Impact of Diabetes on Long-Term Survival After Acute Myocardial Infarction

Comparability of risk with prior myocardial infarction

KENNETH J. MUKAMAL, MD, MPH, MA[1]
RICHARD W. NESTO, MD[2]
MYLAN C. COHEN, MD, MPH[3]
JAMES E. MULLER, MD[4]
MALCOLM MACLURE, SCD[5]
JANE B. SHERWOOD, RN[6]
MURRAY A. MITTLEMAN, MD, DRPH[5,7]

OBJECTIVE — To determine the effect of diabetes on long-term survival after acute myocardial infarction and to compare its effect with that of a previous myocardial infarction.

RESEARCH DESIGN AND METHODS — In a prospective cohort study, we followed 1,935 patients hospitalized with a confirmed acute myocardial infarction at 45 U.S. medical centers between 1989 and 1993, as part of the Determinants of Myocardial Infarction Onset Study. Trained interviewers performed chart reviews and face-to-face interviews with all patients. We analyzed survival using Cox proportional hazards regression to control for potentially confounding factors.

RESULTS — Of the 1,935 patients, 320 (17%) died during a mean follow-up of 3.7 years. A total of 399 patients (21%) had previously diagnosed diabetes. Diabetes was associated with markedly higher total mortality in unadjusted (hazard ratio [HR] 2.4; 95% CI 1.9–3.0) and adjusted (1.7; 1.3–2.1) analyses. The magnitude of the effect of diabetes was identical to that of a previous myocardial infarction. The effect of diabetes was not significantly modified by age, smoking, household income, use of thrombolytic therapy, type of hypoglycemic treatment, or duration of diabetes, but the risk associated with diabetes was higher among women than men (adjusted HRs 2.7 vs. 1.3, $P = 0.01$).

CONCLUSIONS — Diabetes is associated with markedly increased mortality after acute myocardial infarction, particularly in women. The increase in risk is of the same magnitude as a previous myocardial infarction and provides further support for aggressive treatment of coronary risk factors among diabetic patients.

Diabetes Care 24:1422–1427, 2001

Compared with individuals without diabetes, diabetic patients have a two- to fourfold increased risk of coronary heart disease (CHD) (1,2). Diabetic patients also have an approximately two-fold higher risk of short-term mortality after acute myocardial infarction (AMI), even after adjustment for the extent of CHD (3). However, in the thrombolytic era, ~90% of diabetic patients will survive beyond the early 30-day period (3). How diabetes affects the long-term prognosis of these early survivors of AMI is less certain.

Some (4–13), but not all (14,15), recent studies have found that diabetes is independently associated with late mortality after hospitalization for AMI. However, these studies were limited to 6- to 12-month follow-up of subjects enrolled in therapeutic trials. They also could not control for behavioral and sociodemographic characteristics that differ between diabetic and nondiabetic patients and may influence mortality, such as alcohol consumption, physical exertion, and educational attainment (16–18).

Investigators have also recently tried to compare the magnitude of risk associated with diabetes with that of other established risk factors for mortality. Two studies have found that diabetes is associated with the same risk of long-term mortality as a prior myocardial infarction, but neither study specifically followed patients with AMI (19,20).

To address these issues, we studied patients enrolled in the Determinants of Myocardial Infarction Onset Study (The Onset Study) (21). This prospective cohort study included chart reviews and personal interviews with patients hospitalized with confirmed AMI.

RESEARCH DESIGN AND METHODS

Onset Study enrollment and data collection

The Onset Study was conducted in 45 medical centers in the U.S. (21). Between August 1989 and September 1994, 1,935 patients (601 women and 1,334 men) were interviewed a median of 4 days after sustaining an AMI. Trained research interviewers identified eligible patients by reviewing coronary care unit admission logs and patient charts. For inclusion, patients were required to have CK-MB

From the [1]Division of General Medicine and Primary Care at the Beth Israel Deaconess Medical Center, Boston, Massachusetts; the [2]Department of Cardiovascular Medicine, Lahey Clinic Medical Center, Burlington, Massachusetts; the [3]Division of Cardiology, Maine Medical Center, Portland, Maine; the [4]Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts; the Departments of [5]Epidemiology and [6]Health and Social Behavior, Harvard School of Public Heath, Boston, Massachusetts; and the [7]Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Address correspondence and reprint requests to Kenneth J. Mukamal, MD, MPH, MA, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, LY-303, Boston, MA 02215. E-mail: kmukamal@caregroup.harvard.edu.

Received for publication 16 January 2001 and accepted in revised form 3 April 2001.

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; HR, hazard ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

isoenzyme levels above the upper limit of normal for each center, an identifiable onset of symptoms of infarction, and the ability to complete a structured interview. The institutional review board of each center approved this protocol, and each patient gave informed consent.

Interviewers used a structured data abstraction and questionnaire form. Information collected from each interview and chart review included patient age, sex, medical history, and medication use (prescription and nonprescription). During the chart review, interviewers recorded complications of congestive heart failure or ventricular tachycardia.

We defined diabetes as a history of diabetes obtained during chart review or the current use of any hypoglycemic medication. When available, we also determined the type of diabetes (type 1 versus type 2) ($n = 381$) and the duration of time from diagnosis of diabetes to onset of AMI ($n = 310$).

We defined aspirin use as the use of aspirin or any aspirin-containing product in the 4 days before the index AMI. We used 1990 U.S. Census data to derive median household income from U.S. Postal Service zip codes (22). We considered patients to have had a previous myocardial infarction if it was noted on either the patient interview or the chart review; the agreement rate between these two sources was 98.6%.

We searched the National Death Index for deaths of Onset Study patients through 31 December 1995 and requested death certificates from state offices of vital records for all probable matches, using a validated algorithm (23). Three physicians independently reviewed each death certificate to verify the match. Two physicians categorized each death as due to cardiovascular or noncardiovascular causes. Disagreements among raters were resolved by discussion. For all analyses, total mortality was the primary end point.

Table 1—*Characteristics of Onset Study patients according to medical history of diabetes*

Diabetes	Yes	No	*P* value*
n	399	1,536	
Age (years)	65 ± 11	61 ± 13	<0.001
Female	164 (41)	437 (28)	<0.001
White race‡	342 (87)	1,394 (92)	0.002
BMI (kg/m^2)§	27.6 ± 5.7	27.1 ± 4.7	0.05
Current smoker‖	81 (21)	556 (37)	<0.001
Former smoker	174 (44)	626 (41)	0.31
Previous myocardial infection¶	153 (39)	393 (26)	<0.001
Angina	128 (32)	363 (24)	<0.001
Hypertension	248 (62)	607 (40)	<0.001
Regular use:			
Aspirin	135 (34)	516 (34)	0.95
Ca blockers#	152 (38)	324 (21)	<0.001
β-blockers	89 (22)	303 (20)	0.26
Angiotensin-converting enzyme inhibitors	77 (19)	152 (10)	<0.001
Thrombolytic therapy	111 (28)	580 (38)	<0.001
Congestive heart failure**	88 (22)	195 (13)	<0.001
Ventricular tachycardia††	35 (9)	203 (13)	0.02
Q-wave infarction‡‡	111 (52)	483 (57)	0.17
Regular exertion§§	46 (12)	311 (20)	<0.001
Alcohol abstention‖‖	358 (90)	1,083 (71)	<0.001
Education¶¶			0.05
Less than high school	105 (27)	351 (24)	
Completed high school	172 (44)	603 (41)	
Some college	115 (29)	531 (36)	
Income ($)##	36,905 ± 12,432	38,686 ± 13,268	0.02

Data are *n* (%) or means ± SD. **P* values for binary and continuous variables derive from exact tests and analysis of variance, respectively; ‡race was missing for 22 patients; §the BMI was missing for 22 patients; ‖smoking status was missing for 20 patients; ¶previous myocardial infarction was missing for 14 patients; #Ca blockers indicates calcium channel blockers; **congestive heart failure during the index hospitalization; ††ventricular tachycardia during the index hospitalization; ‡‡electrocardiographic interpretations were available for 1,045 patients; §§regular exertion was defined as exertion ≥6 metabolic equivalents at least once per week; ‖‖alcohol use was missing for five patients; ¶¶educational attainment was missing for 58 patients; ##household income was derived from zip codes according to 1990 U.S. Census Bureau data and was missing for 56 patients.

Statistical analysis

We analyzed continuous and binary variables using Student's *t* tests and exact tests, respectively. We compared unadjusted Kaplan-Meier survival plots using the log-rank test. We used Cox proportional hazards models to examine the effect of diabetes on survival after adjustment for potentially confounding factors. The factors we included were age, sex, previous myocardial infarction, angina, hypertension, medication use before hospitalization (aspirin, β-adrenergic antagonists, calcium-channel blockers, and angiotensin-converting enzyme inhibitors), current smoking, previous smoking, BMI, use of thrombolytic therapy, usual frequency of exertion (in three categories), alcohol consumption (in three categories), household income (in quartiles), education (in three categories), and complications of congestive heart failure or ventricular tachycardia during hospitalization. In the smaller treatment-specific models, we adjusted for age, sex, smoking status, BMI, previous myocardial infarction, angina, use of angiotensin-converting enzyme inhibitors, use of thrombolytic therapy, alcohol abstention, usual frequency of exertion, and congestive heart failure; results from the complete sample were essentially identical when the truncated model was used.

Patients with missing information on household income ($n = 56$) or educational attainment ($n = 58$) were assigned indicator variables. For all other covariates, patients missing a specific variable (≤22 patients for any variable) were assigned mean levels of continuous covariates and modal levels of binary covariates. Models that deleted patients with any missing information yielded similar results. We tested the proportionality of hazards using time-varying covariates and found no significant violations. We present hazard ratios (HRs) from Cox models with their 95% CIs. All probability values presented are two-sided.

RESULTS

Patient characteristics

The characteristics of the Onset Study patients have been reported (21) and are shown in Table 1. Diabetic participants were generally older and more likely to be women, obese, sedentary, and abstainers from alcohol. They had more comorbidity and used cardiac medication more frequently. They were less likely to be white or current smokers, and they reported lower educational attainment and median household income. During the index hospitalization, they were more likely to develop congestive heart failure but less likely to develop ventricular tachycardia.

Of the 399 patients with diabetes, 121 took insulin alone, 184 took oral hypoglycemic agents alone, 3 took insulin and oral agents, and 91 took no hypoglycemic medications. For the 381 patients with available information, 49 (13%) had type 1 diabetes and 332 (87%) had type 2 diabetes.

Diabetes and mortality

During a mean follow-up of 3.7 years, 116 (29%) of the diabetic patients died, as compared with 204 (13%) of the nondiabetic patients. The unadjusted HR for total mortality for diabetes was 2.4 (95% CI 1.9–3.0; $P < 0.001$). After controlling for potentially confounding factors, we found an HR of 1.7 (1.3–2.1; $P < 0.001$). Exclusion of deaths within 30 days of the index infarction did not change the results. The association of diabetes with cardiovascular mortality was similar (adjusted HR 1.7, 95% CI 1.3–2.3; $P < 0.001$).

Comparison of diabetes and previous myocardial infarction

The unadjusted HR for total mortality for a previous myocardial infarction was 2.4 (95% CI 1.9–2.9), identical to that for diabetes. Figure 1 shows the comparable effects of diabetes and previous myocardial infarction on estimated survival. Table 2 shows unadjusted and adjusted HRs for total and cardiovascular mortality among patients with diabetes, previous AMI, both diabetes and previous AMI, or neither. In every model, the effect of diabetes was at least as strong as the effect of a previous infarction, and the two conditions seemed to be independently associated with risk of mortality.

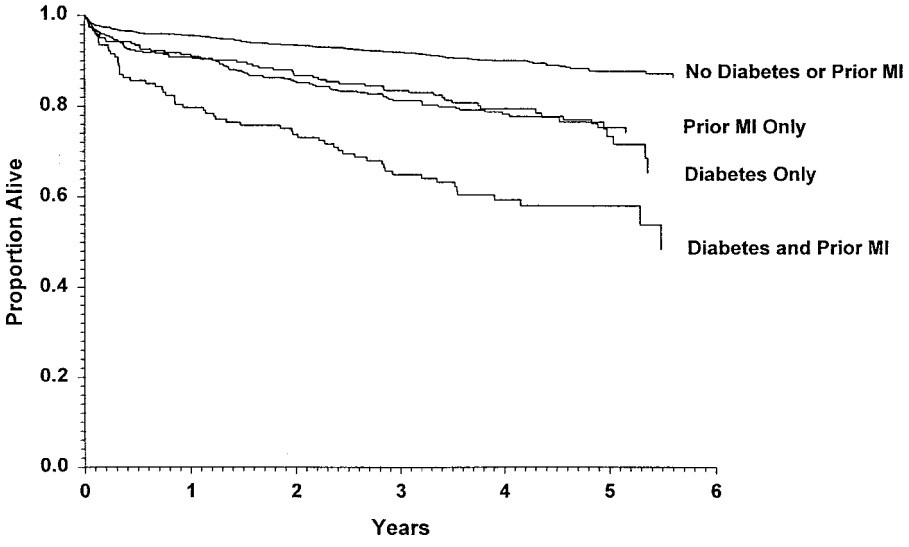

Figure 1—*Kaplan-Meier estimates of survival after AMI according to presence of diabetes and prior myocardial infarction. The curves for patients with only a prior infarction or diabetes were both significantly different from the curves for patients with neither or both conditions (log-rank test for all comparisons,* $P < 0.001$*).*

Effect of diabetes according to selected clinical characteristics

In adjusted analyses, we found a statistically significant interaction between diabetes and sex ($P = 0.01$). The HR for diabetes among women (2.7; 95% CI 1.8–4.2) was approximately twice as high as the HR for diabetes among men (1.3; 1.0–1.8). Among women, the HR for diabetes was actually greater than that for a previous AMI (2.7 vs. 1.4; $P = 0.03$), whereas the HRs for diabetes and previous AMI were comparable in men (1.3 vs. 1.5; $P = 0.59$). In other adjusted analyses, diabetes had a consistent effect on mortality in subgroups defined by age, obesity, thrombolytic therapy, hypertension, smoking, and income (data not shown).

We found that the effect of diabetes was similar regardless of treatment type, even after controlling for confounding factors. Compared with nondiabetic patients, the HR for mortality of diabetic patients was similar among those reporting use of insulin (1.8, 95% CI 1.2–2.6), oral agents (1.5, 1.1–2.1), or neither therapy (1.9, 1.3–2.9) ($P = 0.49$ for comparison across three groups).

Among diabetic patients, the median time period between the diagnosis of diabetes and the index myocardial infarction was 7 years (range 0–65). We found no relationship between the duration of diagnosed diabetes and the risk of long-term mortality (adjusted HR for every 10-year period of diabetes = 1.0, 95% CI 0.8–1.3; $P = 0.82$).

CONCLUSIONS— Among early survivors of AMI, we found that diabetes was associated with nearly twofold higher long-term mortality after infarction. The magnitude of the risk associated with diabetes was similar in magnitude to that associated with a previous myocardial infarction. This association was not substantially altered by treatment type, duration of diabetes, or patient subgroup, but the effect of diabetes was greater in women than men.

In a population-based study, Haffner et al. (19) found that diabetes confers a similar risk of mortality as a previous myocardial infarction, itself a powerful determinant of mortality. The generalizability of that study may have been limited by restriction to Finnish subjects, who have strikingly high rates of type 1 diabetes (24) and coronary mortality, particularly among men (25). Among patients with unstable angina and non–Q-wave infarction, Malmberg et al. (20) found that diabetes and previous vascular disease confer similar risks of mortality, although the authors did not distinguish between patients with and without confirmed infarctions. In confirming the equivalence of diabetes and previous AMI as risk factors for mortality among patients following AMI, we highlight the ad-

Table 2—*HRs for total mortality according to diabetes and previous myocardial infarction among Onset Study participants, with nondiabetic participants with no previous myocardial infarction representing the reference group*

	Nondiabetic first myocardial infarction	Nondiabetic previous myocardial infarction	Diabetic first myocardial infarction	Diabetic previous myocardial infarction
*n**	1,132	393	243	153
Unadjusted	—	2.2 (1.7–2.9)	2.3 (1.7–3.1)	4.6 (3.4–6.3)
Full model†	—	1.5 (1.1–2.0)	1.7 (1.2–2.3)	2.4 (1.7–3.4)
CV mortality‡	—	1.5 (1.1–2.2)	1.8 (1.2–2.6)	2.7 (1.8–4.0)

Data are HR (95% CI). *History of previous infarction was missing for 14 patients; †this model adjusted for age, sex, hypertension, angina, BMI, current smoking, former smoking, educational attainment, race, household income, usual frequency of exertion, abstention from alcohol, use of thrombolytic therapy, use of cardiac medications (aspirin, β-blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors), and congestive heart failure or ventricular tachycardia during hospitalization; ‡CV mortality indicates mortality from cardiovascular causes.

verse prognostic impact of diabetes at all stages of CHD.

Our results generally agree with previous studies of diabetes and long-term mortality after AMI (Table 3). However, none of those studies controlled for potentially important lifestyle characteristics that differ between patients with and without diabetes. For example, Onset Study participants with diabetes were more sedentary, less likely to consume alcohol, lived in lower income areas, and reported lower educational attainment than participants without diabetes (Table 1); all of these factors can influence survival after AMI (8–10). Our results confirm that diabetes is associated with nearly twofold higher long-term mortality among AMI survivors, as suggested by Table 3, even after adjustment for confounding factors.

Our finding that diabetes is associated with a greater risk of long-term mortality among women than men after AMI agrees with other studies of this topic (26,27). Mortality during hospitalization for AMI may not differ between men and women with diabetes (28).

Mechanisms for the adverse prognosis of diabetic patients

As much as diabetes and prior myocardial infarction confer similar risks of mortality after AMI, the mechanisms that mediate the adverse effects of diabetes resemble the detrimental effects of a previous myocardial infarction, particularly related to the left ventricle, as previously described (2,29,30). For many diabetic patients, a silent infarction may have preceded their first recognized AMI, partly related to more extensive coronary atherosclerosis. Diabetic patients may have cardiac autonomic neuropathy, with attendant systolic and diastolic dysfunction. Diabetes leads to exaggerated cardiac fibrosis among patients with hypertensive heart disease. Diabetic individuals have lower left ventricular fractional shortening than nondiabetic individuals. Metabolic derangements of diabetes may cause myocardial dysfunction by depressing adenosine triphosphate production. Finally, patients with diabetes have an increased risk of sudden death, like those with a previous myocardial infarction, in part related to sympathovagal imbalance.

Diabetes may also impair prognosis in ways that do not resemble a previous myocardial infarction. For example, glycosylated end products may generate oxygen free radicals, depleting nitric oxide and impairing vasodilatation. Endothelial dysfunction accompanies diabetes, as do higher left ventricular mass and wall thickness and higher arterial stiffness. Diabetic individuals have impaired fibrinolytic potential, higher platelet aggregability, and higher fibrinogen levels. These hematologic factors can contribute to recurrent infarction, a common and important complication among diabetic individuals.

Study limitations

A possible limitation of our study is inaccuracy in the identification of diabetes.

Table 3—*Effect of diabetes on long-term mortality after acute myocardial infarction in recent studies*

Study	*n* (Diabetic)	Follow-up	RR	Adjusted	Early Deaths	Comments
Sahlgrenska (1993)[15]	858 (97)	1 year	1.6	No	Excluded	Adjusted RR NS
TAMI (1993)[14]	1,071 (148)	~3 years	NS	Yes	Included	
GISSI-2 (1993)[6]	11,667 (1838)	6 months	0.7–7.3	Yes	Excluded	Insulin Rx worse only in women
TIMI-II (1993)[11]	2,173 (294)	3 years	2.25	No	Included	
ITPA/SMT (1993)[5]	8,055 (883)	6 months	1.74	Yes	Excluded	Insulin Rx same as other Rx
MIDAS (1994)[12]	42,595 (9695)	3 years	1.15–1.84	Yes	Excluded	Lower RR with higher age
GUSTO-1 (1997)[4]	41,021 (5944)	1 year	1.6	No	Excluded	Adjusted RR significant; insulin Rx worse than other Rx
SPRINT (1997)[7]	5,839 (624)	10 years	1.32–2.59	Yes	Included	Insulin Rx worse than other Rx
FINMONICA (1998)[9]	4,065 (620)	1 year	1.97/4.17 Men/Women	Yes	Excluded	
ISIS-2 (1998)[13]	17,187 (1289)	10 years	1.55	No	Included	
Augsburg (2000)[18]	2,210 (468)	5 years	1.64	Yes	Excluded	
CCP (2001)[10]	117,599 (36,767)	1 year	1.26–1.48	Yes	Included	Insulin Rx worse than other Rx

Data are *n* unless otherwise indicated. Superscript numbers indicate reference numbers for individual studies. NS, not statistically significant; RR, relative risk; Rx, therapy.

We relied on clinical diagnoses made by treating clinicians in the medical record and may have misclassified patients with unrecognized diabetes. Such misclassification would tend to minimize the effect of diabetes, so the relative risks reported here may be overly conservative.

In this analysis, follow-up was limited to an average of ~3.7 years, and longer follow-up would improve how precisely we can measure the impact of diabetes on long-term mortality. However, this length of follow-up is longer than many previous studies in the thrombolytic era, and inspection of Fig. 1 shows no evidence that the effect of diabetes would change with longer follow-up.

We do not have information on what secondary prevention strategies Onset Study patients received after their index hospitalization. Considering the established benefits of aspirin, statins, and β-blockers for diabetic individuals (31–33), this information could help further clarify the long-term prognosis among patients with diabetes. Nonetheless, our results reflect the usual care of diabetic patients in medical centers across the U.S. in the thrombolytic era.

Our patients were hospitalized before studies confirmed that intensive blood glucose control lowers the risk of AMI and decreases mortality during and after AMI among patients with diabetes (34,35). Therefore, the benefits of strict management of blood glucose were not as apparent during the time period of our study as they are now. Unfortunately, glucose control remains suboptimal throughout the U.S. even today (36).

Given our findings, we believe that attention to the short-term prognosis of diabetic patients after AMI is insufficient. Even after hospitalization, diabetic patients carry an adverse prognosis that fails to narrow over several years. Clinicians should ensure that diabetic patients with AMI receive all recommended secondary prevention measures (37). We also encourage research on specialized primary and secondary prevention strategies for diabetic patients, such as targeted screening for CHD (38) or the preferential use of bypass surgery for revascularization (39). Specialized strategies for the acute treatment of AMI among diabetic patients, such as insulin-glucose infusions, have already shown promise (35).

In summary, diabetes is associated with a nearly twofold higher long-term mortality after AMI among Onset Study participants. This finding is consistent across subgroups, although diabetes carries a particularly ominous prognosis for women. The magnitude of risk associated with diabetes is as large as that associated with a previous myocardial infarction, highlighting the powerful negative impact of diabetes among patients surviving the early phase of AMI.

Acknowledgments— This study was supported by grants from the National Heart, Lung, and Blood Institute (R01HL41016), Bethesda, MD; the National Institute on Alcohol Abuse and Alcoholism (K23AA00299), Bethesda, MD; and the American Heart Association (9630115N), Dallas, TX.

We thank Kate Dwyer, BS, for administrative assistance and Alexander Georgakis, MA, MBA, for determining household income.

References

1. Kannel WB, McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 2:20–26, 1979
2. Jacoby RM, Nesto RW: Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course, and prognosis. *J Am Coll Cardiol* 20:736–744, 1992
3. Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, Deychak Y, Simoons ML, Califf RM, Topol EJ, Ross AM: Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience. *J Am Coll Cardiol* 28:1661–1669, 1996
4. Mak K-H, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox RG, Califf RM, Topol EJ: Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. *J Am Coll Cardiol* 30:171–179, 1997
5. Barbash GI, White HD, Modan M, van de Werf F: Significance of diabetes mellitus in patients with acute myocardial infarction receiving thrombolytic therapy. *J Am Coll Cardiol* 22:707–713, 1993
6. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG: Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. *J Am Coll Cardiol* 22:1788–1794, 1993
7. Behar S, Boyko V, Reicher-Reiss H, Goldbourt U: Ten-year survival after acute myocardial infarction: comparison of patients with and without diabetes. *Am Heart J* 133:290–296, 1997
8. Lowel H, Koenig W, Engel S, Hormann A, Keil U: The impact of diabetes mellitus on survival after myocardial infarction: can it be modified by drug treatment? *Diabetologia* 43:218–226, 2000
9. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilehto J: Impact of diabetes on mortality after the first myocardial infarction. *Diabetes Care* 21:69–75, 1998
10. Berger AK, Breall JA, Gersh BJ, Johnson AE, Oetgen WJ, Marciniak TA, Schulman KA: Effect of diabetes mellitus and insulin use on survival after acute myocardial infarction in the elderly (the Cooperative Cardiovascular Project). *Am J Cardiol* 87: 272–277, 2001
11. Terrin ML, Williams DO, Kleiman NS, Willerson J, Mueller HS, Desvigne-Nickens P, Forman SA, Knatterud GL, Braunwald E: Two- and three-year results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II clinical trial. *J Am Coll Cardiol* 22:1763–1772, 1993
12. Kostis JB, Wilson AC, O'Dowd K, Gregory P, Chelton S, Cosgrove NM, Chirala A, Cui T: Sex differences in the management and long-term outcome of acute myocardial infarction: a statewide study. *Circulation* 90:1715–1730, 1994
13. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R for the ISIS-2 Collaborative Group: ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 316: 1337–1343, 1998
14. Granger CB, Califf RM, Young S, Candela R, Samaha J, Worley S, Kereiakes DJ, Topol EJ: Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. *J Am Coll Cardiol* 22:920–925, 1993
15. Karlson BW, Herlitz J, Hjalmarson A: Prognosis of acute myocardial infarction in diabetic and non-diabetic patients. *Diabet Med* 10:449–454, 1993
16. Muntwyler J, Hennekens CH, Buring JE, Gaziano JM: Mortality and light to moderate alcohol consumption after myocardial infarction. *Lancet* 352:1882–1885, 1998
17. Alter DA, Naylor CD, Austin P, Tu JV: Effects of socioeconomic status on access to invasive cardiac procedures and on mortality after acute myocardial infarction. *N Engl J Med* 341:1359–1367, 1999
18. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA: Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. *JAMA* 260:945–950, 1988
19. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.

N Engl J Med 339:229–234, 1998
20. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A: Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction. *Circulation* 102:1014–1019, 2000
21. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE: Triggering of acute myocardial infarction by heavy physical exertion: protection against triggering by regular exertion. *N Engl J Med* 329:1677–1683, 1993
22. Bureau of the Census: *Census of Population and Housing: Summary Tape File 3* (1990). Washington DC, Bureau of the Census, 1992
23. Rich-Edwards JW, Corsano KA, Stampfer MJ: Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol* 140:1016–1019, 1994
24. Nejentsev S, Koskinen S, Sjoroos M, Reijonen H, Schwartz EI, Kovalchuk L, Sochnev A, Adojaan B, Podar T, Knip M, Simell O, Koskenvuo M, Akerblom HK, Ilonen J: Distribution of insulin-dependent diabetes mellitus (IDDM)-related HLA alleles correlates with the difference in IDDM incidence in four populations of the Eastern Baltic region. *Tissue Antigens* 52:473–477, 1998
25. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P: Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. *Lancet* 353:1547–1557, 1999
26. Abbott RD, Donahue RP, Kannel WB, Wilson PW: The impact of diabetes on survival following myocardial infarction in men vs women: the Framingham Study. *JAMA* 260:3456–3460, 1988
27. Donahue RP, Goldberg RJ, Chen Z, Gore JM, Alpert JS: The influence of sex and diabetes mellitus on survival following acute myocardial infarction: a community-wide perspective. *J Clin Epidemiol* 46: 245–252, 1993
28. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM: Impact of history of diabetes mellitus on hospital mortality in men and women with first acute myocardial infarction. *Am J Cardiol* 85:1486–1489, 2000
29. Nesto RW, Zarich S: Acute myocardial infarction in diabetes mellitus: lessons learned from ACE inhibition. *Circulation* 97:12–15, 1998
30. Aronson D, Rayfield EJ, Chesebro JH: Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. *Ann Intern Med* 15:296–306, 1997
31. ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *JAMA* 268:1292–1300, 1992
32. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. *Circulation* 98:2513–2519, 1998
33. Kjekshus J, Gilpin E, Cali G, Blackey A, Henning H, Ross J: Diabetic patients and beta-blockers after acute myocardial infarction. *Eur Heart J* 11:43–50, 1990
34. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352:837–853, 1998
35. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57–65, 1995
36. Harris MI, Eastman RC, Cowie CC, Flegal K, Eberhardt MS: Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 22:403–408, 1999
37. Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE 3rd, Weaver WD, Gibbons RJ, Alpert JS, Eagle KA, Gardner TJ, Garson A Jr, Gregoratos G, Smith SC Jr: Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations. *Circulation* 100: 1016–1030, 1999
38. Nesto RW: Screening for asymptomatic coronary artery disease in diabetes. *Diabetes Care* 22:1393–1395, 1999
39. Detre KM, Lombardero MS, Brooks MM, Hardison RM, Holubkov R, Sopko G, Frye RL, Chaitman BR: The effect of previous coronary-artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. *N Engl J Med* 342:989–997, 2000