

# Short- and Long-Term Mortality After Myocardial Infarction in Patients With and Without Diabetes

## Changes from 1985 to 2008

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**OBJECTIVE**—To study temporal trends in short- and long-term outcome after myocardial infarction (MI) according to diabetes status.

**RESEARCH DESIGN AND METHODS**—We included all 14,434 consecutive patients admitted for ST-segment elevation MI or non-ST-segment elevation MI at our center between 1985 and 2008. The study patients were compared according to prevalent diabetes. Temporal trend analyses were performed by comparing decades of admission (1985–1989 vs. 1990–1999 vs. 2000–2008).

**RESULTS**—A total of 2,015 (14%) of the patients had prevalent diabetes. The risk of presenting with diabetes increased from 8 to 17% from 1985 to 2008. Diabetic patients presented with a higher prevalence of cardiovascular risk factors. With time, the use of evidence-based therapies increased in both patients with and without diabetes. Diabetes is associated with a 1.5-fold increased risk of mortality at the 20-year follow-up. Ten-year mortality decreased over time in patients with diabetes, from 53% in 1985–1989 to 39% in 2000–2008 (adjusted hazard ratio 0.56 [95% CI 0.43–0.73]), and in those without diabetes, from 38% in 1985–1989 to 29% in 2000–2008 (0.66 [0.60–0.73]; *P* interaction = 0.83). Patients with diabetes benefitted from a higher 30-day and 10-year absolute survival increase.

**CONCLUSIONS**—Temporal mortality reductions after MI between 1985 and 2008 were at least as high in patients with diabetes compared with those without diabetes. However, long-term mortality remained higher in diabetic patients. Awareness of the high-risk profile of diabetic patients is warranted and might stimulate optimal medical care and outcome.

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Over the last decades, the prevalence of diabetes in patients with a myocardial infarction (MI) has increased significantly (1–3). Current figures indicate that cardiovascular events are responsible for 80% of all deaths in patients with diabetes (3). Within the past 25 years, the management and prognosis of MI has shown substantial progress; clinical evidence and guidelines have introduced thrombolytic therapy, primary percutaneous coronary intervention (PCI), tailored treatment according to individual risk, as well as improved secondary prevention (1,4–8). However, some studies have shown that patients with

diabetes suffering from acute MI are less likely to receive evidence-based therapies (9–11). Furthermore, recent data have also suggested that patients with diabetes have not benefitted from the temporal long-term mortality reductions after MI, as opposed to patients without diabetes (9). Therefore, the need for management that improves long-term post-MI survival in patients with diabetes has been underlined (9).

We aimed to investigate the effect of diabetes on (20-year) mortality in a cohort of consecutive MI patients hospitalized from 1985 to 2008. Further, we aimed to determine whether temporal

improvements in survival after MI have occurred equally in patients with and without diabetes.

### RESEARCH DESIGN AND METHODS

We included all consecutive patients >18 years of age admitted for ST-segment elevation MI (STEMI) or non-ST-segment elevation MI (NSTEMI) to the Intensive Coronary Care Unit (ICCU) of the Thoraxcenter between June 1985 and December 2008 (12).

The primary discharge diagnosis of MI was made in the presence of the following characteristics: chest pain or equivalent symptoms in combination with dynamic electrocardiogram changes consistent with MI and a typical serial rise (to at least three times the upper normal value) and fall in serum biochemical markers of cardiac necrosis such as creatine kinase-muscle brain type or troponin-T (as of 2002). Patients were diagnosed as STEMI in the presence of ST-segment elevation >0.1 mV in at least two contiguous peripheral leads on the electrocardiogram, or >0.2 mV in at least two contiguous precordial leads on the electrocardiogram, and as NSTEMI otherwise. For patients admitted more than once, only the first hospitalization was taken into account.

### Data collection

Diabetes was defined as previously diagnosed by a physician or as receiving medication to lower glucose levels. Trained physicians and nurses accustomed to the use of standardized case report forms collected the data. Demographic characteristics (age and sex), cardiac history (previous MI, PCI, or coronary artery bypass surgery [CABG]), risk factors (hypertension, family history, and smoking status), anemia (hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women), renal dysfunction (creatinine >150 μmol/L), and pharmacological and invasive treatment modalities (thrombolysis and PCI) were collected. Hypertension was defined as previously diagnosed by a physician or

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receiving medication to lower blood pressure. Family history was defined as one or more relatives (parent or sibling) with an MI diagnosed before the age of 60 years.

**Follow-up and end points**

The primary end point was all-cause mortality. Survival status and date were assessed through municipal civil registries in 2010 and were available for 99% of all patients.

**Ethics**

This project was carried out in accordance with current rules of ethics and legislature. No additional actions involving the study participants were undertaken because of this registry. Register-based studies are approved by the ethical committee of the Erasmus Medical Center and do not require informed consent according to Dutch laws (Medical Research Including Human Species Act).

**Statistical analysis**

The study patients were categorized into two groups of patients according to prevalent diabetes. Patients were stratified into three groups according to the year of hospitalization: 1985–1989, 1990–1999, and 2000–2008. These strata were chosen according to important improvements in therapy, with complete introduction of thrombolytic therapy in 1990 and a substantial increase in the use of primary PCI since 2000. Categorical variables were summarized as frequencies and percentages. Cochran statistic with correction for study period was used to calculate *P* values. We assessed temporal mortality trends by comparing one-minus-survival curves that were constructed using the Kaplan-Meier method. The log-rank test was used to compare survival curves. We examined the independent association between decade of hospitalization and mortality according to diabetes status, using logistic regression for 30-day outcome and the Cox proportional hazards model for long-term outcome. Adjustment was performed for age, sex, previous MI, previous CABG, hypertension, dyslipidemia, family history, smoking status, renal dysfunction, anemia, and discharge diagnosis.

Results are reported as odds ratios (for 30-day mortality) and hazard ratios (HRs) (for long-term mortality) and their respective 95% CIs. For all analyses that compared decades of hospitalization, we analyzed up to 10 years of follow-up, because longer follow-up is unavailable for patients hospitalized in the last decade

(2000–2008). Interaction between diabetes status and study period and mortality was assessed using multivariable regression models. All statistical tests were two tailed, and *P* values were considered significant at <0.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, IL).

**RESULTS**

**Patient characteristics**

We included 14,434 patients, of whom 2,015 (14%) had prevalent diabetes. For each calendar year, the relative risk of presenting with diabetes increased by 5%, from a prevalence of 8% in the 1980s to 17% in the last decade. The distribution of risk factors at baseline varied according to diabetes status and according to decade

of admission (Table 1). Patients with diabetes were older and more often female, and more often had a history of previous MI, hypertension, dyslipidemia, anemia, and renal impairment. Patients with diabetes were less often current smokers and more often had a discharge diagnosis of NSTEMI.

**Medical and invasive care during the study period**

The medical care provided to MI patients with and without diabetes was comparable, with no clinically relevant sex differences. The use of reperfusion therapy (either by thrombolytic therapy or PCI) increased over time in both groups with STEMI (*P* < 0.001), and STEMI patients with diabetes were equally likely to receive primary PCI as those without

**Table 1—Baseline characteristics and clinical presentation of patients hospitalized for MI according to diabetes status**

	Diabetes			No diabetes			Overall <i>P</i> *
	1985–1989	1990–1999	2000–2008	1985–1989	1990–1999	2000–2008	
No. of patients	174	525	1,316	2,042	4,075	6,302	
Total in decade	8%	11%	17%	92%	89%	83%	
Baseline							
Elderly (>65 years)	47%	45%	50%	37%	42%	41%	<0.001
Sex (female)	40%	40%	34%	24%	28%	26%	<0.001
Cardiac history							
Previous MI	49%	39%	32%	41%	32%	31%	<0.01
Previous PCI	11%	13%	18%	8%	10%	19%	0.47
Previous CABG	13%	12%	10%	13%	9%	9%	0.03
Risk factors							
Hypertension	41%	50%	59%	34%	29%	34%	<0.001
Dyslipidemia	9%	30%	50%	11%	21%	32%	<0.001
Family history	20%	21%	28%	24%	23%	29%	0.10
Current smoker	25%	26%	25%	40%	31%	33%	<0.001
Renal dysfunction	11%	15%	13%	9%	9%	6%	<0.001
Anemia	40%	47%	52%	34%	42%	42%	<0.001
Discharge diagnosis							
NSTEMI	55%	41%	57%	57%	58%	46%	<0.001
Reperfusion therapy**							
Primary PCI	8%	14%	82%	4%	12%	85%	0.45
Thrombolytic therapy	25%	47%	7%	32%	54%	8%	0.03
Medication at ICCU discharge							
Statin	0%	NA	74%	0%	NA	72%	0.12
Aspirin	17%	57%	85%	14%	61%	87%	0.02
β-Blocker	49%	45%	62%	58%	54%	61%	0.02
ACE inhibitor or ARB	0%	15%	40%	0%	13%	27%	<0.001
Ca antagonist	52%	30%	10%	54%	31%	9%	0.44
Nitrates	33%	13%	11%	31%	14%	6%	<0.001
Diuretics	41%	21%	16%	25%	12%	7%	<0.001
Antiarrhythmics	7%	3%	4%	7%	4%	3%	0.04

NA, not available. \*The overall *P* value compares patients with and without diabetes with adjustment for calendar decade of admission. \*\*STEMI patients only, *n* = 6,820.

diabetes. Prescription of evidence-based medical care (class 1A), including aspirin,  $\beta$ -blockers, statins, and ACE inhibitors/angiotensin-receptor blockers (ARBs), also increased over time in both groups. Overall, patients with diabetes were more likely to receive ACE inhibitors/ARBs and less likely to receive aspirin and  $\beta$ -blockers. However, these differences were small and did not persist over time. Prescription of diuretics was higher in patients with diabetes. Other medical therapies with a lower level of evidence for the treatment of MI, including calcium antagonists, were prescribed at equal rates in both study groups (Table 1).

**Temporal trends in mortality**

A total of 106,517 person-years were analyzed. At 10-year follow-up, a total of 663 patients with and 3,285 patients without baseline diabetes had died. The unadjusted risk of 30-day mortality decreased between 1985 and 2008, both in the diabetes group, from 17% in 1985–1989 to 5% in 2000–2008, and in the nondiabetes group, from 10% in 1985–1989 to 4% in 2000–2008 (Fig. 1). Also, unadjusted 10-year mortality decreased between 1985 and 2008, both in the diabetes group, from 53% in 1985–1989 to 39% in 2000–2008, and in the nondiabetes group, from 38% in 1985–1989 to 29% in 2000–2008.

29% in 2000–2008. Patients with diabetes benefitted from a higher 30-day and long-term absolute survival increase (Fig. 1).

From 1985 to 2008, the adjusted risk of 30-day mortality decreased by ~80%, both in the diabetes group (adjusted odds ratio 0.17 [95% CI 0.10–0.30]) and in the nondiabetes group (0.29 [0.24–0.37]) (Table 2). The risk of 10-year mortality decreased by ~40%, both in the diabetes group (adjusted HR 0.56 [95% CI 0.43–0.73]) and in the nondiabetes group (0.66 [0.60–0.73]) (Table 2). There was no significant interaction between diabetes status and study period ( $P = 0.39$  and  $P = 0.83$  for interaction for 30-day and 10-year mortality, respectively). Hence, the relative risk reductions in 30-day and long-term mortality over the 24-year study period were at least as high for MI patients with diabetes compared with those without.

**Diabetes and mortality**

As expected, the risk of mortality was higher in MI patients with prevalent diabetes. The increased mortality risk persisted up to the 20-year follow-up (Fig. 2). Patients with diabetes had a median survival of 11 years compared with 15 years for those without. Patients in the diabetes group had a 50% increased adjusted long-term mortality risk in all three decades studied (adjusted HR for 10-year mortality = 1.5, 1.5, and 1.4 in 1985–1989, 1990–1999, and 2000–2008, respectively;  $P < 0.001$  for all).

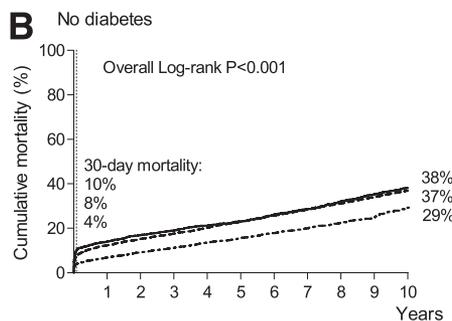
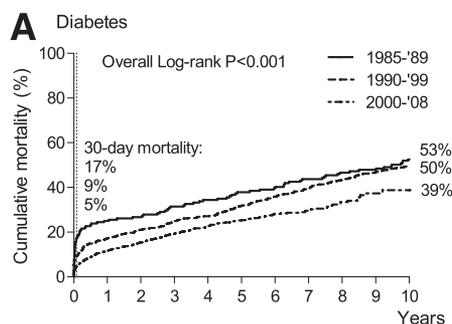
**CONCLUSIONS**—In this study comprising a cohort of 14,434 patients with acute MI, studied over a period of 24 years, we showed that there is an increasing prevalence of diabetes in patients with an acute MI. More important, we showed

that the temporal reductions in all-cause mortality in patients suffering acute MI, achieved between 1985 and 2008, were at least as high in patients with diabetes as in those without diabetes. This improvement in outcome is most likely related to the fact that during the study period, the use of MI-related medical care improved significantly both for patients with and without diabetes. Indeed, in the most recent decade, diabetes was no longer associated with underuse of treatment. Finally, we demonstrated that the increased mortality risk associated with diabetes persisted for up to 20 years of follow-up.

A previous study (13) demonstrated the increasing burden of diabetes in relation to cardiovascular disease mortality in the general population. Relatively few studies have evaluated temporal trends in (long-term) mortality of MI patients with and without diabetes (9,11,14). Moreover, the results of these studies were inconsistent. Two studies (11,14) show temporal mortality reductions in patients with and without diabetes, whereas one study (9) concludes that patients with diabetes do not benefit from a reduction in long-term post-MI mortality over time.

**Treatment**

The awareness of the higher cardiovascular risk associated with diabetes has probably intensified cardioprotective treatment in these patients over time. We and others (9,10,15) showed that from 1985 to 1999, the use of thrombolytic therapy and  $\beta$ -blockers was lower in patients with diabetes compared with those without. Studies (15,16) have shown the effectiveness of these therapies in patients with diabetes. It is therefore encouraging to observe that these inequalities in medical care are no longer present in the last

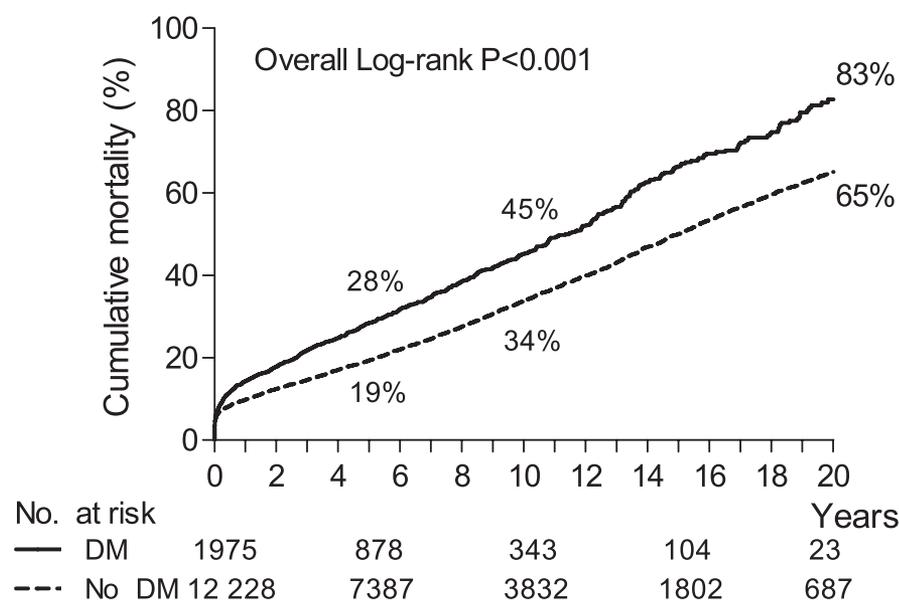


**Figure 1**—Temporal trends. Kaplan-Meier curves of mortality according to a decade of hospitalization in patients with and without diabetes.

**Table 2**—Temporal trends in 30-day and 10-year mortality in MI patients

Calendar period	Odds ratios for 30-day mortality			
	Diabetes		No diabetes	
	Unadjusted	Adjusted	Unadjusted	Adjusted
1985–1989	Reference	Reference	Reference	Reference
1990–1999	0.49 (0.30–0.81)	0.40 (0.23–0.69)	0.73 (0.60–0.88)	0.63 (0.52–0.78)
2000–2008	0.23 (0.14–0.37)	0.17 (0.10–0.30)	0.37 (0.31–0.45)	0.29 (0.24–0.37)
	HRs for 10-year mortality			
1985–1989	Reference	Reference	Reference	Reference
1990–1999	0.88 (0.69–1.1)	0.83 (0.65–1.1)	0.96 (0.88–1.0)	0.96 (0.88–1.1)
2000–2008	0.63 (0.50–0.80)	0.56 (0.43–0.73)	0.64 (0.58–0.70)	0.66 (0.60–0.73)

Adjusted for age, sex, previous MI, previous CABG, hypertension, dyslipidemia, family history, smoking status, renal dysfunction, anemia, and discharge diagnosis.



**Figure 2**—Kaplan-Meier curves of mortality according to diabetes for all MI patients.

decade of observation. Further, our data showed that in the last decade, ~40% of diabetic patients were treated with ACE inhibitors/ARBs at ICCU discharge (a median of 1–2 days after admission), a percentage higher than that for nondiabetic patients. ACE inhibitors/ARBs slow myocardial remodeling and the progression of diabetic nephropathy (17). This finding is consistent with other recent data (10,15). Diabetic patients received diuretics more often compared with nondiabetic patients probably due to the higher risk profile in diabetic patients, with more frequent hypertension and heart failure (9).

### Mortality

We found a reduction in both 30-day and long-term mortality rates over time for MI patients with and without diabetes. Patients with diabetes benefitted from a higher 30-day and long-term absolute mortality reduction. The relative mortality reductions were statistically equal for patients with and without diabetes, which is consistent with another study reporting on patients hospitalized with an MI between 1979 and 1998 (11). Furthermore, other studies in the general population have shown that mortality from coronary heart disease has decreased over the past decades, and some of these studies speculated that patients with diabetes have also benefitted from this reduction (18–20). The temporal mortality reduction observed in the current study may be a result of several factors, including improved treatment in the acute phase of

MI and increased long-term survival resulting from aggressive secondary prevention (1,4,5,7,8,21). Although patients with diabetes benefitted at least equally from improved mortality rates over the last 25 years, their absolute long-term mortality remained ~1.5-fold higher compared with patients without diabetes. Therefore, optimal medical care for diabetes patients and awareness of their high-risk profile remains warranted and may even further improve outcomes in these patients in the future.

### Strengths and limitations

To our knowledge, this is the first article investigating temporal trends in clinical characteristics and treatment and outcome of MI patients with diabetes over a time period of 24 years and with follow-up data of up to 20 years.

Although the current study has unique strengths, some limitations should be mentioned. First, the present data are derived from a single center. Although this could result in a lower external validity, we think that this is unlikely to be the case given the uniform definition and therapeutic modalities of MI. Second, we did not distinguish patients with type I and type II diabetes. Also, our definition of diabetes did not include patients who were diagnosed on the basis of glucose values during hospitalization for acute MI only. Therefore, the real prevalence of diabetes might have been underestimated; alternatively, our definition is not biased by altered glucose

levels resulting from the acute event (22) and allows for better comparison of our results with previous studies. Last, given the nature of diabetes, this study reveals important associations but cannot prove causation.

In conclusion, we show that there is an increasing prevalence of diabetes in patients with an MI. Medical care improved substantially for MI patients both with and without diabetes during the 24 years of observation. In the most recent decade, diabetes was not associated with underuse of evidence-based therapies, including primary PCI for STEMI. In the study period, outcome improved and temporal mortality reductions were at least as high in patients with diabetes compared with those without diabetes. However, the absolute long-term mortality rate remained about 1.5-fold higher in patients with diabetes compared with those without. Therefore, optimal medical care for diabetes patients and awareness of their high-risk profile remains warranted.

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S.T.N., J.W.D., K.M.A., and R.T.v.D. conceived and designed the study, analyzed and interpreted data, drafted the manuscript, and critically revised the manuscript for important intellectual content and approved the final version submitted. J.W.D. and R.T.v.D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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