td>
<td>.071</td>
</tr>
<tr>
<td>Captopril assignment</td>
<td>880 (50.7)</td>
<td>235 (47.4)</td>
<td>.19</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31.2 ± 6.7</td>
<td>30.5 ± 6.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>111.2 ± 14.3</td>
<td>110.1 ± 16.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>69.9 ± 9.5</td>
<td>70.4 ± 9.4</td>
<td>.25</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77.2 ± 12.5</td>
<td>78.8 ± 12.7</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, aspirin; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); bpm, beats per minute; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction; PTCA, percutaneous transluminal angioplasty.

†Data are given as number (percentage) of patients or mean ± SD value unless otherwise specified.

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U/L; \( P < .001 \), yet their radionuclide LVEF was slightly but significantly lower (30.4 vs 31.2%; \( P = .03 \)). Patients with diabetes were also more likely to manifest Killip class II or higher prior to randomization.

**UNIVARIATE ANALYSES OF CLINICAL EVENTS**

After a mean follow-up of 3.5 years, patients with diabetes experienced a higher frequency of total and cardiovascular mortality as well as each of the prespecified major cardiovascular end points (recurrent MI and development of congestive heart failure) (**Table 2**). Indeed, 50% of the patients with diabetes experienced at least 1 major cardiovascular end point compared with 32.3% of nondiabetic patients (\( P < .001 \)).

**MULTIVARIATE ANALYSES OF CLINICAL EVENTS**

Cox multivariate models were constructed in an attempt to adjust for imbalances in baseline characteristics. Diabetes remained an independent predictor of all-cause mortality (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.14-1.68; \( P = .001 \)) (Figure 1); cardiovascular mortality and morbidity (HR, 1.49; 95% CI, 1.28-1.74; \( P < .001 \)) (**Table 3**); cardiovascular mortality (HR, 1.40; 95% CI, 1.13-1.72; \( P = .002 \)) (Figure 2); recurrent MI (HR, 1.54; 95% CI, 1.20-1.97; \( P = .001 \)); and development of heart failure (HR, 1.65; 95% CI, 1.35-2.01; \( P < .001 \)). Additional significant baseline predictors of total and cardiovascular mortality included age, Killip class II or greater, diabetes, thrombolytic therapy, \( \beta \)-blocker use, and captopril assignment.

**SUBGROUP ANALYSES OF INSULIN VS NON–INSULIN-TREATED PATIENTS WITH DIABETES**

Among the 496 patients with diabetes, the 168 insulin-treated patients were younger, more likely to be women, and smoke less compared with the 328 non–insulin-treated patients (**Table 4**). There were no differences in terms of body mass index, history of MI or hypertension, or presenting Killip class. Among the patients with

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**Table 3. Multivariate Analyses of Diabetes and Other Significant Predictors of Total and Cardiovascular Mortality Among Post-MI Patients With LV Dysfunction**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Mortality</th>
<th>CV Mortality/Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>HR (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.37 (1.14-1.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.39 (1.14-1.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class II or greater</td>
<td>1.31 (1.1-1.57)</td>
<td>.003</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.73 (0.58-0.91)</td>
<td>.005</td>
</tr>
<tr>
<td>( \beta )-Blocker use</td>
<td>0.76 (0.62-0.93)</td>
<td>.009</td>
</tr>
<tr>
<td>Captopril assignment</td>
<td>0.81 (0.68-0.96)</td>
<td>.02</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.22 (0.98-1.56)</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction.

* Cox proportional hazard models were used to determine the multivariable association of the presence of diabetes with total mortality and CV morbidity/mortality. The following variables were considered in the model and are listed in the table in decreasing order of their contribution to the Wald statistic (per total mortality): age (per additional year), sex, history of MI, LVEF (per 5% unit decrease), Killip class II or greater, diabetes, thrombolytic therapy, \( \beta \)-blocker use, and captopril assignment.
diabetes treated with insulin, peak creatine kinase analysis suggested a possible but nonsignificant trend to a smaller size of presenting infarct (*P* = .07) but lower LVEF. In univariate analyses, insulin-treated patients had higher total (41.1% vs 26.2%; *P* = .001) and cardiovascular (36.9% vs 21.7%; *P* < .001) mortality rates compared with non–insulin-treated patients with diabetes (*P* = .001). Patients with diabetes not treated with insulin were also at increased risk of cardiovascular mortality and morbidity compared with non–insulin-treated patients with diabetes as well as nondiabetic patients, insulin treatment was associated with a worse prognosis at 6-month and 1-year follow-up. Community-based studies, including the Corpus Christi Heart Project, reported that after adjustment for age, sex, and ethnicity, the risks of death were 37.4% among patients with diabetes and 23.3% among those without after 44 months. In contrast, in a study with a small sample size, diabetes was not an independent risk factor for increased mortality after MI.

In this large prospective cohort analysis of post-MI patients with left ventricular dysfunction, diabetes is a significant and an independent predictor of total and cardiovascular mortality. Some but not all previous studies have reported increased mortality for patients with diabetes following MI. Specifically, Zuanetti et al and Mak et al reported that diabetes was associated with a worse prognosis at 6-month and 1-year follow-up.

### EFFECT OF CAPTOPRIL

In multivariate analyses captopril significantly decreased total mortality (HR, 0.81; 95% CI, 0.68-0.96) as well as cardiovascular mortality and morbidity (HR, 0.75; 95% CI, 0.65-0.86). Furthermore, the significant benefit of captopril was similar among patients with (HR, 0.83; 95% CI, 0.63-0.87) and without (HR, 0.80; 95% CI, 0.64-0.94) diabetes. Finally, there was no significant heterogeneity of effect of captopril between patients with diabetes and those without (*P* = .45).

### COMMENT

In this large prospective cohort analysis of post-MI patients with left ventricular dysfunction, diabetes is a significant and an independent predictor of total and cardiovascular mortality. Some but not all previous studies have reported increased mortality for patients with diabetes following MI. Specifically, Zuanetti et al and Mak et al reported that diabetes was associated with a worse prognosis at 6-month and 1-year follow-up. Community-based studies, including the Corpus Christi Heart Project, reported that after adjustment for age, sex, and ethnicity, the risks of death were 37.4% among patients with diabetes and 23.3% among those without after 44 months. In contrast, in a study with a small sample size, diabetes was not an independent risk factor for increased mortality after MI.

A prior study that preceded the thrombolytic era reported 5-year mortality of 55% in patients with diabetes compared with 30% in those without. Our study demonstrated overall mortality rates of 31.4% in patients with diabetes and 17.2% in those without over a mean follow-up of 3.5 years. It is interesting to note that in our data patients with diabetes appeared to have had less elevation of biomarkers of necrosis as measured by a lower peak creatine kinase. Nonetheless, after adjustment for all available variables, patients with diabetes experienced a higher incidence of heart failure and death. This may be due, at least in part, to a more rapid progression of coronary heart disease and cardiac fail-
ure related to the effect of diabetes on processes such as thrombogenesis and atherosclerosis.\textsuperscript{35}

Left ventricular dysfunction is a marker of prognosis in patients after MI,\textsuperscript{36,37} especially in patients with diabetes. Furthermore, patients with diabetes develop cardiomyopathy more frequently than those without owing, at least in part, to decreases in global LVEF and regional contractility of the noninfarcted areas.\textsuperscript{7,26,38} These mechanisms are compatible with the possibility that the worse left ventricular remodeling after MI is related to direct effects of diabetes on the residual myocardium,\textsuperscript{2,3,14} but recent data from the SAVE echo cohort suggest that this is not the case.\textsuperscript{39} On the other hand, in patients with diabetes, small changes in ejection fraction produce large increases in risk of heart failure symptoms. These subtle changes in ejection fraction are associated with definite hemodynamic compromise and suggest that in patients with diabetes, diastolic dysfunction plays an important role in the etiology of heart failure.\textsuperscript{4} Indeed, for similar ejection fraction and peak creatine kinase, patients with diabetes in SAVE were more likely to have Killip class II or more and later developed heart failure. Diastolic dysfunction may contribute to the poor prognosis of patients with diabetes,\textsuperscript{9} specifically contributing to the early development of heart failure despite comparable degrees of left ventricular dysfunction compared with nondiabetic patients. Indeed, diabetes has been associated with primary cardiomyopathy,\textsuperscript{10} a condition that may be due to microangiopathy, increased extracellular collagen deposition, or abnormality of calcium transport in the sarcoplasmic reticulum. These factors may lead to more extensive scar formation, diffuse fibrosis, and impaired left ventricular dysfunction, individually or in combination.\textsuperscript{10} Other possible factors related specifically to the higher mortality risk of individuals with diabetes include a higher frequency of silent myocardial ischemia, abnormalities in myocardial fuel metabolism,\textsuperscript{27} and disturbed autonomic tone consequent to diabetic neuropathy. In fact, this latter observation may be a direct cause of arrhythmic death.\textsuperscript{31}

We observed significantly more recurrent MI in patients with diabetes compared with those without. Diabetes is associated with a hypercoagulable state because of abnormal fibrinolytic state and platelet function. These problems of coagulation are thought to be due to increased platelet aggregation and factor VII, increased fibrinogen level, and defective fibrinolysis,\textsuperscript{10} all of which may increase the risk of recurrent MI. Aggressive insulin treatment may restore impaired platelet function,\textsuperscript{42} correct the disturbed lipoprotein pattern, and decrease plasma activity of plasminogen activator inhibitor.

Following MI, patients with diabetes have a higher incidence of postinfarction angina, infarct extension, heart failure, and death.\textsuperscript{6} Indeed, among patients with diabetes, the contractile function of the noninfarcted zone is often significantly worse than among nondiabetic patients, suggesting the inability of the noninfarcted myocardium to compensate as effectively. Angiotensin-converting enzyme inhibitors are of clear benefit among patients with diabetes in reducing subsequent risks of major cardiovascular events as well as to slow their deterioration of renal function. In these data, captopril had a similar relative benefit among patients with and without diabetes and a similar absolute benefit among non-diabetic patients compared with patients with diabetes.

In the present study the subgroup of patients with diabetes treated with insulin had significantly higher mortality and morbidity compared with the non–insulin-treated diabetics. This finding is compatible with several possible explanations. Insulin treatment may be a marker for more severe vascular disease, more rapid progression of disease, or both. In the UK Prospective Diabetes Study,\textsuperscript{30} patients with diabetes assigned to insulin therapy had no increase in MI risk. In addition in that study, there was no evidence for adverse cardiovascular outcomes for patients receiving insulin or sulfonylurea therapy. In another recently reported randomized trial, patients at risk of development of diabetes assigned to sulfonylurea treatment had a 34\% risk reduction, but those assigned to sulfonylurea treatment and therapeutic life style changes had a 68\% risk reduction.\textsuperscript{37}

With respect to plausible alternative explanations for the observed findings, chance, bias, and confounding require elaboration. While SAVE was a randomized trial, the present analyses are observational. Nonetheless, these data are prospective and the sample size is large. Chance seems unlikely because both the crude and the adjusted analyses yielded consistent and significant results. Bias was avoided from the prospective design with the high follow-up rates. In subgroup analyses, size of infarct is largest in patients without diabetes and smallest in insulin-treated patients. Non–insulin-treated patients with diabetes are in between. Current smoking follows the same pattern as infarct size. It is plausible that many of the diabetic patients with large infarct size or who were current smokers might not have survived to be enrolled in

| Table 6. Multivariate Analyses of Insulin- and Non–Insulin-Treated Patients With Diabetes Compared With Those Without Diabetes as Predictors of Total Mortality and CV Mortality/Morbidity in Patients With MI and LV Dysfunction* |
|----------------------------------|------------------|------------------|
| Diabetic Subgroups | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Non–insulin treated | 1.14 (0.90-1.45) | .27 | 1.35 (1.12-1.62) | .001 |
| Insulin treated | 1.91 (1.46-2.48) | <.001 | 1.81 (1.45-2.26) | <.001 |

*The following variables were included in the Cox model: age (per additional year), sex, history of MI, LV ejection fraction (per 5\% unit decrease), Killip class II or greater, diabetic subgroups, thrombolytic therapy, \( \beta \)-blocker use, and captopril assignment.

Abbreviations: CV, cardiovascular; CI, confidence interval; HR, hazard ratio; LV, left ventricular; MI, myocardial infarction.
SAVE if they had more severe diabetes requiring insulin treatment. If real, the effect of this survival bias would be to underestimate the impact of severe diabetes requiring insulin treatment on survival. Uncontrolled confounding is plausible, but SAVE was a particularly well-characterized population, so it was possible to adjust for a large number of confounders.

Despite these and other possible limitations, we believe the most plausible interpretation of the data to be that diabetic patients with left ventricular dysfunction following MI have higher risk of death as well as other adverse cardiovascular outcomes compared with their non-diabetic counterparts. Among patients with diabetes, this finding was particularly notable for the subgroup treated with insulin, a marker of higher risk. This increase in risk is considerable, ranging from 35% to 78%.

In conclusion, patients with diabetes who survived MI with left ventricular dysfunction, in particular those receiving insulin, are at high risk of mortality and cardiovascular events and require intensive risk factor modification as well as evaluation for novel therapies.

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REFERENCES


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Themes may be wide ranging. For instance, some may render the therapeutic encounter, others may depict emotions of physical or mental illness. Some may be interested in artistic renderings of anatomy, physiology, microbiology, medical equipment, historical medical documents, or medicinal herbs. Others may be interested in social or environmental roots of illness or social/spiritual rituals used in response to illness. Some may depict pieces from other art forms such as drama, music, or dance that have a medical theme.

Sculpture, paintings, drawings, photography, fabric art, graphic art, metalwork, crafts, computer art, depictions of medical specimens—perhaps historical artifacts—and other forms of art are all acceptable so long as they can be captured in a photographic submission. A series of related pieces can also be submitted, although publication of a complete set cannot be guaranteed. The picture may be black and white or color and at least 3.5 × 5 inches but no larger than 8 × 10 inches. If you wish to submit a digital photograph, please see the digital art submission guidelines on our Web site at www.archinternmed.com. The picture must be oriented horizontally. No recognizable people should appear in the picture.

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