Diabetes and Mortality Following Acute Coronary Syndromes

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THE PRESENCE OF ELEVATED blood glucose levels, diabetes mellitus, or both contributes to more than 3 million cardiovascular deaths worldwide each year.[1] With the increase in obesity, insulin resistance, and the metabolic syndrome, the worldwide prevalence of diabetes is expected to double by the year 2030.[2-4] This burgeoning diabetes epidemic will increase the burden of cardiovascular disease attributable to diabetes.

In the United States, one-third of the population born in 2000 will develop diabetes, with an estimated 30% reduction in life expectancy, mostly related to atherosclerosis.[5,6] More than 1.5 million adults in the United States were newly diagnosed with diabetes in 2005 alone.[7] Nearly 65% of individuals with diabetes die from cardiovascular disease in the United States, establishing it as the leading cause of death among this growing segment of the population.[8]

More than 30 years ago, the Framingham Heart Study followed 239 patients with diabetes and observed a 3-fold increase in age-adjusted cardiovascular

See also Patient Page.

Context The worldwide epidemic of diabetes mellitus is increasing the burden of cardiovascular disease, the leading cause of death among persons with diabetes. The independent effect of diabetes on mortality following acute coronary syndromes (ACS) is uncertain.

Objective To evaluate the influence of diabetes on mortality following ACS using a large database spanning the full spectrum of ACS.

Design, Setting, and Patients A subgroup analysis of patients with diabetes enrolled in randomized clinical trials that evaluated ACS therapies. Patients with ACS in 11 independent Thrombolysis in Myocardial Infarction (TIMI) Study Group clinical trials from 1997 to 2006 were pooled, including 62 036 patients (46 577 with ST-segment elevation myocardial infarction [STEMI] and 15 459 with unstable angina/non-STEMI [UA/NSTEMI]), of whom 10 613 (17.1%) had diabetes. A multivariable model was constructed to adjust for baseline characteristics, aspects of ACS presentation, and treatments for the ACS event.

Main Outcome Measures Mortality at 30 days and 1 year following ACS among patients with diabetes vs patients without diabetes.

Results Mortality at 30 days was significantly higher among patients with diabetes than without diabetes presenting with UA/NSTEMI (2.1% vs 1.1%, $P<.001$) and STEMI (8.5% vs 5.4%, $P<.001$). After adjusting for baseline characteristics and features and management of the ACS event, diabetes was independently associated with higher 30-day mortality after UA/NSTEMI (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.24-2.56) or STEMI (OR, 1.40; 95% CI, 1.24-1.57). Diabetes at presentation with ACS was associated with significantly higher mortality 1 year after UA/NSTEMI (hazard ratio [HR], 1.65; 95% CI, 1.30-2.10) or STEMI (HR, 1.22; 95% CI, 1.08-1.38). By 1 year following ACS, patients with diabetes presenting with UA/NSTEMI had a risk of death that approached patients without diabetes presenting with STEMI (7.2% vs 8.1%).

Conclusion Despite modern therapies for ACS, diabetes confers a significant adverse prognosis, which highlights the importance of aggressive strategies to manage this high-risk population with unstable ischemic heart disease.

JAMA. 2007;298(7):765-775   www.jama.com

mortality.[9] Subsequent studies demonstrated patients with type 2 diabetes without prior myocardial infarction (MI) have a similar risk of death from coronary artery disease as patients without diabetes with prior MI.[10] Diabetes is now considered to be a risk equivalent of coronary artery disease for future MI and cardiovascular death.[11] The acute and

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long-term management of acute coronary syndromes (ACS) does not differ for persons with diabetes, yet previous studies have suggested patients with diabetes have not had a similar reduction in cardiovascular mortality as patients without diabetes despite receiving modern therapies.[12,13]

In addition to being a risk factor for the development of coronary disease, diabetes influences outcomes following ACS. Subgroup analysis of patients with diabetes with ST-segment elevation MI (STEMI) in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial[14] demonstrated significantly higher all-cause mortality at 30 days compared with patients without diabetes (10.5% vs 6.2%). Similarly, the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry[15] of patients with unstable angina/non-STEMI (UA/NSTEMI) observed an increased rate of post-MI complications and mortality among patients with diabetes compared with patients without diabetes (odds ratio [OR], 1.57) during 2 years of follow-up. Both the GUSTO-1 and OASIS studies were conducted more than 10 years ago in a different era of coronary care and before the modern definition of diabetes. Moreover, a large, prospective multinational registry, Global Registry of Acute Coronary Events (GRACE),[16] revealed in-hospital case fatality rates for patients with diabetes with ACS were almost twice as high as those of patients without diabetes. In this same registry, however, diabetes was not a significant risk score predictor of 6-month postdischarge death or MI for patients hospitalized with an ACS.[17,18]

The independent association of diabetes with mortality following ACS in the present era of coronary care remains uncertain. Our study evaluated the independent effect of diabetes on mortality following ACS at 30 days and 1 year from a large clinical trial database spanning the full spectrum of ACS.

METHODS

Patient Population

Patients in our analysis were pooled from 11 independent Thrombolysis in Myocardial Infarction (TIMI) Study Group clinical trials. The methods of each individual trial has been previously reported.[19-29] The number of patients enrolled in each trial, type of ACS evaluated, prespecified duration of follow-up, and randomized interventions are summarized in TABLE 1. Trials were included in the pooled analysis if they began enrollment after 1997 when the American Diabetes Association created the latest guidelines for the diagnosis of diabetes mellitus.[30] Pooled trials also had to be completed by 2006, to collect information on both ACS and diabetes status, and must have included at least 30 days of clinical follow-up (FIGURE 1).[30,31]

This established a cohort of 62 036 patients from 55 countries and more than 900 clinical sites. Each patient gave written informed consent to participate in a clinical trial and none were enrolled in more than 1 TIMI trial. Observations began at trial randomization following the index coronary event and each patient was followed up until cessation of the trial or death.

Definitions

Study participants were classified as having diabetes or not having diabetes by self-report, then stratified by ACS type. Patients who controlled

Table 1. Pooled TIMI Trials

| Trial | Total No. of Patients Enrolled | No. (%) of Patients | | Type of ACS Evaluated | Duration of Follow-up[a] | Intervention |
		With Diabetes	Without Diabetes			
OPUS-TIMI 16[19]	10 267	2164 (21.1)	8103 (78.9)	UA/NSTEMI	10 mo	Oral glycoprotein IIb/IIIa inhibition with orbofiban
InTIME-II-TIMI 17[20]	14 995	2100 (14.0)	12 895 (86.0)	STEMI	30 d	Single bolus lanoteplase vs accelerated alteplase
TACTICS-TIMI 18[21]	2220	613 (27.6)	1607 (72.4)	UA/NSTEMI	6 mo	Early invasive vs conservative strategies in patients treated with the glycoprotein IIb/IIIa inhibitor tirofiban
INTEGRITI-TIMI 20[22]	418	60 (14.4)	358 (85.6)	STEMI	30 d	Combination reperfusion therapy with eptafibitide and reduced-dose tenecteplase
A to Z-TIMI 21[23]	4492	940 (20.9)	3552 (79.1)	Any ACS	6-24 mo	Early intensive vs delayed conservative simvastatin
PROVE-IT-TIMI 22[24]	4160	734 (17.6)	3426 (82.4)	Any ACS	18-36 mo	Intensive vs moderate lipid lowering with statins
ENTIRE-TIMI 23[25]	488	66 (13.5)	422 (86.5)	STEMI	30 d	Enoxaparin as adjuvant antithrombin therapy
FASTER-TIMI 24[26]	409	60 (14.7)	349 (85.3)	STEMI	30 d	Tenecteplase and dose-ranging tirofiban
ExTRACT-TIMI 25[27]	20 249	3060 (15.1)	17 189 (84.9)	STEMI	30 d	Enoxaparin vs unfractionated heparin with fibrinolysis
JUMBO-TIMI 26[28]	903	241 (26.7)	662 (73.3)	Any ACS	30 d	Prasugrel vs clopidogrel in percutaneous coronary intervention
CLARITY-TIMI 28[29]	3435	575 (16.7)	2860 (83.3)	STEMI	30 d	Addition of clopidogrel to aspirin and fibrinolytic therapy
Total	62 036	10 613 (17.1)	51 423 (82.9)			

Abbreviations: ACS, acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UA/NSTEMI, unstable angina/non-STEMI.
[a] Prespecified follow-up in trial protocol.

their diabetes by diet were included. Patients diagnosed with diabetes mellitus after trial enrollment were not considered to have diabetes for purposes of this analysis. Recorded baseline characteristics were age, sex, height, weight, geographic region, and prerandomization medications (aspirin, β-blockers, angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs], and hypolipidemic therapy, mostly statins). Relevant past medical history included smoking, hypertension, known prior hyperlipidemia, previous MI, prior coronary artery bypass graft (CABG) surgery, or heart failure.

The index ACS event was further characterized by systolic blood pressure and heart rate at enrollment, creatinine clearance, location of infarction if STEMI, Killip class, and TIMI risk index. The TIMI risk index is a triage tool to risk stratify patients at presentation with ACS using heart rate, age, and systolic blood pressure, and has been validated in both STEMI and UA/NSTEMI.[32,33] In-hospital treatment included fibrinolytics, glycoprotein IIb/IIIa inhibitors, thienopyridines, aspirin, β-blockers, ACE inhibitors or ARBs, and hypolipidemic therapy, as well as revascularization by percutaneous coronary intervention or CABG surgery. Coronary angiography was performed among a subset of study participants according to individual trial design or at the discretion of the treating physician. Major epicardial coronary arteries were considered diseased if they had 70% or more stenosis. Multivessel disease was defined as 70% or more stenosis in at least 2 major epicardial arteries or 50% or more stenosis of the left main coronary artery. Discharge medications were examined to determine if there were disparities in management between patients with and without diabetes after the ACS event.

Main Outcome Measures

The coprimary outcomes measured were 30-day and 1-year post-ACS mortality. Mortality rates were compared between patients with diabetes and patients without diabetes in all patients with ACS, and then derived separately for patients with UA/NSTEMI and STEMI. After multivariable adjustment, the risk of all-cause mortality based on the presence of diabetes was calculated.

Statistical Methods

All analyses were performed in 3 populations: all patients with ACS, patients with UA/NSTEMI, and patients with STEMI. Mortality rates at 30 days were calculated for patients with and without diabetes and then stratified by baseline characteristics, features of the index ACS event, and ACS management. These groups were compared using the Pearson χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Candidate covariates for entry into the multivariable model were identified by focusing on factors that differed significantly ($P < .05$) in the univariate analyses between patients with and without diabetes. All analyses were performed using Stata version 9.2 (StataCorp LP, College Station, Texas).

Logistic regression was used to construct the 30-day mortality model. The ORs for mortality at 30 days were adjusted for age, sex, region of enrollment, smoking status, history of hypertension, prior MI, congestive heart failure, CABG surgery, heart rate, systolic blood pressure, creatinine clearance, use of aspirin, β-blockers, ACE inhibitors or ARBs, hypolipidemic therapy before randomization, and the administration of aspirin, β-blockers, ACE inhibitors or ARBs, glycoprotein IIb/IIIa inhibitors, thienopyridines, and hypolipidemic therapy during hospitalization for ACS.

A separate multivariable model was generated for 1-year mortality using Cox proportional hazards regression models. At 1 year, the use of aspirin, β-blockers, ACE inhibitors or ARBs, thienopyridines, and hypolipidemic therapy at time of discharge was added

Figure 1. Flow Diagram of the TIMI Diabetes Database
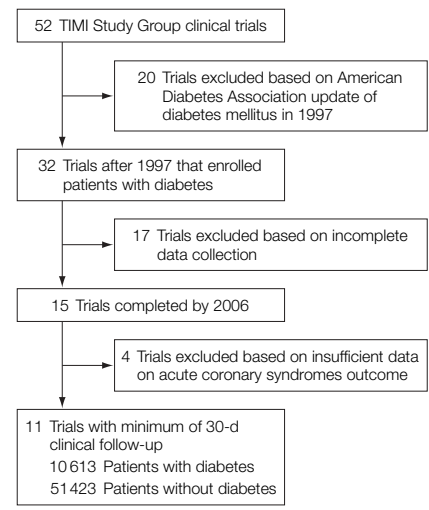
TIMI indicates Thrombolysis in Myocardial Infarction.

into the model. Infarct location and administration of fibrinolytics were also included in the STEMI models. A term was introduced for each individual TIMI trial to account for intertrial variability. These multivariable models had the power to accommodate these variables given the large number of outcome events.[34]

Survival analysis through the first year following ACS was performed using the Kaplan-Meier method. Mortality curves were generated separately for patients with and without diabetes with either STEMI or UA/NSTEMI, and then compared using the log-rank test. An interaction of diabetes on mortality by ACS type was tested at the prespecified time points of 30 days and 1 year following ACS presentation. The numbers at risk are included to indicate the completeness of follow-up through 1 year, which was primarily determined by the individual trial design.

A landmark analysis was performed between 30 days and 1 year. Landmark analysis is a form of survival analysis that classifies patients based on an intermediate event during follow-up, and prognosis is then evaluated from that time point. The

landmark used in our analysis was survival at 30 days to discriminate the early vs longer-term influence of diabetes. Patients who survived 30 days after the index ACS event were evaluated for mortality through 1 year on the basis of diabetes status and type of ACS.

RESULTS

Baseline Characteristics

Of the 62 036 patients in this analysis, 46 577 presented with STEMI and 15 459 with UA/NSTEMI. In total, 10 613 patients (17.1%) had diabetes (Table 1). Baseline characteristics at the time of ACS for patients with and without diabetes are shown in TABLE 2. Consistent with prior observations, patients with diabetes at ACS presentation were older, more often women, had higher body mass index (calculated as weight in kilograms divided by height in meters squared), and were more likely to have a history of hypertension, known hyperlipidemia, MI, CABG surgery, and heart failure compared with patients without diabetes. However, patients with diabetes were less likely to be current smokers. Patients with diabetes had a higher TIMI risk index, especially those patients with STEMI, and were more likely to have heart failure (Killip classes 2-4) at ACS presentation. There was little difference in creatinine clearance between patients with and without diabetes.

The majority of patients with UA/NSTEMI were enrolled in North America whereas the patients with STEMI were predominantly from regions other than North America (Table 2). Furthermore, there was a higher prevalence of diabetes at enrollment in North American sites compared with sites in other regions of the world. Patients with UA/NSTEMI had

Table 2. Baseline Characteristics of Patients With and Without Diabetes and Presenting With UA/NSTEMI or STEMI

	All Patients With ACS			Patients With UA/NSTEMI			Patients With STEMI		
	With Diabetes (n = 10 613)	Without Diabetes (n = 51 423)	P Value	With Diabetes (n = 3457)	Without Diabetes (n = 12 002)	P Value	With Diabetes (n = 7156)	Without Diabetes (n = 39 421)	P Value
Age, median (IQR), y	63 (55-71)	59 (51-69)	<.001	63 (55-70)	60 (52-69)	<.001	63 (55-71)	59 (50-68)	<.001
Age ≥75 y, No./total No. (%)	1373/10 591 (13.0)	5641/51 388 (11.0)	<.001	442/3440 (12.9)	1354/11 974 (11.3)	.01	931/7151 (13.0)	4287/39 414 (10.9)	<.001
Male sex, No. (%)	7073 (66.6)	39 747 (77.3)	<.001	2220 (64.2)	8781 (73.2)	<.001	4853 (67.8)	30 966 (78.6)	<.001
Geographic region, No. (%)									
North America	3504 (33.0)	12 808 (24.9)	<.001	2151 (62.2)	6595 (55.0)	<.001	1353 (18.9)	6213 (15.8)	<.001
Western Eurupe	2950 (27.8)	17 148 (33.4)		560 (16.2)	2859 (23.8)		2390 (33.4)	14 289 (36.3)	
Other[a]	4159 (39.2)	21 467 (41.8)		746 (21.6)	2548 (21.2)		3413 (47.7)	18 919 (48.0)	
BMI, median (IQR)	28.2 (25.4-31.5)	26.6 (24.2-29.4)	<.001	29.7 (26.6-33.3)	27.6 (25.0-30.7)	<.001	27.7 (25.0-30.9)	26.4 (24.2-29.3)	<.001
Current smoker, No./total No. (%)[b]	2970/10 590 (28.1)	23 630/51 321 (46.0)	<.001	734/3450 (21.3)	4228/11 979 (35.3)	<.001	2236/7140 (31.3)	19 402/39 342 (49.3)	<.001
Cardiac history, No./total No. (%)									
Hypertension	6473/10 562 (61.3)	19 644/51 157 (38.4)	<.001	2449/3456 (70.9)	5819/12 001 (48.5)	<.001	4024/7106 (56.6)	13 825/39 156 (35.3)	<.001
Known prior hyperlipidemia	2870/6872 (41.8)	8265/30 545 (27.1)	<.001	1538/2942 (52.3)	4059/9655 (42.0)	<.001	1332/3930 (33.9)	4206/20 890 (20.1)	<.001
Prior MI	2587/10 549 (24.5)	8386/51 267 (16.4)	<.001	1254/3453 (36.3)	3266/11 994 (27.2)	<.001	1333/7096 (18.8)	5120/39 273 (13.0)	<.001
Prior CABG surgery	853/10 612 (8.0)	2104/51 417 (4.1)	<.001	640/3457 (18.5)	1427/12 001 (11.9)	<.001	213/7155 (3.0)	677/39 416 (1.7)	<.001
Prior heart failure	754/10 558 (7.1)	1483/51 304 (2.9)	<.001	371/3452 (10.8)	548/11 996 (4.6)	<.001	383/7106 (5.4)	935/39 308 (2.4)	<.001
TIMI risk index, median (IQR)[c]	21.8 (16.4-28.5)	18.9 (13.7-25.8)	<.001	21.2 (16.4-27.0)	19.2 (14.2-25.5)	<.001	22.2 (16.5-29.2)	18.8 (13.6-26.0)	<.001
Killip classes 2-4, No./total No. (%)[d]	1191/8765 (13.6)	4362/45 362 (9.6)	<.001	209/2088 (10.0)	424/7413 (5.7)	<.001	982/6677 (14.7)	3938/37 949 (10.4)	<.001
Creatinine clearance, median (IQR), mL/min	83.0 (62.9-107.8)	84.7 (65.8-107.6)	<.001	90.4 (68.7-117.9)	90.5 (70.0-115.7)	.62	79.8 (60.7-103.1)	83.2 (64.7-105.5)	<.001

Abbreviations: ACS, acute coronary syndromes; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; STEMI, ST-segment elevation MI; UA/NSTEMI, unstable angina/non-STEMI.
SI conversion factor: To convert creatinine clearance to mL/s, multiply by 0.0167.
[a] Other includes Argentina, Australia, Belarus, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Croatia, Czech Republic, Estonia, Hong Kong, Hungary, India, Israel, Jordan, Korea, Latvia, Lebanon, Lithuania, Malaysia, New Zealand, Poland, Romania, Russia, South Africa, Singapore, Slovakia, Slovenia, Taiwan, Thailand, Turkey, Ukraine, Uruguay, and Venezuela.
[b] Current smokers are patients self-identified as currently smoking tobacco, irrespective of length of smoking history or number of packs per day.
[c] The range of scores for TIMI risk index for all patients with ACS are 3.3 to 107.5 for patients with diabetes and 1.6 to 131.2 for patients without diabetes; for patients with UA/NSTEMI, 4.0 to 80.8 with diabetes and 1.7 to 120.1 without diabetes; and for patients with STEMI, 3.3 to 107.5 with diabetes and 1.6 to 131.2 without diabetes.
[d] Killip class is a grading system of heart failure at ACS. Class 1 is defined as the absence of rales over the lung fields and the absence of an S3; class 2, the presence of rales, does not clear with coughing, over one-half or less of the lung fields or the presence of an S3; class 3, the presence of rales, does not clear with coughing, over more than half the lung fields; and class 4, cardiogenic shock.

diabetes more often than those presenting with STEMI (22.4% vs 15.4%, $P<.001$). The UA/NSTEMI population also had significantly more comorbid conditions than the STEMI population, including an increased prevalence of hypertension, known hyperlipidemia, prior MI, and a history of heart failure.

Therapies for ACS

Medical therapies prerandomization, in-hospital, and at discharge along with revascularization rates during the index hospitalization for both patients with and without diabetes are shown in TABLE 3. When compared with patients without diabetes prerandomization, patients with diabetes were treated more frequently with proven risk-modifying therapies, including aspirin (37.2% vs 24.8%, $P<.001$), β-blockers (29.2% vs 22.1%, $P<.001$), ACE inhibitors or ARBs (35.1% vs 17.7%, $P<.001$), and hypolipidemic therapy (18.8% vs 10.9%, $P<.001$). When stratified by a history of previous MI, percutaneous coronary inter-

Table 3. Medical Therapies Prerandomization, In-hospital, and at Discharge in Patients With and Without Diabetes Presenting With UA/NSTEMI or STEMI

	All ACS			UA/NSTEMI			STEMI		
	No./Total No. (%) of Patients			No./Total No. (%) of Patients			No./Total No. (%) of Patients		
	With Diabetes (n = 10 613)	Without Diabetes (n = 51 423)	P Value	With Diabetes (n = 3457)	Without Diabetes (n = 12 002)	P Value	With Diabetes (n = 7156)	Without Diabetes (n = 39 421)	P Value
Prerandomization medications									
Aspirin	3949/10 605 (37.2)	12 741/51 391 (24.8)	<.001	2007/3454 (58.1)	5687/11 985 (47.5)	<.001	1942/7151 (27.2)	7054/39 406 (17.9)	<.001
β-Blockers	3101/10 608 (29.2)	11 371/51 399 (22.1)	<.001	1411/3456 (40.8)	4787/11 990 (39.9)	.34	1690/7152 (23.6)	6584/39 409 (16.7)	<.001
ACE inhibitor or ARBs	3725/10 606 (35.1)	9075/51 369 (17.7)	<.001	1344/3455 (38.9)	2849/11 965 (23.8)	<.001	2381/7151 (33.3)	6226/39 404 (15.8)	<.001
Hypolipidemic therapy	1998/10 604 (18.8)	5600/51 392 (10.9)	<.001	935/3451 (27.1)	2293/11 985 (19.1)	<.001	1063/7153 (14.9)	3307/39 407 (8.4)	<.001
In-hospital medical therapy									
Aspirin	10 382/10 612 (97.8)	50 581/51 421 (98.4)	<.001	3298/3456 (95.4)	11 547/12 001 (96.2)	.04	7084/7156 (99.0)	39 034/39 420 (99.0)	.83
Thienopyridine	2770/9666 (28.7)	13 213/47 833 (27.6)	.04	806/2965 (27.2)	2884/9779 (29.5)	.02	1964/6701 (29.3)	10 329/38 054 (27.1)	<.001
β-Blockers	8075/10 610 (76.1)	41 121/51 410 (80.0)	<.001	2520/3456 (72.9)	9027/12 000 (75.2)	.006	5555/7154 (77.7)	32 094/39 410 (81.4)	<.001
ACE inhibitor or ARBs	6978/10 606 (65.8)	29 540/51 385 (57.5)	<.001	1864/3453 (54.0)	4519/11 986 (37.7)	<.001	5114/7153 (71.5)	25 021/39 399 (63.5)	<.001
Hypolipidemic therapy	6292/10 610 (59.3)	29 268/51 403 (56.9)	<.001	2129/3457 (61.6)	7470/12 002 (62.2)	.49	4163/7153 (58.2)	21 798/39 401 (55.3)	<.001
Glycoprotein IIb/IIIa inhibitor	3204/10 611 (30.2)	12 501/51 394 (24.3)	<.001	2114/3457 (61.2)	6954/11 996 (58.0)	.001	1090/7154 (15.2)	5547/39 398 (14.1)	.01
Fibrinolytic	6224/9996 (62.3)	35 301/49 797 (70.9)	<.001	0/2841 (0)	6/10 381 (0.1)	.35	6224/7155 (87.0)	35 295/39 416 (89.5)	<.001
In-hospital procedures									
Revascularization	3230/10 608 (30.5)	14 199/51 412 (27.6)	<.001	1232/3457 (35.6)	3955/12 002 (33.0)	.003	1998/7151 (27.9)	10 244/39 410 (26.0)	.001
Percutaneous coronary intervention	2677/10 611 (25.2)	12 440/51 420 (24.2)	.02	925/3457 (26.8)	3197/12 002 (26.6)	.89	1752/7154 (24.5)	9243/39 418 (23.5)	.056
CABG surgery	585/10 610 (5.5)	1860/51 415 (3.6)	<.001	320/3457 (9.3)	797/12 002 (6.6)	<.001	265/7153 (3.7)	1063/39 413 (2.7)	<.001
Discharge medications									
Aspirin	9488/10 511 (90.3)	46 783/50 898 (91.9)	<.001	3103/3455 (89.8)	10 981/11 985 (91.6)	.001	6385/7056 (90.5)	35 802/38 913 (92.0)	<.001
Thienopyridine	2270/7509 (30.2)	10 675/34 608 (30.9)	.30	742/2965 (25.0)	2699/9779 (27.6)	.006	1528/4544 (33.6)	7976/24 829 (32.1)	.046
β-Blockers	5559/8503 (65.4)	27 125/38 487 (70.5)	<.001	1991/3451 (57.7)	7094/11 968 (59.3)	.10	3568/5052 (70.6)	20 031/26 519 (75.5)	<.001
ACE inhibitor or ARBs	5283/8503 (62.1)	21 732/38 487 (56.5)	<.001	1700/3451 (49.3)	4160/11 968 (34.8)	<.001	3583/5052 (70.9)	17 572/26 519 (66.3)	<.001
Hypolipidemic therapy	5406/8508 (63.5)	24 514/38 508 (63.7)	.84	2049/3453 (59.3)	7261/11 987 (60.6)	.19	3357/5055 (66.4)	17 253/26 521 (65.1)	.06

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; ARBs, angiotensin II receptor blockers; CABG, coronary artery bypass graft; STEMI, ST-segment elevation myocardial infarction; UA/NSTEMI, unstable angina/non-STEMI.

vention, or CABG surgery, there were higher rates of prior ischemic heart disease in patients with diabetes and presenting with UA/NSTEMI, likely explaining the disparities in medication use before randomization (data available upon request). Also, patients with diabetes presenting with UA/NSTEMI were more frequently taking insulin than those patients who presented with STEMI (26.8% vs 19.3%, $P<.001$).

While hospitalized for ACS, patients with diabetes received β-blockers less frequently (76.1% vs 80.0%, $P<.001$), but received ACE inhibitors or ARBs more frequently (65.8% vs 57.5%, $P<.001$). Patients with diabetes were more likely to undergo revascularization procedures during index hospitalization than patients without diabetes irrespective of presentation (for UA/NSTEMI, 35.6% vs 33.0%; $P=.003$; and for STEMI, 27.9% vs 26.0%; $P=.001$). The higher revascularization rate among patients with diabetes was a consequence of more frequent CABG surgery following ACS.

Extent of Coronary Artery Disease

Coronary angiography data from the index ACS hospitalization were available for 15 574 patients (25.1%). Among this subset, patients with diabetes were more likely to have multivessel coronary disease than patients without diabetes (62.0% vs 48.1%, $P<.001$) (TABLE 4). More multivessel coronary disease was present among patients with diabetes compared with patients without diabetes presenting with UA/NSTEMI (65.9% vs 50.8%, $P<.001$) or STEMI (56.5% vs 45.4%, $P<.001$). There was a corresponding tendency for angiography among patients without diabetes to reveal either no obstructive disease or only single-vessel disease.

Mortality at 30 Days

Mortality was significantly higher among patients with diabetes than among patients without diabetes at 30 days following either UA/NSTEMI (2.1% vs 1.1%, $P<.001$) or STEMI (8.5% vs 5.4%, $P<.001$) (TABLE 5).

The unadjusted 30-day mortality risk for patients with diabetes was consistently higher than for patients without diabetes across key subgroups in the UA/NSTEMI and STEMI cohorts (FIGURE 2). Patients older than 75 years, with Killip classes 2-4, decreased creatinine clearance, and increased TIMI risk index had the highest absolute mortality at 30 days regardless of whether they had STEMI or UA/NSTEMI. There was no significant interaction between diabetes status and type of ACS at 30 days. There was also no significant difference in 30-day mortality between patients with diabetes taking insulin and those not taking insulin before ACS among both STEMI (7.8% vs 8.7%, $P=.26$) and UA/NSTEMI (2.4% vs 1.8%, $P=.31$) cohorts.

After multivariable modeling, the independent risk conferred by diabetes at 30 days among patients with UA/NSTEMI was higher (OR, 1.78; 95% confidence interval [CI], 1.24-2.56)

Table 4. Angiographic Data in Patients With and Without Diabetes Presenting With UA/NSTEMI or STEMI

	All ACS			UA/NSTEMI			STEMI		
	No. (%) of Patients			No. (%) of Patients			No. (%) of Patients		
	With Diabetes (n = 3006)	Without Diabetes (n = 12 568)	P Value	With Diabetes (n = 1755)	Without Diabetes (n = 6221)	P Value	With Diabetes (n = 1251)	Without Diabetes (n = 6347)	P Value
No obstructive disease	166 (5.5)	996 (7.9)	<.001	120 (6.8)	663 (10.7)	<.001	46 (3.7)	333 (5.3)	.02
Single-vessel disease	976 (32.5)	5531 (44.0)	<.001	478 (27.2)	2397 (38.5)	<.001	498 (39.8)	3134 (49.4)	<.001
Multivessel disease	1864 (62.0)	6041 (48.1)	<.001	1157 (65.9)	3161 (50.8)	<.001	707 (56.5)	2880 (45.4)	<.001

Abbreviations: ACS, acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; UA/NSTEMI, unstable angina/non-STEMI.

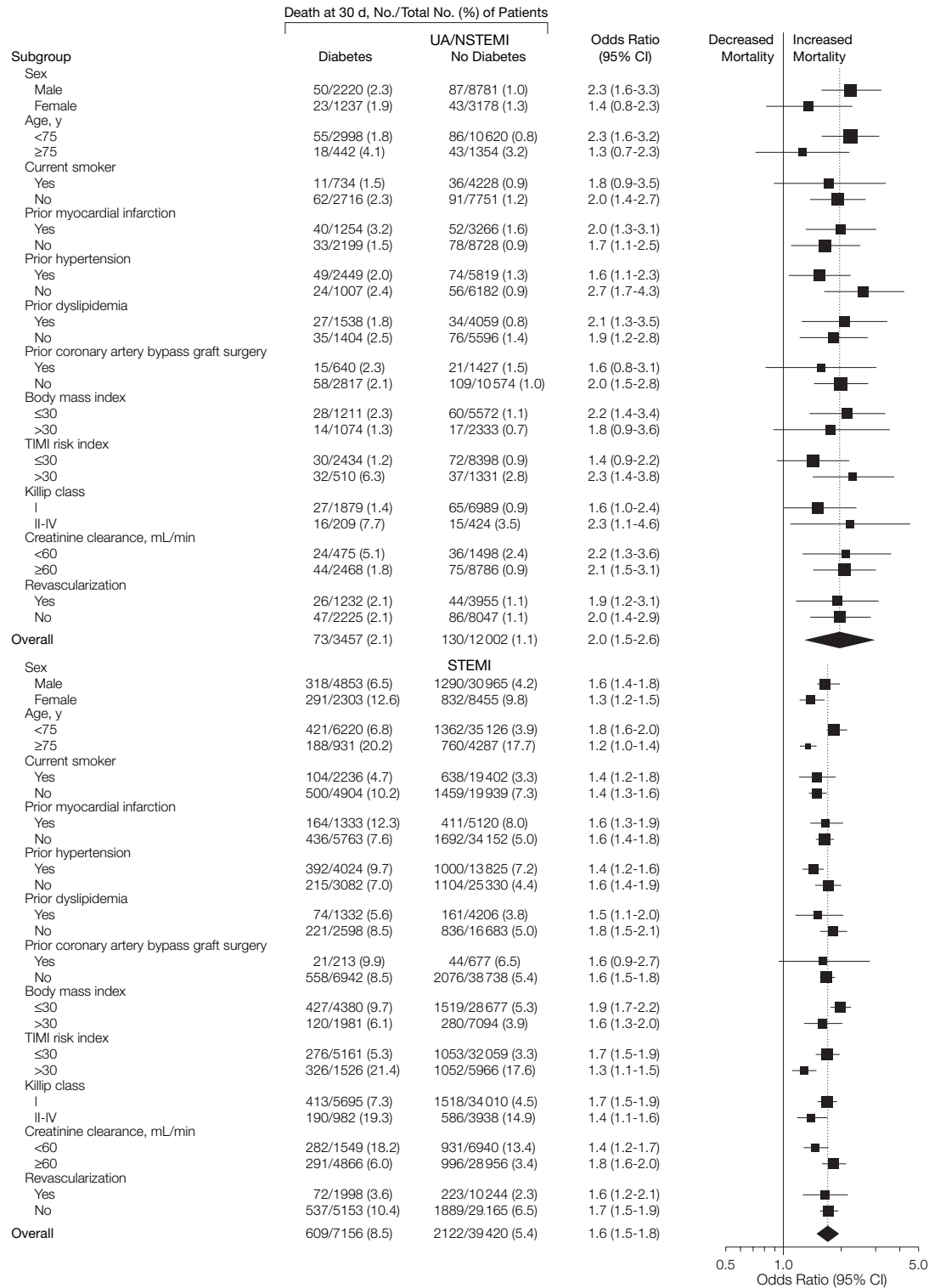**Table 5.** The Risk of Death Attributable to Diabetes Following ACS

	Mortality at 30 Days			Mortality at 1 Year[a]		
	No./Total No. (%) of Patients			Patients, %		
	With Diabetes	Without Diabetes	Adjusted OR (95% CI)[b]	With Diabetes	Without Diabetes	Adjusted HR (95% CI)[c]
UA/NSTEMI	73/3457 (2.1)	130/12 002 (1.1)	1.78 (1.24-2.56)	7.2	3.1	1.65 (1.30-2.10)
STEMI	609/7156 (8.5)	2122/39 421 (5.4)	1.40 (1.24-1.57)	13.2	8.1	1.22 (1.08-1.38)
All ACS	682/10 613 (6.4)	2252/51 423 (4.4)	1.40 (1.26-1.56)	11.2	6.8	1.33 (1.20-1.48)

Abbreviations: ACS, acute coronary syndromes; CI, confidence interval; HR, hazard ratio; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction; UA/NSTEMI, unstable angina/non-STEMI.
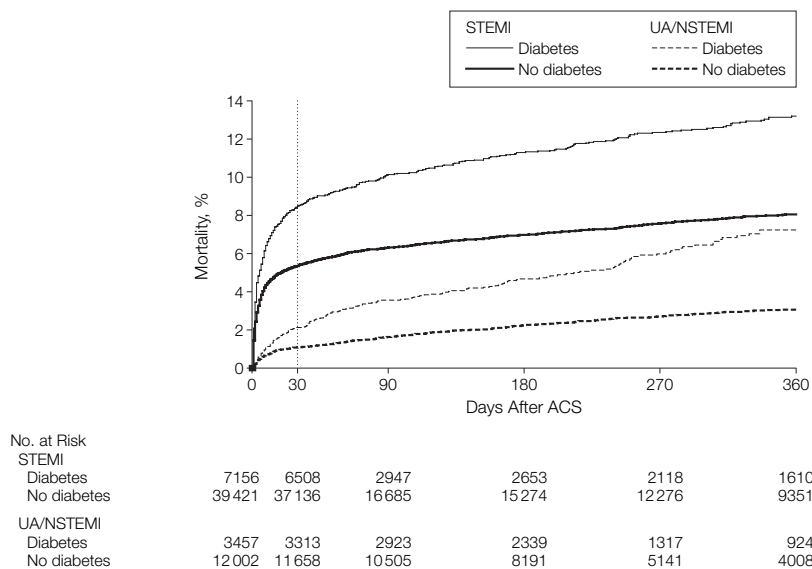[a] Reported as Kaplan-Meier event rates at 12 months (360 days).
[b] Adjusted for age, sex, region of enrollment, smoking status, history of hypertension, prior myocardial infarction, congestive heart failure, coronary artery bypass graft surgery, systolic blood pressure, heart rate, creatinine clearance at enrollment, use of aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), hypolipidemic therapy before randomization, and the administration of aspirin, β-blockers, ACE inhibitors or ARBs, glycoprotein IIb/IIIa inhibitors, thienopyridines, and hypolipidemic therapy during hospitalization for ACS. Infarct location and administration of thrombolytics were also included in the STEMI model.
[c] Aspirin, β-blockers, ACE inhibitors or ARBs, thienopyridines, and hypolipidemic therapy at time of discharge were added into the model.

Figure 2. Unadjusted Odds of Mortality at 30 Days After Acute Coronary Syndromes in UA/NSTEMI and STEMI

Subgroup	Death at 30 d, No./Total No. (%) of Patients		Odds Ratio (95% CI)
	UA/NSTEMI Diabetes	No Diabetes	
Sex			
Male	50/2220 (2.3)	87/8781 (1.0)	2.3 (1.6-3.3)
Female	23/1237 (1.9)	43/3178 (1.3)	1.4 (0.8-2.3)
Age, y			
<75	55/2998 (1.8)	86/10 620 (0.8)	2.3 (1.6-3.2)
≥75	18/442 (4.1)	43/1354 (3.2)	1.3 (0.7-2.3)
Current smoker			
Yes	11/734 (1.5)	36/4228 (0.9)	1.8 (0.9-3.5)
No	62/2716 (2.3)	91/7751 (1.2)	2.0 (1.4-2.7)
Prior myocardial infarction			
Yes	40/1254 (3.2)	52/3266 (1.6)	2.0 (1.3-3.1)
No	33/2199 (1.5)	78/8728 (0.9)	1.7 (1.1-2.5)
Prior hypertension			
Yes	49/2449 (2.0)	74/5819 (1.3)	1.6 (1.1-2.3)
No	24/1007 (2.4)	56/6182 (0.9)	2.7 (1.7-4.3)
Prior dyslipidemia			
Yes	27/1538 (1.8)	34/4059 (0.8)	2.1 (1.3-3.5)
No	35/1404 (2.5)	76/5596 (1.4)	1.9 (1.2-2.8)
Prior coronary artery bypass graft surgery			
Yes	15/640 (2.3)	21/1427 (1.5)	1.6 (0.8-3.1)
No	58/2817 (2.1)	109/10 574 (1.0)	2.0 (1.5-2.8)
Body mass index			
≤30	28/1211 (2.3)	60/5572 (1.1)	2.2 (1.4-3.4)
>30	14/1074 (1.3)	17/2333 (0.7)	1.8 (0.9-3.6)
TIMI risk index			
≤30	30/2434 (1.2)	72/8398 (0.9)	1.4 (0.9-2.2)
>30	32/510 (6.3)	37/1331 (2.8)	2.3 (1.4-3.8)
Killip class			
I	27/1879 (1.4)	65/6989 (0.9)	1.6 (1.0-2.4)
II-IV	16/209 (7.7)	15/424 (3.5)	2.3 (1.1-4.6)
Creatinine clearance, mL/min			
<60	24/475 (5.1)	36/1498 (2.4)	2.2 (1.3-3.6)
≥60	44/2468 (1.8)	75/8786 (0.9)	2.1 (1.5-3.1)
Revascularization			
Yes	26/1232 (2.1)	44/3955 (1.1)	1.9 (1.2-3.1)
No	47/2225 (2.1)	86/8047 (1.1)	2.0 (1.4-2.9)
Overall	73/3457 (2.1)	130/12 002 (1.1)	2.0 (1.5-2.6)
Sex	STEMI		
Male	318/4853 (6.5)	1290/30 965 (4.2)	1.6 (1.4-1.8)
Female	291/2303 (12.6)	832/8455 (9.8)	1.3 (1.2-1.5)
Age, y			
<75	421/6220 (6.8)	1362/35 126 (3.9)	1.8 (1.6-2.0)
≥75	188/931 (20.2)	760/4287 (17.7)	1.2 (1.0-1.4)
Current smoker			
Yes	104/2236 (4.7)	638/19 402 (3.3)	1.4 (1.2-1.8)
No	500/4904 (10.2)	1459/19 939 (7.3)	1.4 (1.3-1.6)
Prior myocardial infarction			
Yes	164/1333 (12.3)	411/5120 (8.0)	1.6 (1.3-1.9)
No	436/5763 (7.6)	1692/34 152 (5.0)	1.6 (1.4-1.8)
Prior hypertension			
Yes	392/4024 (9.7)	1000/13 825 (7.2)	1.4 (1.2-1.6)
No	215/3082 (7.0)	1104/25 330 (4.4)	1.6 (1.4-1.9)
Prior dyslipidemia			
Yes	74/1332 (5.6)	161/4206 (3.8)	1.5 (1.1-2.0)
No	221/2598 (8.5)	836/16 683 (5.0)	1.8 (1.5-2.1)
Prior coronary artery bypass graft surgery			
Yes	21/213 (9.9)	44/677 (6.5)	1.6 (0.9-2.7)
No	558/6942 (8.5)	2076/38 738 (5.4)	1.6 (1.5-1.8)
Body mass index			
≤30	427/4380 (9.7)	1519/28 677 (5.3)	1.9 (1.7-2.2)
>30	120/1981 (6.1)	280/7094 (3.9)	1.6 (1.3-2.0)
TIMI risk index			
≤30	276/5161 (5.3)	1053/32 059 (3.3)	1.7 (1.5-1.9)
>30	326/1526 (21.4)	1052/5966 (17.6)	1.3 (1.1-1.5)
Killip class			
I	413/5695 (7.3)	1518/34 010 (4.5)	1.7 (1.5-1.9)
II-IV	190/982 (19.3)	586/3938 (14.9)	1.4 (1.1-1.6)
Creatinine clearance, mL/min			
<60	282/1549 (18.2)	931/6940 (13.4)	1.4 (1.2-1.7)
≥60	291/4866 (6.0)	996/28 956 (3.4)	1.8 (1.6-2.0)
Revascularization			
Yes	72/1998 (3.6)	223/10 244 (2.3)	1.6 (1.2-2.1)
No	537/5153 (10.4)	1889/29.165 (6.5)	1.7 (1.5-1.9)
Overall	609/7156 (8.5)	2122/39 420 (5.4)	1.6 (1.5-1.8)

Odds Ratio (95% CI) — Decreased Mortality / Increased Mortality — 0.5 1.0 5.0

STEMI indicates ST-segment elevation myocardial infarction; UA/NSTEMI, unstable angina/non-STEMI; CI, confidence interval. The overall unadjusted odds of death associated with diabetes is shown by the diamond (edges represent upper and lower 95% CIs) and the dotted vertical line. For each subgroup, the square is proportional to the number of patients and represents a point estimate of mortality risk conferred by diabetes, with the horizontal lines representing 95% CIs.

Figure 3. Cumulative Incidence of All-Cause Mortality Through 1 Year After ACS

No. at Risk						
STEMI						
Diabetes	7156	6508	2947	2653	2118	1610
No diabetes	39 421	37 136	16 685	15 274	12 276	9351
UA/NSTEMI						
Diabetes	3457	3313	2923	2339	1317	924
No diabetes	12 002	11 658	10 505	8191	5141	4008

ACS indicates acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; UA/NSTEMI, unstable angina/non-STEMI. Vertical dotted line represents 30 days after ACS. Patients with diabetes are at higher risk of death at 30 days following either UA/NSTEMI (2.1% vs 1.1%, $P<.001$) or STEMI (8.5% vs 5.4%, $P<.001$). By 1 year after ACS, the cumulative mortality in patients with diabetes vs without diabetes was higher in UA/NSTEMI (7.2% vs 3.1%, $P<.001$) and STEMI (13.2% vs 8.1%, $P<.001$), and accrues at a higher rate in patients with diabetes than in patients without diabetes. The relative increase in mortality for the patients with diabetes following UA/NSTEMI exceeds that of STEMI ($P=.004$ for interaction between diabetes status and ACS stratum).

than among patients with STEMI (OR, 1.40; 95% CI, 1.24-1.57) (Table 5). Results were similar with the inclusion of body mass index, Killip class, known prior hyperlipidemia, or a term for the individual trial interventions in the model.

Mortality at 1 Year

Mortality at 1 year was significantly higher among patients with diabetes than in patients without diabetes presenting with UA/NSTEMI (7.2% vs 3.1%, $P<.001$) or STEMI (13.2% vs 8.1%, $P<.001$) (**FIGURE 3**). The unadjusted risk of death at 1 year associated with diabetes among patients presenting with UA/NSTEMI was higher (hazard ratio [HR], 2.24; 95% CI, 1.86-2.70; $P<.001$) than among patients presenting with STEMI (HR, 1.64; 95% CI, 1.51-1.78; $P<.001$), with a significant interaction between diabetes and ACS type on mortality ($P=.004$) (Figure 3).

There was an early mortality risk associated with STEMI among both pa-

tients with and without diabetes. However, mortality during the first year following ACS accrued at a higher rate among patients with diabetes and presenting with UA/NSTEMI than with STEMI. In a landmark analysis between 30 days and 1 year, there was an interaction between diabetes status and ACS type on mortality ($P=.049$). By 1 year following ACS, patients with diabetes and presenting with UA/NSTEMI had a mortality that approached patients without diabetes and presenting with STEMI (7.2% vs 8.1%).

At 1 year, diabetes remained a significant independent factor associated with all-cause mortality for patients presenting with UA/NSTEMI (HR, 1.65; 95% CI, 1.30-2.10) and for patients presenting with STEMI (HR, 1.22; 95% CI, 1.08-1.38) (Table 5).

COMMENT

Our analysis demonstrates a statistically robust association between dia-

betes at time of presentation with ACS and all-cause mortality at 30 days and at 1 year, even after adjusting for baseline characteristics as well as features and management of the index event. Despite advances in the treatment of ACS, the magnitude of excess mortality among patients with diabetes was considerable and observed among all of the major subgroups within both the UA/NSTEMI and STEMI populations.

Diabetes had an even greater adverse impact on long-term mortality following UA/NSTEMI than STEMI. The burden of cardiovascular risk inherent among the patients presenting with UA/NSTEMI marked the index ACS presentation as a sentinel event in a chronic, progressive course that was more accelerated among patients with diabetes. By 1 year, the mortality of patients with diabetes presenting with UA/NSTEMI approached that of patients without diabetes presenting with STEMI. As demonstrated in our study, the UA/NSTEMI population is enriched with this high-risk diabetic population.

Our study was systematically conducted from prospectively collected data within the context of a randomized clinical trial. We analyzed patients from centers throughout the world implementing modern therapies across the full spectrum of ACS. Our findings extend prior observations on the adverse effect of diabetes on STEMI from the GUSTO-1 data and from the OASIS registry of patients with UA/NSTEMI. The GRACE multinational registry also demonstrated diabetes at ACS to be a significant contributor to in-hospital and 6-month out-of-hospital mortality. Diabetes did not meet criteria for inclusion in the GRACE risk prediction tool, which excluded in-hospital mortality and was by necessity simplified to maintain its utility.[18]

Diabetes status, however, was included in the TIMI risk scores for both UA/NSTEMI and STEMI.[35,36] Neither score attempted to quantify the independent impact of diabetes at the ini-

tial presentation with ACS. By pooling these 11 TIMI trials with a large cumulative number of outcome events, we had the statistical power to determine the independent effect of diabetes on all-cause mortality.

Therapeutic Implications

The magnitude of risk conferred by diabetes following ACS demands a major research effort to reduce the influence of diabetes on coronary artery disease.[37] Reducing coronary risk from diabetes requires a multifactorial approach to manage all atherogenic influences.[38] Long-term, targeted, intensive use of proven therapies for the traditional coronary risk factors must be widely promoted for patients with diabetes, particularly following ACS. As with lipids levels, more stringent targets for patients with diabetes may be better all around.

In the United States, a reduction in coronary deaths has been observed during the past 2 decades from the prevention and modification of high blood pressure, high cholesterol, and tobacco use. But these gains have been partially offset by the increased burden of cardiovascular disease attributable to diabetes.[39] There must be ongoing reevaluation of traditional guidelines for diabetes management to further mitigate this critical, independent risk factor.[40,41] Collaboration between medical societies, national health care organizations, and industry will be vital to halt the epidemic of diabetes-related cardiovascular disease.[42,43]

Novel targets for diabetes management in patients with coronary artery disease must be identified and tested. For example, glucagon-like peptide-1 receptor agonists reduce both fasting and postprandial glucose concentrations and may even improve myocardial function following an acute MI, as demonstrated in a small, nonrandomized pilot study.[44] Such agents are worthy of investigation in large, longitudinal clinical trials to assess their efficacy on cardiovascular end points.

An important ongoing clinical trial, Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D),[45] will study whether insulin replacement or an insulin-sensitizing agent will improve mortality following ACS among patients with diabetes. This study will also compare medical management and revascularization in patients with diabetes with multivessel coronary artery disease. Meanwhile, the FREEDOM trial will provide data to guide the choice between percutaneous coronary intervention and CABG surgery among patients with diabetes requiring revascularization.[46]

Study Limitations

Our analysis has several limitations. The database merged several clinical trials and intertrial variability in care could have influenced patient enrollment, administered therapies, and outcome. We focused on a subgroup of patients with diabetes that was not prespecified at the individual trial design. Fasting glucose measurements were not universally collected, so our study was unable to evaluate the subgroup of patients who had previously unrecognized diabetes, which might have been discovered during the qualifying presentation.[47] It is also possible that each site enrolling patients had adopted varying diagnostic guidelines for diabetes.[48] These factors, along with diabetes definition by self-report, could bias the risk assessment of diabetes to the null. We were unable to assess the type and duration of diabetes, features of diabetes management, and degree of glycemic control. Measurement of glycated hemoglobin, serial blood glucoses during ACS, or insulin resistance may identify a gradient of risk among patients with diabetes with coronary artery disease.[49,50] Cause of death data was not available for each patient so it was impossible to determine whether reinfarction, stroke, cardiovascular death, or noncardiovascular death was driving mortality in the first year following ACS.

CONCLUSION

Despite modern therapies for ACS, diabetes conferred a significant independent excess mortality risk at 30 days and 1 year following ACS. Current strategies are insufficient to ameliorate the adverse impact of diabetes. Given the increasing burden of cardiovascular disease attributable to diabetes worldwide, our study highlights the need for a major research effort to identify aggressive new strategies to manage unstable ischemic heart disease among this high-risk population.

ance at many steps along the way. The genesis of the TIMI diabetes database and preliminary analysis would not have been possible without the efforts of Amy Shui, MA, of the TIMI Data Coordinating Center. We also thank Jie Qin, MS, at the TIMI Data Coordinating Center for her help with the statistical analysis. No additional financial compensation was provided to the acknowledged individuals for their participation in this project.

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The public thinks it strange to hear physicians speak of the fascination that accompanies the study of our art. Literature, painting, and music do not yield an enjoyment more keen than that which is afforded by the study of medicine, and whoever does not find in it, from the commencement of his career, an almost irresistible attraction, ought to renounce the intention of following our profession.

—Armand Trousseau (1801-1867)