

Diabetes Mellitus and Trends in Hospital Survival After Myocardial Infarction, 1994 to 2006

Data From the National Registry of Myocardial Infarction

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Background—Patients with diabetes mellitus (DM) are at high risk for mortality after myocardial infarction (MI). Despite an overall trend of reduced mortality after MI, the mortality gap between MI patients with and without DM did not decrease over time in previous analyses. We assessed recent trends in hospital mortality for patients with MI according to DM status.

Methods and Results—We analyzed data from the National Registry of Myocardial Infarction, a contemporary registry of MI patients treated in 1964 hospitals, representing approximately one fourth of all US acute care hospitals. The study comprised 1 734 431 MI patients enrolled from 1994 to 2006, including 502 315 (29%) with DM. Crude hospital mortality decreased in all patients between 1994 and 2006 but remained higher in patients with DM compared with those without DM throughout the study. The absolute difference in mortality between patients with and without DM significantly narrowed over time, from 15.6% versus 11.5% in 1994 to 8.0% versus 6.8% in 2006 ($P<0.001$ for DM $\times$ time interaction). The adjusted odds ratio for mortality associated with DM declined from 1.24 (95% confidence interval, 1.16–1.32) in 1994 to 1.08 (95% confidence interval, 0.99–1.19) in 2006 ($P<0.001$ for trend). The largest improvement in hospital mortality was observed in diabetic women (17.9% in 1994 versus 8.4% in 2006; $P<0.001$).

Conclusions—The hospital mortality gap between MI patients with and without DM narrowed significantly from 1994 to 2006, with the greatest improvement observed in women with DM. (*Circ Cardiovasc Qual Outcomes*. 2012;5:791-797.)

Key Words: diabetes mellitus ■ acute myocardial infarction ■ mortality ■ temporal trends ■ outcome and process assessment

Higher in-hospital mortality rates after acute myocardial infarction (MI) in patients with diabetes mellitus (DM), compounded by a relative underuse of evidence-based therapies after MI in this patient population, are important contributors to the worse cardiovascular (CV) outcomes associated with DM.^{1–3} Despite significant reductions in overall CV mortality in the United States reported in the 1990s,⁴ the incremental CV risk associated with DM remained largely unchanged.^{5,6} However, more recent mortality data in the DM population are lacking. This is especially important because the estimated prevalence of DM in the United States has more than doubled over the past decade, from 4% in 2000 to 8.3% in 2010.^{7,8} To address

whether the gap in post-MI care and in-hospital outcomes between patients with and without DM has narrowed over time, we analyzed recent temporal trends in hospital mortality and use of selected evidence-based therapies in patients with DM compared with those without DM in a large national cohort of patients hospitalized with MI between 1994 and 2006.

Methods

Study Population

The National Registry of Myocardial Infarction (NRM) was a voluntary, prospective, industry-sponsored observational study of patients admitted to participating hospitals with acute MI

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WHAT IS KNOWN

- Diabetes mellitus increases independently the risk of mortality after myocardial infarction.

WHAT THE STUDY ADDS

- On the basis of data from over 1.7 million patients hospitalized with myocardial infarction between 1994 and 2006, a decreasing trend in the diabetes mellitus-associated incremental risk of hospital mortality after myocardial infarction has been observed for the first time in the United States.

(ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation MI [NSTEMI]). NRMI data collection has been described previously,⁹ and includes demographic and clinical information, clinical presentation details, therapies, and in-hospital outcomes collected by trained abstractors, and was submitted to a central coordinating center. There was no independent, on site validation of the data collected, but the completeness and accuracy of data collection in NRMI have been validated in a sample of >25 000 patients enrolled in both NRMI and Medicare's Cooperative Cardiovascular Project, using the detailed chart abstraction process of the Cooperative Cardiovascular Project as the gold standard.¹⁰

Study data collection occurred in 5 phases, NRMI 1 to 5, with constant study eligibility requirements, but with slightly different data collection elements obtained in each phase. Because NRMI 1 (1990 to 1994) did not systematically collect data on DM status, we analyzed data from NRMI 2 through 5 (1994 to 2006). All patients transferred to or from nonparticipating centers were excluded because admission and outcome data were often incomplete or missing. The final sample included in this analysis comprised 1 734 431 patients from 1964 centers, representing approximately one fourth of US acute care hospitals.

Study Variables and Definitions

MI was defined by local hospital criteria, usually including a history suggestive of acute MI accompanied by elevated cardiac markers (creatinine kinase or creatine kinase-isoenzymes M and B $\geq$ twice the upper limit of normal or troponin elevation above local decision limit) or electrocardiographic evidence of MI; or, in the absence of these criteria, alternative enzymatic, scintigraphic, echocardiographic, or autopsy evidence resulting in an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code 410.X1 (acute MI in the initial episode of care; X=any single digit).¹¹ Patients with diagnosis codes 410.X2 (subsequent episode of care), 410.X0 (unspecified episode of care), or 410.__ (missing the fourth or fifth digit) were not included. In-hospital mortality was defined as death of any cause during the course of the initial hospitalization for MI. DM was defined by either medical record or patient information at the time of hospitalization. Of note, the diagnostic criteria for DM changed during the study period,¹² likely leading to inclusion of patients with less severe hyperglycemia in the DM group after 1997. Reperfusion-eligible patients were those with STEMI (including, by convention, patients with left bundle-branch block), evaluated <12 hours after onset of symptoms, and with no contraindications for reperfusion therapy.

Statistical Analyses

The χ^2 test was used to study associations between categorical data, and Student *t* test or ANOVA for continuous data. For trend analyses, data were grouped according to the calendar year of each patient's hospital admission. Trends in mortality rates and in rates of use of CV therapies were assessed using the Cochran-Armitage trend test

on unadjusted data. Multivariable logistic regression techniques were used to adjust for differences in patient mix between groups and by study period. Interaction terms including year of study entry were used to assess for differences in rates of change in mortality by DM status, stratified by sex and by STEMI versus NSTEMI. Statistical comparisons of the rates of change by year between DM versus no DM strata and DM-by-sex substratifications were tested using multivariate logistic regression models. Hierarchical modeling techniques were used. Separate models were analyzed as follows: unadjusted; adjusted for age and race; adjusted for age, race, and medical history; and adjusted for age, race, medical history, and presenting characteristics. Variables allowed to enter the final model included age, race, smoking status, previous MI, history of hypertension, family history of coronary artery disease, history of chronic heart failure, prior percutaneous coronary intervention, prior coronary artery bypass grafting, medical history of stroke, medical history of angina, presentation of ST-segment elevation or left bundle-branch block, anterior MI, chest pain at presentation, Killip class, systolic blood pressure, and pulse rate. To correct for changes in the characteristics of participating centers over time (because many hospitals dropped out or dropped in the NRMI database during the course of the study), all summary data and inferential statistics were weighed based on a 12-category cross-classification of hospital facility type and number of beds, as previously described.¹³ All summary data, inferential statistics, and confidence intervals were computed using SAS procedures that account for the design effect associated with weighted data. All statistical analyses were performed using SAS software (version 8.0; SAS Institute, Cary, NC).

Results**Characteristics of Patients**

Among 1 734 431 patients hospitalized with MI at 1964 participating NRMI centers between 1994 and 2006, 502 314 patients (29%) had DM. Quadrennial baseline characteristics of the DM cohort are presented in the Table, and demonstrate increasing age and overall worsening CV risk profile throughout the study period. Baseline characteristics of the entire cohort stratified by DM status are presented in online-only Data Supplement Table I, and further stratified by DM status and sex in online-only Data Supplement Table II. Patients with DM were older, more often women, had a greater prevalence of hypertension, and more commonly reported an antecedent history of coronary artery disease. The prevalence of DM in the study cohort increased from 25.3% in 1994 to 30.6% in 2006 (20.9% increase, adjusted $P<0.001$ for trend) (online-only Data Supplement Figure I).

Use of Evidence-Based Therapies

The rates of use of selected coronary heart disease risk-modifying therapies (aspirin, angiotensin-converting enzyme inhibitors, β -blockers, and reperfusion among reperfusion-eligible patients) in the first 24 hours after admission in patients with and without DM throughout the study period are presented in online-only Data Supplement Table III. With the exception of angiotensin-converting enzyme inhibitors, which were used more commonly in DM patients compared with non-DM patients at the beginning of the study (19.1% versus 10.8%, respectively; $P<0.0001$), all other treatments assessed were used less often in patients with versus without DM in 1994, including β -blockers, 31.7% versus 37% ($P<0.0001$); aspirin, 67.6% versus 73.1% ($P<0.0001$); and reperfusion therapy among those eligible, 59.0% versus 72.1% ($P<0.0001$). The

Table. Baseline Characteristics of the Diabetes Cohort During the Study Period

	1994	1998	2002	2006	Trend <i>P</i>
Median age (25th%–75th%)	69.7 (60.7, 77.2)	70.7 (61.2, 78.4)	72.0 (61.0, 80.0)	71.0 (60.0, 80.0)	<0.0001
Female, %	46.7	46.2	46.6	44.8	<0.0001
Race/ethnicity, %					
White	81.7	80.2	78.2	81.8	<0.0001
Non white	18.3	19.8	21.8	18.2	<0.0001
Black	9.0	9.5	10.1	9.2	
Hispanic	4.2	4.4	4.9	3.4	
Asian/Pacific islander	1.4	2.2	3.0	3.0	
Native American/Alaska native	0.5	0.6	0.6	0.6	
Other	3.1	3.2	3.3	1.9	
ST-segment elevation MI or left bundle-branch block at presentation, %	45.6	37.1	27.3	26.4	<0.0001
Current smoker, %	18.3	17.4	21.3	22.3	<0.0001
Hypertension, %	60.4	67.4	73.9	79.7	<0.0001
Prior MI, %	30.3	30.3	30.1	31.0	0.8098
Prior stroke, %	11.0	14.1	14.7	14.0	<0.0001
Chronic heart failure, %	20.7	25.4	27.4	25.7	<0.0001
Prior percutaneous coronary intervention, %	8.0	11.3	14.8	22.5	<0.0001
Prior coronary artery bypass grafting, %	13.5	16.7	19.9	21.0	<0.0001
Atypical presentation (no chest pain at presentation), %	31.1	37.9	44.3	39.9	<0.0001
Mean TIMI risk index	31.9	33.0	35.1	33.8	<0.0001

MI indicates myocardial infarction; TIMI, thrombolysis in myocardial infarction.

rates of use of each of these therapies increased in both patients with and without DM throughout the study period, with greater increases in the use of aspirin and β -blockers among patients with DM— in particular, among diabetic women. This resulted in no statistically significant differences in the rate of use of β -blockers by DM status ($P>0.05$) in 2006, and a much narrower gap in the use of aspirin (86.3% versus 88.9%; $P<0.0001$), with no statistically significant difference in the use of aspirin among diabetic women by study end ($P=0.13$).

To assess further the trends and contrasts in the use of evidence-based therapies by diabetes mellitus status, we analyzed the composite proportion of selected therapies received among the eligible subset of patients for each therapy (all patients for aspirin and angiotensin-converting enzyme inhibitors, all patients except those with Killip score >1 for β -blockers, reperfusion-eligible patients as defined in Methods for reperfusion, and patients with thrombolysis in MI risk index >12.5 for cardiac catheterization).¹⁴ The mean composite proportion was significantly lower in patients with DM versus those without DM throughout the study, and exhibited a continuous and parallel increase in both groups from 43.8% versus 46.2% ($P<0.0001$) in 1994 to 65.3% versus 68.7% ($P<0.0001$) in 2006 (online-only Data Supplement Figure II).

Hospital Mortality

Hospital mortality declined for the overall cohort from 12.6% in 1994 to 7.2% in 2006 (42.9% relative risk reduction; $P<0.001$ for trend). In analyses of the overall cohort stratified by DM status (Figure 1A), a reduction in mortality risk was observed both in patients without DM (11.5% to 6.8%, 40.9%

relative risk reduction; $P<0.001$ for trend) and in patients with DM (15.6% to 8.0%, 48.7% relative risk reduction; $P<0.001$ for trend). However, the magnitude of decline in mortality was significantly greater among DM versus non-DM patients ($P<0.001$ for interaction). In analyses stratified according to both sex and DM status (Figure 1B), the observed reduction in mortality risk over time for both men and women with DM exceeded those of patients without DM, with diabetic women experiencing the greatest rate of improvement (17.9% in 1994 and 8.4% in 2006, 52.8% relative risk reduction; adjusted $P<0.001$ for trend).

The adjusted odds ratio for mortality associated with DM declined over the period of observation in both the overall cohort and within each sex stratum (for all, adjusted $P<0.001$ for trend; Figure 2). By study end, the incremental risk associated with DM was of borderline statistical significance in men and in the overall cohort, and no longer statistically significant in women.

The proportion of qualifying events coded as STEMI declined throughout the study period from 45.3% in 1994 to 28.1% in 2006, with similar changes in patients without and with DM (Figure 3A). The adjusted odds ratio for mortality associated with DM within the subsets of patients with STEMI and NSTEMI (Figure 3B) decreased over the study period in a manner similar to that observed in the overall cohort, with the incremental risk associated with DM in both groups no longer statistically significant by study end. The thrombolysis in MI risk index, a predictor of short- and long-term mortality in patients with acute MI (including STEMI and NSTEMI),^{15,16} was higher in the DM cohort and increased

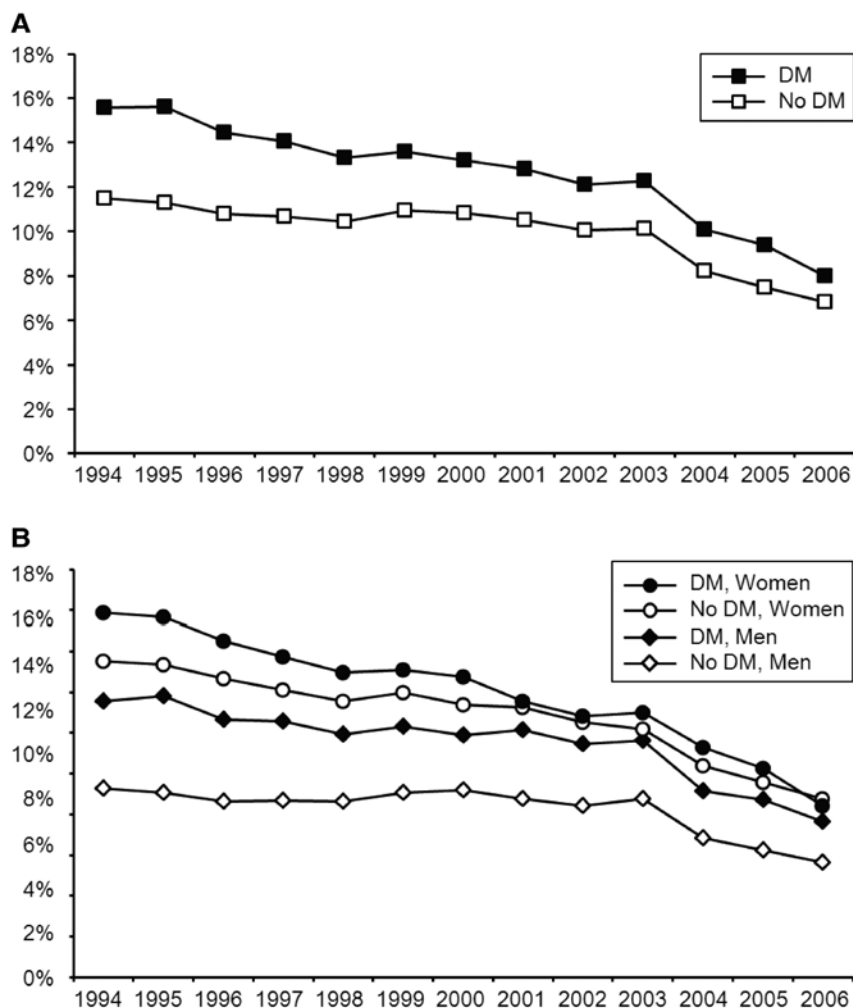


Figure 1. Unadjusted annual hospital mortality after myocardial infarction (in-hospital deaths as percentage of total number of patients enrolled during each year of the study) according to diabetes mellitus (DM) status (**A**) and according to sex and DM status (**B**). Mortality decreased over the study period in all groups (P for trend <0.001 for all).

similarly in patients with and without DM throughout the study period (online-only Data Supplement Figure III).

Discussion

There are 3 key observations from this study. First, although post-MI hospital mortality decreased between 1994 and 2006 in all patients, the reduction in mortality was greater for patients with DM than without DM, resulting in a narrowing in the mortality gap associated with DM. To our knowledge, this is the first report to document a decrease in the incremental risk for mortality after MI associated with DM. Second, improved survival among patients with DM was especially evident in women, resulting in the elimination of the gender gap in DM-associated post-MI mortality risk. Third, similar to reports showing increasing DM prevalence in the general population (now approaching 10% in the United States), the prevalence of DM among patients with MI in our study increased significantly over time, with almost 1 in 3 MI patients having DM by study end.

The modification of diagnostic criteria for DM in mid 1997 that lowered the glucose thresholds for diagnosis¹² could have, in part, contributed to the observed increase in DM prevalence, and by inclusion of relatively lower risk patients in the DM subset could have influenced the relative reduction in

incremental mortality risk among patients with DM. However, a number of observations suggest that the change in definition had, at most, a modest effect on each of these results. First, the increasing DM prevalence and the mortality reduction trends were evident prior to mid 1997 and were linear spanning this period. Second, despite the modified DM definition, the overall age and CV risk profile of the DM cohort actually increased throughout the study period, and the estimated CV risk (as reflected by the thrombolysis in the MI risk index) of patients with and without DM increased in parallel. Finally, any influence of the modified criteria for the diagnosis of DM would be expected to have commensurate effects on mortality outcomes for both sexes, whereas we observed significantly greater improvements in women compared with men. Therefore, although we are unable to quantitate the influence of the change in DM diagnostic criteria on our results, given these considerations, it is improbable that this alone had more than a modest effect on the current results.

The definition of MI also changed during the study period because of the use of increasingly sensitive troponin assays.¹⁷ As we have previously published, DM is associated with an increased prevalence of detectable troponin among ambulatory adults, which may have confounded the classification of MI in DM patients entering the registry.¹⁸ However, the proportion of MI events classified as STEMI declined to a similar extent

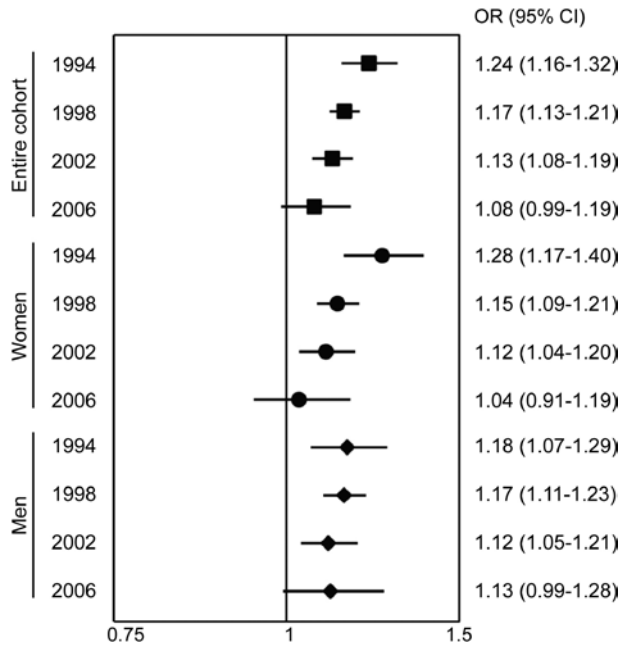


Figure 2. Adjusted* estimates of mortality risk attributable to diabetes mellitus over the period of observation: odds ratio (OR) and 95% confidence intervals (CI) for diabetes mellitus vs no diabetes mellitus. *Adjusted for age, race, family history of coronary artery disease, smoking status, hypertension, history of chronic heart failure, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior stroke, history of angina, presentation of ST-segment elevation or left bundle-branch block, anterior myocardial infarction, chest pain at presentation, Killip class, systolic blood pressure, pulse rate, and hospital characteristics.

among patients with and without DM throughout the study period. Moreover, when we restricted the analyses to patients with STEMI, in whom changes in the troponin assays would not be expected to influence the diagnostic classification, the mortality trends and contrasts by DM status were similar to those in the overall cohort. Analyses restricted to the subset of patients with NSTEMI did reveal a steeper decrease in incremental risk over time compared with the STEMI subset; however, trends in both subsets were qualitatively similar, culminating in incremental risks that were no longer statistically significant by study end.

Incremental CV Risk Following MI in Patients With Diabetes

DM independently augments the risk of short- and long-term mortality in patients with acute coronary syndromes.^{19,20} A variety of explanations have been proposed to account for the adverse influence of DM on clinical outcomes after MI, including differences in atherosclerotic disease burden and distribution,²¹ metabolic perturbations,²² autonomic neuropathy,²³ endothelial dysfunction,^{24,25} derangements in the proteo fibrinolytic system and platelet effects,²⁶ and exaggerations of inflammatory processes²⁷, all factors that are difficult or impossible to adjust for in statistical modeling. In addition, the relative contributions to adverse outcomes of hyperglycemia, and of drugs or combinations of drugs to treat hyperglycemia, remain poorly understood.²⁸⁻³⁰

Beyond pathophysiology, differences in processes of care may also contribute to the poor prognosis associated with

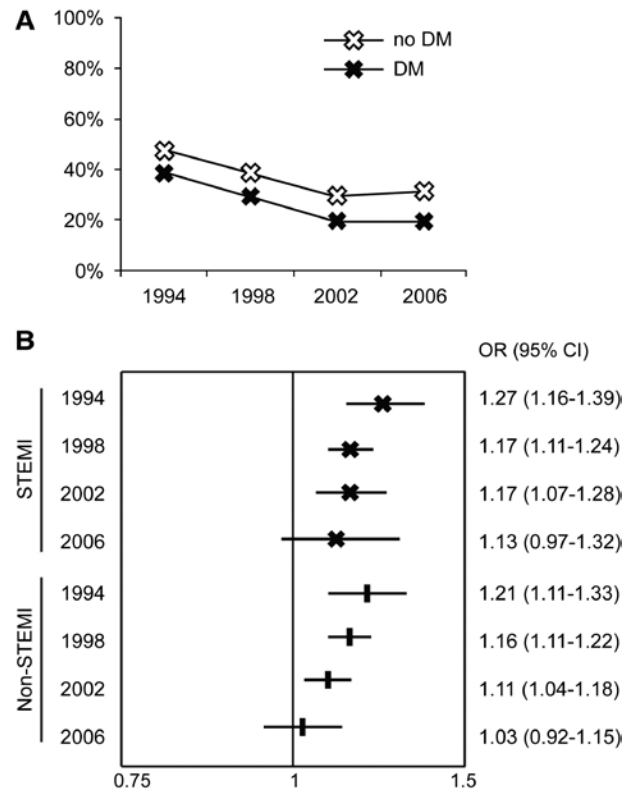


Figure 3. **A**, Proportion of patients with ST-segment elevation myocardial infarction (STEMI) throughout the study period. **B**, Adjusted* estimates of mortality risk attributable to diabetes mellitus (DM) over the period of observation in subsets of patients with STEMI and non-STEMI: odds ratio (OR) and 95% confidence intervals (CI) for diabetes mellitus vs no diabetes mellitus. *The same adjustments as in Figure 2, except for ST-segment elevation or left bundle-branch block.

DM, with disparities commonly reported regarding the under-use of evidence-based therapies in patients with DM despite their well-documented increased risk.³ In addition to differences in treatments, delayed hospital presentation and delayed clinical recognition of MI because of atypical symptoms may also contribute to worse outcomes in patients with DM.

Trends in Post-MI Outcomes in Patients With Diabetes

Data from the National Health and Nutrition Examination Survey suggest that, although the risk of coronary heart disease mortality declined significantly in the US population between 1971 and 2000 in non diabetic patients, a smaller decline was observed in men with DM and no decline in risk was seen among women with DM.⁵ In contrast, in the Framingham Heart Study cohort, coronary heart disease mortality over the last half of the 20th century declined similarly in individuals of both sexes, with and without DM, and the incremental risk associated with DM remained largely unchanged.⁶

The current observations reveal for the first time a reduction in the incremental risk of post-MI hospital mortality associated with DM, using data from a very large, recent US cohort. The reduction in incremental mortality risk associated with DM was particularly robust among women. This finding is encouraging given the high rate of mortality after MI among women with DM at the beginning of the study period. The

elimination of the gender gap among patients with DM may, in part, be because of increasing focus given to women and heart disease in the United States, resulting in improved primary and secondary prevention that may mitigate in-hospital risk after MI.³¹ In addition, on the basis of previously published analyses from this same database, wider use of emergency medical services has been reported among patients with DM and women compared with non-DM patients and men, respectively, and use of these services was associated with improvements in subsequent quality of care.³² However, whether these positive trends in hospital outcome will translate into narrowing of the long-term post-MI survival gap between patients with and without DM remains to be established.

Trends in Use of Evidence-Based Therapies During MI in Patients With Diabetes

Prior studies have demonstrated vast underutilization of evidence-based therapies during acute coronary events among patients with DM in the United States and globally.^{2,33–37} This could be because of a prevalent clinical tendency to provide more conservative therapies to patients with increasing comorbidity, as well as by theoretical concerns such as masked hypoglycemia with β -blockers and vitreous hemorrhage with fibrinolytics, despite a lack of clinical evidence supporting such concerns.^{38,39} Our study reveals improving trends over time in the use of evidence-based therapies in patients with and without DM, with little absolute difference in use between DM and non-DM patients by study end. Although relatively modest, these improvements in aggregate could have, in part, contributed to the improved mortality trends observed in our study, changes that have been previously estimated to account for approximately half of the reduction in CV disease mortality observed in the United States over the past few decades.⁴⁰

Limitations

There are a number of limitations to this study inherent to the NRMI study design. No data are available on prehospital outcomes or on outcomes beyond the index hospitalization, the qualifying MI was defined locally and without central adjudication, data on non fatal CV events are not available, and consecutive enrollment cannot be independently verified. In addition, data were not available regarding the type and duration of DM, use of glucose-lowering medications before and during hospitalization, intensity and adequacy of glycemic control before and during hospitalization, and presence of concomitant diabetic microvascular disease, all of which may contribute to prognosis among patients with DM.

Clinical Implications

The results of our study show encouraging trends in post-MI hospital outcomes in the United States overall, a reduction in the incremental hospital mortality risk associated with DM in the setting of MI, and elimination of the gender gap in post-MI mortality risk among patients with DM. These favorable trends likely reflect improved and more equitable management of DM patients of both sexes. These data suggest that despite the continually increasing prevalence of DM and the persistent incremental CV risk associated with DM, sustained efforts at implementing evidence-based therapies and

improving the care afforded to these patients can help close the gap in adverse CV outcomes in patients with DM.

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Disclosures

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