Association of Elevated Fasting Glucose With Increased Short-term and 6-Month Mortality in ST-Segment Elevation and Non–ST-Segment Elevation Acute Coronary Syndromes

The Global Registry of Acute Coronary Events

Peter R. Sinnaeve, MD, PhD; P. Gabriel Steg, MD; Keith A. A. Fox, MB, ChB, FRCP; Frans Van de Werf, MD, PhD; Gilles Montalescot, MD, PhD; Christopher B. Granger, MD; Elias Knobel, MD; Frederick A. Anderson, PhD; Omar H. Dabbous, PhD; Álvaro Avezum, MD, PhD; for the GRACE Investigators

Background: Elevated blood glucose level at admission is associated with worse outcome after a myocardial infarction. The impact of elevated glucose level, particularly fasting glucose, is less certain in non–ST-segment elevation acute coronary syndromes. We studied the relationship between elevated fasting blood glucose levels and outcome across the spectrum of ST-segment elevation and non–ST-segment elevation acute coronary syndromes in a large multicenter population broadly representative of clinical practice.

Methods: Fasting glucose levels were available for 13 526 patients in the Global Registry of Acute Coronary Events. A multivariate logistic regression analysis was used for assessing the association between admission or fasting glucose level and in-hospital or 6-month outcome, adjusted for the variables from the registry risk scores.

Results: Higher fasting glucose levels were associated with a graded increase in the risk of in-hospital death (odds ratios [95% confidence intervals] vs <100 mg/dL: 1.51 [1.12-2.04] for 100-125 mg/dL, 2.20 [1.64-2.60] for 126-199 mg/dL, 5.11 [3.52-7.43] for 200-299 mg/dL, and 8.00 [4.76-13.5] for ≥300 mg/dL). When taken as a continuous variable, higher fasting glucose level was related to a higher probability of in-hospital death, without detectable threshold and irrespective of whether patients had a history of diabetes mellitus. Higher fasting glucose levels were found to be associated with a higher risk of postdischarge death up to 6 months. The risk of postdischarge death at 6 months was significantly higher with fasting glucose levels between 126 and 199 mg/dL (1.71 [1.25-2.34]) and 300 mg/dL or greater (2.93 [1.33-6.43]), but not within the 200- to 299-mg/dL range (1.08 [0.60-1.95]).

Conclusions: Short-term and 6-month mortality was increased significantly with higher fasting glucose levels in patients across the spectrum of acute coronary syndromes, thus extending this relation to patients with non–ST-segment elevation myocardial infarction. The relation between fasting glucose level and risk of adverse short-term outcomes is graded across different glucose levels with no detectable threshold for diabetic or nondiabetic patients.

Arch Intern Med. 2009;169(4):402-409

ELEVATED BLOOD GLUCOSE level at admission for myocardial infarction is associated with worse outcome in both nondiabetic and diabetic patients.[1-5] A high glucose level at admission is often attributed to "stress hyperglycemia" and might reflect an acute response to the hyperadrenergic state. The impact of fasting glucose level, as an indicator of glucometabolic state, has been less well studied in the setting of acute coronary syndromes (ACSs) but also appears to be a marker of adverse outcome after ST-segment elevation myocardial infarction (STEMI).[6-8] The role of elevated fasting glucose level in non–ST-segment elevation ACSs is even less clear; to date, only 1 single-center study observed a higher incidence of adverse cardiac events in patients with a "prediabetic" state presenting with either non–ST-segment elevation or ST-segment elevation ACSs, compared with nondiabetic patients.[9]

The respective contributions of admission and fasting glucose level to predicting outcome in ACSs remain uncertain as well.[10] A study in 735 nondiabetic patients with acute myocardial infarction showed a graded relation between admission and fasting glucose levels and 30-day mortality.[11] After adjustment for other risk

Author Affiliations are listed at the end of this article.
Group Information: The Global Registry of Acute Coronary Events (GRACE) Investigators are listed at the end of this article.

factors, only fasting glucose level appeared to be a robust and independent marker of short-term mortality. Two studies in STEMI suggest that failure of elevated nonfasting glucose levels to decrease is especially associated with worse outcome.[12,13]

The aim of the present analysis was to examine whether elevated admission and fasting blood glucose levels are independently associated with higher in-hospital and 6-month total mortality in patients presenting with an ST-segment elevation ACS, and whether a relation between elevated admission or fasting glucose level and outcome is also present in patients with non–ST-segment elevation ACSs included in the Global Registry of Acute Coronary Events (GRACE). This database allows evaluation of these relationships for the first time across the spectrum of ST-segment elevation and non–ST-segment elevation ACSs in a large multicenter population broadly representative of clinical practice and with adjustment using a well-validated risk-assessment tool.

METHODS

Full details of the GRACE methods have been published.[14-16] The GRACE was designed to reflect an unbiased population of patients with ACSs, irrespective of geographic region. A total of 113 hospitals located in 14 countries in North and South America, Europe, Australia, and New Zealand have contributed data to this observational study.

Adult patients (≥18 years old) admitted with a presumptive diagnosis of an ACS at participating hospitals were potentially eligible for this study. Eligibility criteria were a clinical history of ACS accompanied by at least 1 of the following: electrocardiographic changes consistent with ACSs, serial increases in biochemical markers of cardiac necrosis (creatine kinase MB, creatine phosphokinase, or troponin), and documented coronary artery disease. Patients with noncardiovascular causes for the clinical presentation, such as trauma, surgery, or aortic aneurysm, were excluded. Patients were followed up at approximately 6 months by telephone, clinic visits, or calls to their primary care physician to ascertain the occurrence of several long-term outcomes.

To enroll an unselected population of patients with ACSs, sites were encouraged to recruit the first 10 to 20 consecutive eligible patients each month. Regular audits were performed at all participating hospitals. Data were collected by trained coordinators using standardized case report forms. Demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables, clinical diagnoses, and hospital complications and outcomes were used. All cases were assigned to 1 of the following categories: STEMI, non-STEMI (NSTEMI), or unstable angina.

Patients were diagnosed as having STEMI when they had new or presumed new ST-segment elevation of 1 mm or more seen in any location, or new left bundle-branch block on the index or subsequent electrocardiogram with at least 1 positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, at least 1 positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or subsequent electrocardiogram had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in each hospital's laboratory were within the normal range. Full definitions can be found on the GRACE Web site at http://www.outcomes.org/grace.

Admission glucose levels were recorded at initial presentation. If the patient was referred from another acute care facility to a GRACE hospital, the initial glucose level at the referring hospital was used. For fasting glucose levels, the first documented fasting glucose level at any time during hospitalization at the registry hospital was used. Per protocol, fasting glucose levels were not recorded unless documentation was available that the blood was drawn in the fasting state.

For statistical analysis, we expressed categorical variables as frequencies and percentages and continuous variables as medians and interquartile ranges. Differences in demographics, clinical characteristics, and outcomes between the glycemia groups were assessed by χ^2 tests for categorical variables and Wilcoxon rank sum or Kruskal-Wallis tests for continuous variables where appropriate. Primary outcomes in the current analyses were in-hospital all-cause mortality and all-cause mortality occurring up to 6 months after hospital discharge. Patients were categorized according to glucose levels into 5 mutually exclusive groups (<100, 100-125, 126-199, 200-299, and ≥300 mg/dL [to convert glucose to millimoles per liter, multiply by 0.0555]). A multivariate logistic regression analysis was used for assessing the association between admission or fasting glucose level and in-hospital or 6-month postdischarge outcome, adjusted for the variables from the GRACE risk scores (age, history of myocardial infarction or congestive heart failure, pulse, systolic blood pressure, serum creatinine level, cardiac marker elevation, ST-segment depression, and absence of in-hospital percutaneous coronary intervention)[16] as well as country and medical treatment to control glycemia (ie, either oral antidiabetic drugs or insulin) in patients discharged after the initial hospitalization. The time to death in diabetic and nondiabetic patients according to fasting glucose levels was analyzed by means of Kaplan-Meier curves and compared by the log-rank test. All statistical tests were 2 sided and considered statistically significant at $\alpha < .05$. The statistical analysis was performed with SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 57 406 patients enrolled in the GRACE from April 1, 1999, to December 31, 2005, from 106 hospitals in 14 countries, admission and fasting glucose levels were available for 22 001 and 13 526 patients, respectively. Of the latter, 5507 patients (40.7%) had normal fasting glucose levels (<100 mg/dL), whereas 4268 (31.5%) had impaired fasting glucose levels (100-125 mg/dL) and 3751 patients (27.8%) had a level of 126 mg/dL or higher.

Baseline characteristics, medical history, and diagnosis at presentation of the patient cohort according to fasting glucose level are given in **Table 1**. Groups with higher fasting glucose levels included more female patients, patients in higher Killip classes, and more patients with a history of hypertension, previous stroke or transient ischemic attack, or peripheral artery disease. Only 60.3% of patients with a fasting glucose level of 126 mg/dL or higher were previously diagnosed as having diabetes. Conversely, 12.4% and 20.2% of patients with glucose levels less than 100 mg/dL and in the range from 100 to 125 mg/dL, respectively, had a history of diabetes. Pharmacologic antidiabetic treatment at discharge was prescribed to 41.2% of patients with a fasting glucose level between 126 and 199 mg/dL vs 65.7% and 61.7% of patients in the 200- to 299-mg/dL and 300 mg or greater groups, respectively (**Table 2**).

Table 1. Baseline Characteristics According to Fasting Glucose Levels[a]

Characteristic	Fasting Glucose, mg/dL				
	<100 (n=5507)	100-125 (n=4268)	126-199 (n=2862)	200-299 (n=707)	≥300 (n=182)
Age, y	65 (54-75)	67 (56-76)	68 (58-77)	66 (56-75)	66 (57-78)
Sex, % F	31.5	31.8	37.3	39.5	43.4
Weight, kg	75 (65-85)	78 (68-88)	79 (69-90)	81 (71-92)	79 (65-88)
Systolic blood pressure, mm Hg	140 (120-160)	140 (120-160)	141 (120-161)	143 (124-165)	140 (118-160)
Killip class, %					
I	86.9	83.2	78.1	76	66.9
II	10.3	13.0	14.9	16	19.3
III	2.4	3.1	5.6	6.9	11
IV	0.4	0.7	1.5	1.1	2.8
History, %					
MI	28.8	27.6	30.3	34	30.8
Diabetes mellitus	12.4	20.2	54.3	80	72.5
Stroke or TIA	7.6	6.8	10.2	10	11.0
Hypertension	58.6	63.0	71.3	72	65.9
PAD	8.4	8.9	10.7	12	15.4
Renal insufficiency	6.3	6.9	9.6	13	13.2
Initial creatinine level, mg/dL	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.9-1.3)	1.0 (0.9-1.4)	1.0 (0.9-1.4)
Clinical presentation, %					
STEMI	34.9	42.5	43.6	42	38.5
NSTEMI	33.3	33.6	34.7	33	36.7
Unstable angina	31.8	24.0	21.7	25	24.7
Initial markers positive	43.1	48.4	52.4	54	52.7
In-hospital markers positive	68.2	76.0	78.3	75	75.3
ST-segment deviation at admission	53.6	58.0	61.6	58	64.8

Abbreviations: MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.
SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; creatinine to micromoles per liter, multiply by 88.4.
[a]Data are given as median (interquartile range) unless otherwise specified.

Table 2. Long-term Treatments, In-Hospital Management, and Discharge Therapy

Treatment	Fasting Glucose, mg/dL				
	<100 (n=5507)	100-125 (n=4268)	126-199 (n=2862)	200-299 (n=707)	≥300 (n=182)
Long-term therapy, %					
Aspirin	37.8	37.9	40.2	39.0	37.4
β-Blocker	32.3	32.5	35.9	32.9	32.4
ACE inhibitor	27.8	28.2	33.0	36.8	35.7
Statin	26.9	28.2	31.4	31.0	31.9
Thienopyridine	8.2	8.9	8.9	8.9	7.7
In-hospital management, %					
Aspirin	93.8	93.5	93.7	92.6	88.4
Unfractionated heparin	39.4	46.5	46.9	47.2	41.2
Low-molecular-weight heparin	62.8	61.6	63.3	60.0	54.4
Cardiac catheterization	67.8	69.0	66.7	62.9	54.9
Percutaneous coronary intervention	43.5	46.6	43.6	41.0	36.8
Coronary artery bypass graft	4.7	6.0	7.0	6.6	2.2
Discharge medication, %					
Aspirin	93.2	92.8	92.3	90.6	92.1
Thienopyridine	58.0	61.7	59.0	54.6	49.9
β-Blocker	82.1	85.1	81.8	84.2	81.4
ACE inhibitor	65.7	68.8	71.1	71.8	72.7
Statin	78.8	82.0	81.1	79.8	79.2
Warfarin	6.9	6.2	9.0	7.8	5.8
Insulin	3.2	4.9	19.7	40.2	40.9
Oral antidiabetic agents	4.8	8.1	25.0	29.6	23.6
Any antidiabetic treatment	7.9	12.9	41.2	65.7	61.7

Abbreviation: ACE, angiotensin-converting enzyme.
SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

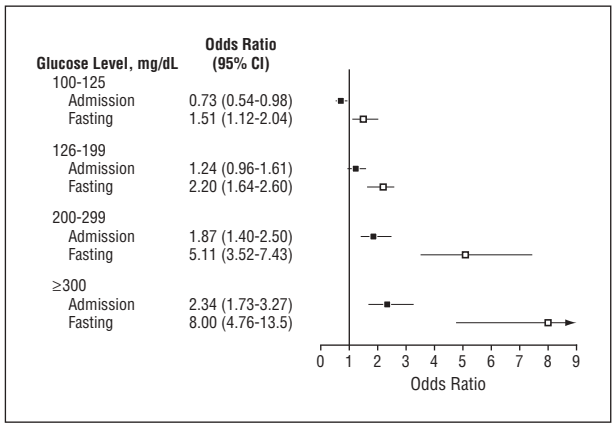

Figure 1. Odds ratios of in-hospital mortality by admission and fasting glucose levels (vs glucose level <100 mg/dL; to convert glucose to millimoles per liter, multiply by 0.0555). Odds ratios are adjusted for risk model and country. Horizontal lines indicate 95% confidence intervals (CIs).

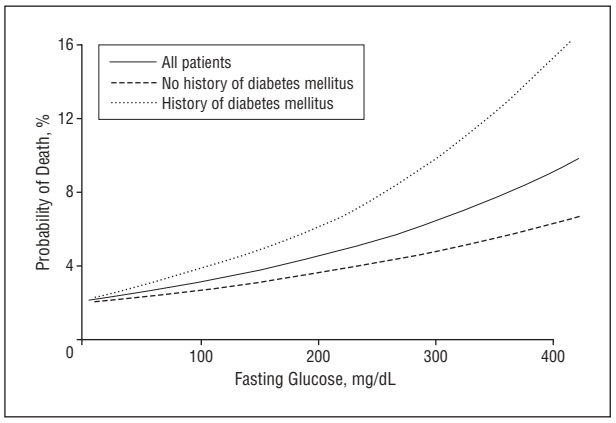

Figure 2. Probability of in-hospital death according to fasting glucose level and history of diabetes mellitus. To convert glucose to millimoles per liter, multiply by 0.0555.

Long-term therapies and in-hospital and discharge management are listed in Table 2. Long-term therapy before admission was not different among the different glycemia groups except for more frequent use of angiotensin-converting enzyme inhibitors in patients with worse glycemia, perhaps reflecting the higher incidence of hypertension or known diabetes in these groups. In-hospital management and discharge therapies, except for antidiabetic treatments, were similar across the groups.

IN-HOSPITAL OUTCOME

Above levels of 125 mg/dL, increasing glucose levels at admission were associated with increased risk of in-hospital death (**Figure 1**). After adjustment for the GRACE risk score and country of origin, in-hospital mortality was more than 2-fold higher in patients with admission glucose level greater than 300 mg/dL compared with those with normoglycemia. Admission glucose levels in the range of 100 to 125 mg/dL, however, were associated with a significantly lower risk of in-hospital death than that in patients with an admission glucose level less than 100 mg/dL.

In contrast, patients with a fasting glucose level between 100 and 125 mg/dL had a 51% higher risk of in-hospital death than patients with normoglycemia (Figure 1). The risk of in-hospital mortality increased dramatically in the higher glycemia groups; mortality was more than 8-fold higher in patients with a fasting glucose level of 300 mg/dL or greater than in those with normoglycemia. When taken as a continuous variable, increasing fasting glucose level was related to a higher probability of in-hospital death, without detectable threshold and irrespective of whether patients had a history of diabetes mellitus (**Figure 2**). Nevertheless, the risk of in-hospital death was higher for patients with a history of diabetes than for those without known diabetes. The increased risk for patients with diabetes in our regression curves appears to be irrespective of fasting glucose level, although raw mortality rates per group (**Table 3**) indicate that this relation is probably mainly driven by a higher risk associated with low or very high fasting glucose levels.

Table 3 and **Figure 3** demonstrate in-hospital mortality and events per increase in admission glucose or fasting glucose level across the glycemia groups. Death, congestive heart failure, and cardiogenic shock increased gradually with increasing glucose levels. This relation was remarkably similar for admission and fasting glucose levels and was consistent among the 3 types of presentation. Major bleeding complications also tended to increase with higher admission or fasting glucose levels. Stroke was uncommon, and its incidence did not differ among the 5 groups (0.7%, 0.8%, 0.6%, 1.0%, and 0.6% from lowest to highest glucose levels, respectively).

POSTDISCHARGE 6-MONTH OUTCOME

Mortality between discharge and 6 months increased according to admission or fasting glucose group, irrespective of type of ACS (Table 3). After adjustment for the GRACE risk model, country, and antidiabetic treatment at discharge, however, increasing admission glucose levels were not associated with a higher risk of death up to 6 months after discharge, irrespective of type of ACS at presentation (**Figure 4**A). In contrast, increasing fasting glucose levels during hospitalization were found to be associated with a higher risk of postdischarge death up to 6 months after presentation (Figure 4B). This association was consistent for STEMI and NSTEMI but less clear for patients with unstable angina, and it appeared to be nonlinear across the fasting glucose groups. The risk of postdischarge death at 6 months was significantly higher with fasting glucose levels between 126 and 199 mg/dL and 300 mg/dL or greater, but not within the range of 200 to 299 mg/dL.

Figure 5 shows mortality curves from admission up to 6 months for patients with known diabetes and for those without known diabetes. Patients with elevated fasting glucose levels below the diabetic threshold of 126 mg/dL (ie, prediabetes) had a lower risk of dying, whereas nondiabetic patients with fasting glucose levels above this threshold, including those within the 200- to 299-mg/dL range, had a higher risk of dying after an ACS than did patients with previously diagnosed diabetes.

Table 3. In-Hospital and Postdischarge Mortality Rates

	Admission or Fasting Glucose, mg/dL				
	<100 (n=5507)	100-125 (n=4268)	126-199 (n=2862)	200-299 (n=707)	≥300 (n=182)
By Admission Glucose Level					
In-hospital death, %					
All	2.39	2.09	4.57	8.85	13.26[a]
STEMI	4.69	3.13	5.75	13.62	16.09[a]
NSTEMI	2.74	2.07	4.54	6.24	10.83[a]
Unstable angina	0.96	0.95	1.87	3.74	10.40[a]
Diabetes	4.97	5.63	4.30	6.60	11.55[a]
No diabetes	2.11	1.90	4.57	13.39	21.55[a]
6-mo Postdischarge death, %					
All	4.72	4.37	6.01	6.56	7.76[a]
STEMI	5.49	4.29	5.78	5.71	8.17
NSTEMI	6.70	6.03	8.39	9.14	8.45[b]
Unstable angina	2.69	2.34	2.63	3.15	3.77
Diabetes	6.72	6.36	7.20	6.43	8.21
No diabetes	3.94	3.86	4.66	7.84	5.60
By Fasting Glucose Level					
In-hospital death, %					
All	1.71	3.03	5.74	9.49	17.22[a]
STEMI	2.30	3.93	8.49	14.67	26.09[a]
NSTEMI	2.13	3.09	4.95	7.73	16.42[a]
Unstable angina	0.63	1.37	1.45	2.89	4.55[c]
Diabetes	3.08	4.53	4.18	7.95	17.42[a]
No diabetes	1.52	2.63	7.56	10.55	16.00[a]
6-mo Postdischarge death, %					
All	3.40	4.71	6.86	5.28	8.74[a]
STEMI	2.87	3.98	8.42	4.55	16.67[a]
NSTEMI	4.66	7.14	7.93	7.14	7.89[b]
Unstable angina	2.56	2.28	2.17	3.77	. . .
Diabetes	5.77	6.54	7.32	6.36	11.57[a]
No diabetes	3.20	4.45	7.41	6.66	4.00

Abbreviations: NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ellipses, not calculated because there were too few patients in this category for a mortality rate to be relevant.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] $P<.001$.

[b] $P<.05$.

[c] $P<.01$.

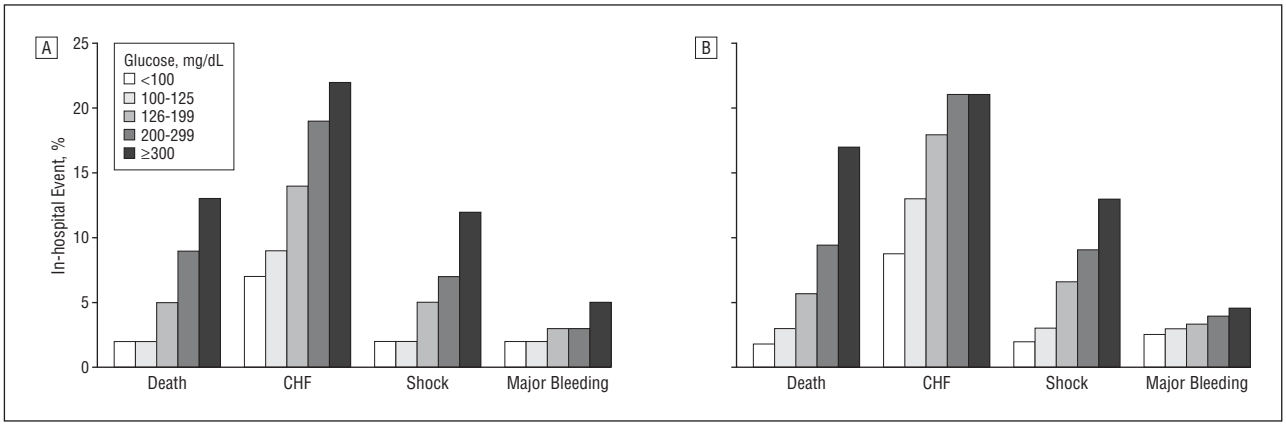

Figure 3. In-hospital outcomes according to admission (A) and fasting (B) glucose levels. To convert glucose to millimoles per liter, multiply by 0.0555. CHF indicates congestive heart failure.

COMMENT

Elevated fasting glucose level is associated with worse outcome after a myocardial infarction.[6,8,11] This analysis from a large multinational observational registry indicates that in-hospital mortality increased significantly with higher fasting glucose levels in patients across the spectrum of ACSs, thus extending this relation to patients with NSTEMI and unstable angina as well. Similarly, 6-month postdischarge mortality also increased significantly with

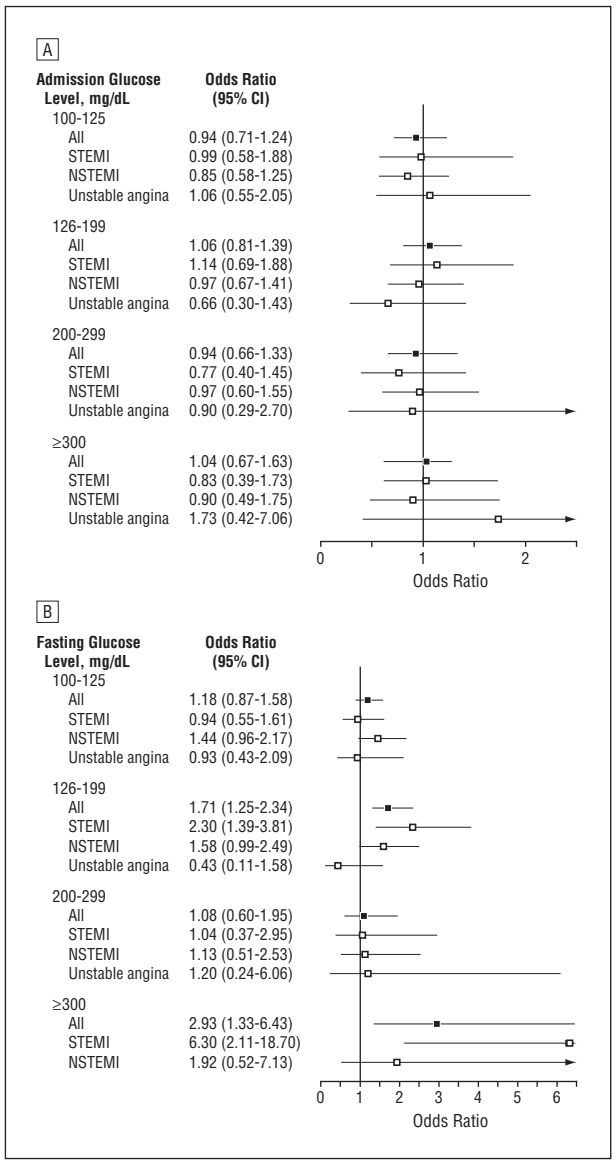

Figure 4. Odds of postdischarge death up to 6 months according to admission (A) and fasting (B) glucose levels and diagnosis at presentation (vs glucose level <100 mg/dL; to convert glucose to millimoles per liter, multiply by 0.0555). Odds ratios are adjusted for risk model, country, and antidiabetic treatment at discharge. No events occurred in patients with unstable angina who had fasting glucose levels of 300 mg or greater. NSTEMI indicates non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. Horizontal lines indicate 95% confidence intervals (CIs).

higher fasting glucose levels in patients with STEMI or NSTEMI, although this relation was less clear in patients with unstable angina. We also observed that heart failure, shock, and bleeding are more common with higher glucose levels. The data from this large and unselected population show that the relation between fasting glucose level and risk of adverse short-term outcomes is graded across different glucose levels with no detectable threshold for diabetic or nondiabetic patients. In contrast, after adjustment for the GRACE risk model and antidiabetic treatment at discharge, the risk of postdischarge death at 6 months was increased only in hospitalization survivors with a fasting glucose level between 126 and 199 mg/dL or 300 mg/dL or greater. The reason for this

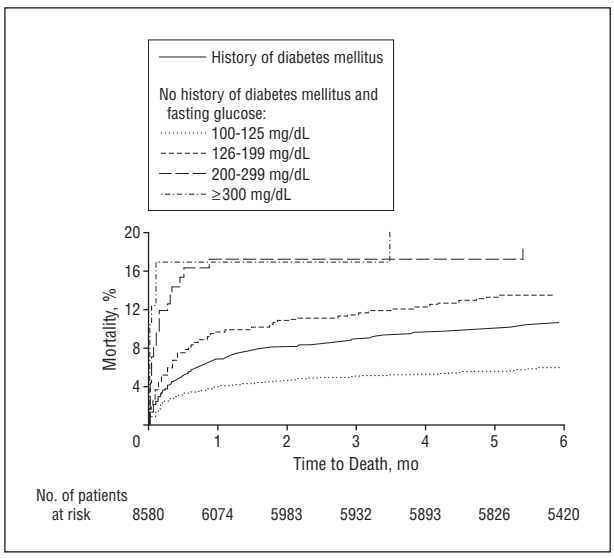

Figure 5. Kaplan-Meier curves for death up to 6 months according to fasting glucose levels and history of diabetes mellitus. To convert glucose to millimoles per liter, multiply by 0.0555.

nonlinear relationship remains unclear. Although this explanation is speculative, nondiabetic patients with a sufficiently high fasting glucose level (ie, >200 mg/dL) might have had more chance of an appropriate diagnosis and treatment at discharge, in contrast to patients with only mildly elevated fasting glucose levels.

A fasting glucose level of 126 mg/dL or greater is diagnostic of type 2 diabetes mellitus, while a fasting glucose level between 100 and 125 mg/dL indicates impaired fasting glucose level or prediabetes.[17] Applying these criteria to the patients in this study, the present data suggest a high prevalence of previously undiagnosed diabetes among patients presenting with an ACS. Similarly, a Swedish prospective study demonstrated that one-third of patients without previously diagnosed diabetes who were admitted for a myocardial infarction had diabetes.[7] Of note, the relationship between elevated fasting glucose levels and adverse outcome after discharge appeared to be more powerful in patients without a history of diabetes in our analysis, although the risk of in-hospital mortality was higher in patients with known diabetes irrespective of their fasting glucose level. Also, using fasting glucose level alone, our study probably underestimated the number of individuals with impaired glucose tolerance or diabetes.

Confirming previous reports,[3,5,12,18-25] we found that elevated admission glucose levels were associated with adverse short-term outcome. In contrast to fasting glucose level, admission glucose level was not predictive of 6-month postdischarge outcome after adjustment for the GRACE risk model. A similar relation between admission glucose level and short-term but not 6-month outcome has been observed in nondiabetic patients hospitalized for heart failure.[26] Our results suggest that the association between elevated admission glucose level and long-term outcome in previous reports is probably mainly driven by an increased risk of early death, consistent with the paradigm that admission glucose level is a marker of stress rather than a reflection of a general glucometa-

bolic state. Furthermore, patients with admission glucose levels within the 100- to 126-mg/dL range had a lower risk of in-hospital death than did those with levels below 100 mg/dL, after adjustment for the GRACE risk model. The U-shaped curve of risk associated with admission glucose level in this broad population of patients with ACSs is consistent with previous reports of adverse outcome associated with low admission blood glucose levels in patients presenting with an acute myocardial infarction and in diabetic patients with an ACS.[3,13,23] Of note, the significantly lower risk of in-hospital death with an admission glucose level between 100 and 126 mg/dL contrasts with a significantly higher risk associated with a fasting glucose level within the same range. The mechanism of these findings remains unclear, but it might be related to inadequate stress response. Since no U-shaped curve was observed for fasting glucose level in both diabetic and nondiabetic patients, it is unlikely that the increased risk associated with admission glucose level less than 100 mg/dL compared with levels between 100 and 125 mg/dL is caused by adverse events in patients with well-controlled diabetes or by complications triggered by therapy-induced hypoglycemia.

Incidences of congestive heart failure and cardiogenic shock also increased gradually with increasing glucose levels, and this relation was remarkably similar for admission and fasting glucose levels. The relationship between elevated fasting glucose level and cardiogenic shock after STEMI has been reported before,[8] and our results extend this association with NSTEMI and unstable angina as well. Although diabetic patients have a higher incidence of bleeding complications after an ACS,[27] the present analysis demonstrates for the first time, to our knowledge, that bleeding complications also increase with higher admission or fasting glucose levels, regardless of diabetic status.

To date, the importance of admission glucose vs fasting glucose levels in predicting risk in a general ACS population remains unclear. Although we did not perform a formal comparison analysis, our study suggests that fasting glucose level might be a better independent marker than admission glucose level for short-term and 6-month postdischarge outcome. Moreover, after adjustment for the GRACE risk model, elevated fasting glucose level but not admission glucose level remained predictive of 6-month mortality in patients who were discharged alive. This finding may be explained by the fact that elevated admission glucose level is at least in part related to baseline risk factors included in the GRACE risk model.

Notwithstanding the large number of patients included in GRACE, the standardized criteria to define diagnostic subgroups, clinical outcomes, and laboratory values, and the quality control and audit measures, the limitations of a registry-type study apply. Although we performed multivariate adjustments, including antidiabetic treatment at discharge, unmeasured variables exist that we did not account for. The present analysis also represents only a subgroup of GRACE patients in whom admission or fasting glucose levels and follow-up data were available; patients without available glucose levels may differ substantially from those included in this analysis. It is also possible that fasting glucose levels taken during hospitalization for an ACS are not representative of the "true" glucometabolic state of a patient, as assessed outside of an acute event. On the other hand, results from a Swedish prospective study in nondiabetic patients suggest that fasting glucose levels during hospitalization for an acute myocardial infarction adequately reflect those taken 3 months after the acute event, when the effect of acute stress and inflammation have subsided.[7] Nevertheless, as our registry represents an unselected population and thus includes severely ill patients, some of the glucose levels recorded in the present analysis probably reflect a severe stress response rather than a true fasting glucose level. Finally, in some patients, glucose levels recorded as "fasting glucose" might have been falsely elevated because of glucose-containing infusions, or were falsely normal due to intravenous insulin administration.

CONCLUSIONS

Our data extend the relation between elevated fasting glucose level and risk of adverse outcomes to the full spectrum of ACSs. Fasting glucose level appeared to be an even more powerful predictor of postdischarge death in patients without a history of diabetes. Also, fasting glucose level appears to be a more robust independent marker of adverse outcome than does admission glucose. These findings underscore the importance of categorizing diabetic patients with an ACS as high risk, as indicated in guidelines, but also indicate that there is room for improvement in identifying and treating patients with ACS who have impaired fasting glucose levels.[10]

Accepted for Publication: September 7, 2008.
Author Affiliations: Department of Cardiology, University Hospitals Leuven Campus Gasthuisberg, Leuven, Belgium (Drs Sinnaeve and Van de Werf); Département de Cardiologie, Hôpital Bichat-Claude Bernard, Assistance Publique–Hôpitaux de Paris, Paris, France (Dr Steg); Cardiovascular Research, Division of Medical and Radiological Sciences, University of Edinburgh, Edinburgh, Scotland (Dr Fox); Institut de Cardiologie, Bureau 2-236, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris (Dr Montalescot); Duke University Medical Center, Durham, North Carolina (Dr Granger); Dante Pazzanese Institute of Cardiology, São Paulo, Brazil (Drs Knobel and Avezum); and University of Massachusetts Medical School, Worcester (Drs Anderson and Dabbous).
Correspondence: Peter R. Sinnaeve, MD, PhD, Department of Cardiology, University Hospitals Leuven Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium (peter.sinnaeve@uzleuven.be).
Author Contributions: *Study concept and design:* Sinnaeve, Steg, Fox, Van de Werf, Granger, and Avezum. *Acquisition of data:* Steg, Montalescot, Granger, Anderson, and Avezum. *Analysis and interpretation of data:* Sinnaeve, Steg, Fox, Knobel, Dabbous, and Avezum. *Drafting of the manuscript:* Sinnaeve and Avezum. *Critical revision of the manuscript for important intellectual content:* Sinnaeve, Steg, Fox, Van de Werf, Montalescot, Granger, Knobel, Anderson, Dabbous, and Avezum. *Statistical analysis:* Sinnaeve and Dabbous. *Obtained fund-*

ing: Anderson. *Administrative, technical, and material support:* Steg. *Study supervision:* Sinnaeve, Steg, Van de Werf, Montalescot, Anderson, and Avezum.

GRACE Scientific Advisory Committee: Keith A. A. Fox, MB, ChB, FRCP, England, and Joel M. Gore, MD, United States (GRACE cochairs); Kim A. Eagle, MD, United States, and P. Gabriel Steg, MD, France (GRACE Publication Committee cochairs); and Frederick A. Anderson, PhD, United States (director, GRACE Study Coordinating Center). Additional members of the GRACE Scientific Advisory Committee: Giancarlo Agnelli, MD, PhD, Italy; Álvaro Avezum, MD, PhD, Brazil; David Brieger, MD, Australia; Andrzej Budaj, MD, PhD, Poland; Marcus D. Flather, MBBS, FRCP, England; Robert J. Goldberg, MD, United States; Shaun G. Goodman, MD, Canada; Christopher B. Granger, MD, United States; Dietrich C. Gulba, MD, PhD, Germany; Enrique P. Gurfinkel, MD, Argentina; Brian M. Kennelly, MD, United States; Werner Klein, MD, Austria (deceased); José López-Sendón, MD, Spain; Gilles Montalescot, MD, PhD, France; and Frans Van de Werf, MD, PhD, Belgium.

Financial Disclosure: None reported.

Funding/Support: The GRACE is supported by an unrestricted educational grant from Sanofi-Aventis to the Center for Outcomes Research, University of Massachusetts Medical School.

Role of the Sponsor: Sanofi-Aventis had no involvement in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Additional Information: Further information about the project, along with the complete list of participants, can be found at http://www.outcomes.org/grace. Requests for access to GRACE data should be addressed to Frederick A. Anderson, PhD, Center for Outcomes Research, University of Massachusetts Medical School at fred.anderson @umassmed.edu. Dr Sinnaeve is a clinical investigator for the Fund for Scientific Research–Flanders.

Additional Contributions: We are grateful to the physicians and nurses participating in the GRACE and to Sophie Rushton-Smith, PhD, who provided editorial support.

REFERENCES

1. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355(9206):773-778.
2. Malmberg K, Ryden L, Wedel H, et al; DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005;26(7):650-661.
3. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J*. 2005;26(13):1255-1261.
4. Timmer JR, van der Horst IC, Ottervanger JP, et al; Zwolle Myocardial Infarction Study Group. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. *Am Heart J*. 2004;148(3):399-404.
5. Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL; ICONS Investigators. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol*. 2002;40(10):1748-1754.
6. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Rydén L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J*. 2004;25(22):1990-1997.
7. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002;359(9324):2140-2144.
8. Zeller M, Cottin Y, Brindisi MC, et al; RICO Survey Working Group. Impaired fasting glucose and cardiogenic shock in patients with acute myocardial infarction. *Eur Heart J*. 2004;25(4):308-312.
9. Otten R, Kline-Rogers E, Meier DJ, et al. Impact of pre-diabetic state on clinical outcomes in patients with acute coronary syndrome. *Heart*. 2005;91(11):1466-1468.
10. Deedwania P, Kosiborod M, Barrett E, et al; American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2008;117(12):1610-1619.
11. Suleiman M, Hammerman H, Boulos M, et al. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. *Circulation*. 2005;111(6):754-760.
12. Goyal A, Mahaffey KW, Garg J, et al. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. *Eur Heart J*. 2006;27(11):1289-1297.
13. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117(8):1018-1027.
14. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J*. 2001;141(2):190-199.
15. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, López-Sendón J; GRACE Investigators. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet*. 2002;359(9304):373-377.
16. Eagle KA, Lim MJ, Dabbous OH, et al; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291(22):2727-2733.
17. American Diabetes Association. Clinical Practice Recommendations 2005. *Diabetes Care*. 2005;28(suppl 1):S1-S79.
18. Bhadriraju S, Ray KK, DeFranco AC, et al. Association between blood glucose and long-term mortality in patients with acute coronary syndromes in the OPUS-TIMI 16 trial. *Am J Cardiol*. 2006;97(11):1573-1577.
19. Cao JJ, Hudson M, Jankowski M, Whitehouse F, Weaver WD. Relation of chronic and acute glycemic control on mortality in acute myocardial infarction with diabetes mellitus. *Am J Cardiol*. 2005;96(2):183-186.
20. Foo K, Cooper J, Deaner A, et al. A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart*. 2003;89(5):512-516.
21. Hadjadj S, Coisne D, Mauco G, et al. Prognostic value of admission plasma glucose and HbA in acute myocardial infarction. *Diabet Med*. 2004;21(4):305-310.
22. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation*. 2005;111(23):3078-3086.
23. Pinto DS, Skolnick AH, Kirtane AJ, et al; TIMI Study Group. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2005;46(1):178-180.
24. Stranders I, Diamant M, van Gelder RE, et al. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med*. 2004;164(9):982-988.
25. Timmer JR, Ottervanger JP, de Boer MJ, et al; Zwolle Myocardial Infarction Study Group. Hyperglycemia is an important predictor of impaired coronary flow before reperfusion therapy in ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2005;45(7):999-1002.
26. Barsheshet A, Garty M, Grossman E, et al. Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. *Arch Intern Med*. 2006;166(15):1613-1619.
27. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24(20):1815-1823.