# Association Between Hyperglycemia at Admission During Hospitalization for Acute Myocardial Infarction and Subsequent Diabetes: Insights From the Veterans Administration Cardiac Care Follow-up Clinical Study

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**OBJECTIVE**

**Among patients with acute myocardial infarction (AMI) without known diabetes, hyperglycemia at admission is common and associated with worse outcomes. It may represent developing diabetes, but this association is unclear. Therefore, we examined the association between hyperglycemia (≥140 mg/dL) at admission and evidence of diabetes among patients with AMI without known diabetes within 6 months of their hospitalization.**

**RESEARCH DESIGN AND METHODS**

**We studied a national cohort of consecutive patients with AMI without known diabetes presenting at 127 Veterans Affairs hospitals between October 2005 and March 2011. Evidence of diabetes either at discharge or in the following 6 months was ascertained using diagnostic codes, medication prescriptions, and/or elevated hemoglobin $A_{1c}$. Association between hyperglycemia at admission and evidence of diabetes was evaluated using regression modeling.**

**RESULTS**

**Among 10,499 patients with AMI without known diabetes, 98% were men and 1,761 (16.8%) had hyperglycemia at admission. Within 6 months following their index hospitalization, 208 patients (11.8%) with hyperglycemia at admission had evidence of diabetes compared with 443 patients (5.1%) without hyperglycemia at admission ($P < 0.001$). After multivariable adjustment, hyperglycemia at admission was significantly associated with subsequent diabetes odds ratio 2.56 (95% CI 2.15–3.06). Among those with new evidence of diabetes, 41% patients (267 of 651) had a hemoglobin $A_{1c}$ ≥6.5% without accompanying diagnostic codes or medication prescriptions, suggesting they had unrecognized diabetes.**

**CONCLUSIONS**

**Hyperglycemia at admission occurred in one of six patients with AMI without known diabetes and was significantly associated with new evidence of diabetes in the 6 months following hospitalization. In addition, two of five patients with evidence of diabetes were potentially unrecognized. Accordingly, diabetes-screening programs for hyperglycemic patients with AMI may be an important component of optimal care.**

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Up to 20% of patients with acute myocardial infarction (AMI) without known diabetes experience hyperglycemia during their hospitalization (1,2). Hyperglycemia in these patients is associated with increased in-hospital, 30-day, and 1-year mortality, at rates even higher than patients with hyperglycemic AMI with known diabetes (2,3). The mechanisms underlying this association are currently unknown, but one potential contributor may be underlying but unrecognized diabetes.

Newly diagnosed diabetes is common among patients hospitalized with AMI (4,5). The acute stress of an AMI may unmask impaired glucose tolerance or frank diabetes. Prompt recognition of diabetes in patients with an AMI would inform optimal risk stratification; secondary prevention therapies (e.g., dietary and lifestyle modifications, use of ACE inhibitors); coronary revascularization decisions; and initiation of glucose-lowering therapies to prevent microvascular complications (6–8).

Hyperglycemia during hospitalization for AMI may serve as a useful marker for emergent diabetes and identify patients for subsequent diabetes screening. However, prior studies of the association between hyperglycemia during hospitalization for AMI and subsequent diabetes are limited (5,9,10). To address this gap in knowledge, we measured the prevalence of hyperglycemia at admission in all patients with AMI without known diabetes who were hospitalized at Veterans Affairs (VA) hospitals between October 2005 and March 2011, and we evaluated its association with evidence of diabetes in the 6 months after hospital discharge.

## RESEARCH DESIGN AND METHODS

### Data Source

Data for this study were collected as a part of Department of VA Cardiac Care Follow-up Clinical Study (CCFCS), which uses national data from the Veterans Health Administration External Peer Review Program for monitoring the quality of a variety of medical conditions and procedures, including AMI and unstable angina. Details of the study methods have been previously published (11,12).

As part of a national VA cardiac care initiative, records of all patients discharged from VA hospitals with a diagnosis of acute coronary syndrome (ACS) were abstracted. All patients with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes 410.xx and 411.xx were identified from the VA Patient Treatment File. Trained abstractors manually abstracted the patient records using standard reporting forms. In addition, data subsequent to the index ACS hospitalization were collected, including health care utilization (e.g., clinic visits, pharmacy records), laboratory results, and clinical outcomes (recurrent hospitalization and mortality). As part of standard procedure for CCFCS, the data undergo extensive quality checks to ensure validity and completeness.

### Study Cohort

We identified all ACS admissions at any VA medical center between 1 October 2005 and 29 March 2011 (Fig. 1). AMI was defined using standard electrocardiographic criteria, elevated troponin levels, and other clinical evidence. We excluded patients hospitalized with unstable angina; patients with a history of diabetes (defined as documented ICD-9-CM code 250.xx, history of diabetes documented in the chart, or use of glucose-lowering medications in the year preceding hospitalization); patients with missing values for glucose at admission (typically from patients with AMI transferred to the VA from an outside facility or who developed AMI as an inpatient); patients discharged to facilities other than home (e.g., skilled nursing facilities, hospice); patients who were provided comfort-care measures only; patients hospitalized for less than 24 h; patients participating in a concurrent research study; and patients who died during the 6 months following the index hospitalization. For patients with multiple hospitalizations during the study period, the first hospitalization for AMI was used as the index hospitalization.

### Independent Variable

Our primary independent variable was presence of hyperglycemia during hospitalization for AMI. We defined hyperglycemia as a random serum glucose value ≥140 mg/dL (7.8 mmol/L) obtained from a venous blood sample at the time of index admission. We used admission glycemic status because *1*) prior work has demonstrated higher in-hospital mortality at this level among patients with AMI (2); *2*) evidence suggests that glucose levels at admission accurately reflect initial metabolic response to AMI-induced stress (13); *3*) it is least likely to be affected by in-hospital therapies (e.g., insulin administration); *4*) it represents the in-hospital glucose value most readily available to treating clinicians; and *5*) it is consistent with the American Heart Association scientific statement on hyperglycemia and ACS (14).

### Outcome

The primary outcome was evidence of diabetes either at hospital discharge or in the subsequent 6 months. The 6-month interval was selected a priori as a time interval sufficient to allow for outpatient evaluation and an opportunity for diabetes detection and diagnosis after hospitalization for AMI. Evidence of diabetes was defined as either presence of an ICD-9-CM code for diabetes (250.xx); outpatient prescription for glucose-lowering medications (including insulin, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, and dipeptidyl peptidase-IV inhibitors); and/or hemoglobin $A_{1c}$ ($HbA_{1c}$) ≥6.5% (48 mmol/mol) during or after the index hospitalization. The validity of these measures as evidence of diabetes among VA patients has been previously established (15,16).

### Covariates

Potential confounders for the association between hyperglycemia and subsequent diabetes were selected based on prior studies and/or clinical rationale (2,5). Selected confounders included patient demographics, comorbidities, factors related to how AMI presented in the patient, in-hospital laboratory values, and medications at discharge. Demographic variables included age (categorized as

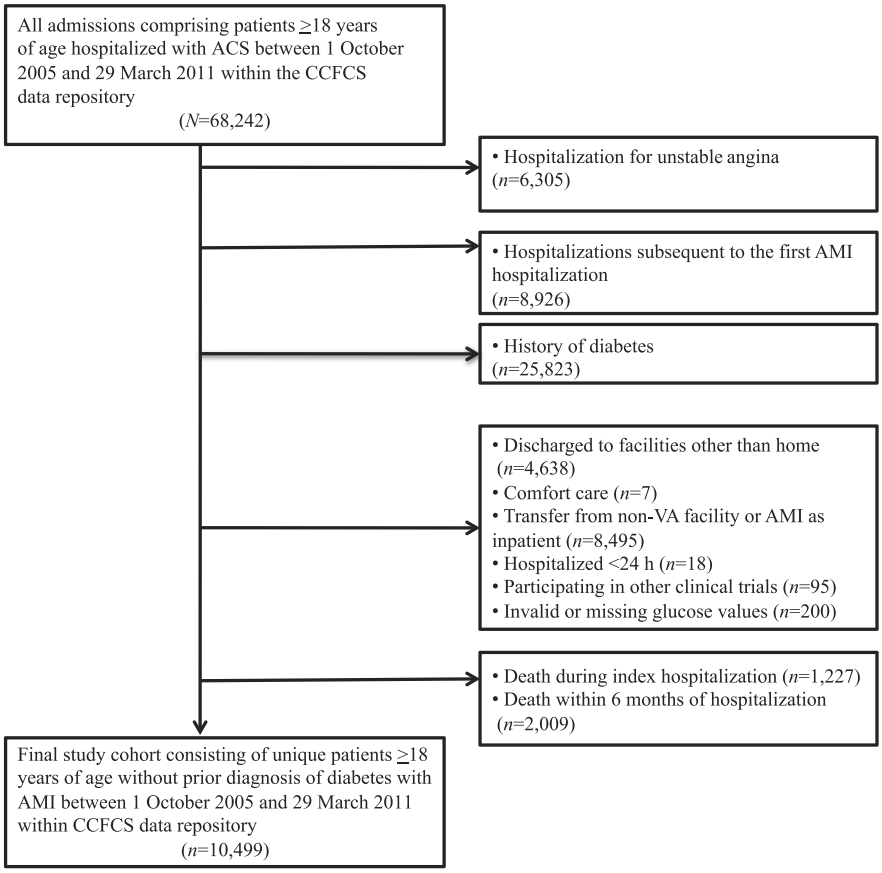


**Figure 1**—Cohort creation. MI, myocardial infarction.

≥65 or <65 years old), sex, race (Caucasian vs. other), and income (median income by ZIP code, dichotomized by median household income >$45,000/year). Clinical comorbidities included obesity (BMI >30 kg/m$^2$), prior myocardial infarction, any prior coronary artery bypass grafting, hypertension, and hypothyroidism. Presentation variables included ST segment elevation myocardial infarction (STEMI), cardiogenic shock, Thrombolysis in Myocardial Infarction (TIMI) risk score >3 at presentation, and use of β-blockers, hydrochlorothiazide (HCTZ), and statins at admission. The TIMI risk scores were calculated based on presenting diagnosis (17,18). Laboratory variables included HDL cholesterol <40 mg/dL and triglycerides >150 mg/dL. Medications at discharge included β-blockers, HCTZ, and statins.

### Statistical Analyses

Patient and treatment characteristics were compared between glycemic groups with and without admission hyperglycemia using $\chi^2$ test for categorical variables, independent samples *t* tests for normally distributed continuous variables, and Wilcoxon rank-sum test for nonnormally distributed continuous variables. We compared the unadjusted association between hyperglycemia at admission and subsequent diabetes and evaluated the timing (in-hospital vs. after discharge) and method of diabetes detection (ICD-9-CM code, medication prescription, elevated $HbA_{1c}$, or a combination of these) by glycemic group. We then constructed a multivariable logistic regression model modeling the overall association between hyperglycemia at admission and evidence of diabetes at discharge or in the 6 months following index hospitalization, incorporating the covariates listed above.

To explore the robustness of our primary analysis we conducted several secondary analyses. First, we assessed two other measures of in-hospital hyperglycemia to determine their association with 6-month rates of diabetes. We used two previously validated definitions of in-hospital hyperglycemia: mean in-hospital glucose ≥140 mg/dL (7.8 mmol/L), defined as average of all serum glucose values obtained from venous blood samples during hospitalization for AMI, and peak in-hospital glucose ≥180 mg/dL (10 mmol/L), defined as the highest recorded serum glucose value obtained from venous blood sample during hospitalization (1). We then determined their association with evidence of diabetes using methods described for our primary analysis. We also compared the discriminatory power of these various metrics using c-statistics. Second, to account for those patients who were evaluated later than 6 months after hospitalization, we repeated our primary analysis using any evidence of diabetes in the 12 months following hospitalization. Third, use of $HbA_{1c}$ as a diagnostic criterion for diabetes was approved by major societies in June 2009 (19). To determine whether

this approval changed the identification of subsequent diabetes in our cohort, we stratified our study cohort into those patients enrolled before and after June 2009 and separately assessed the association between hyperglycemia at admission and evidence of diabetes in the 6 months following the index hospitalization in both of these subcohorts. We also assessed the modality of diabetes diagnoses between these two subcohorts. Fourth, our estimates of prevalence of diabetes may be primarily driven by an inpatient diagnosis of diabetes made by providers who were influenced by the hyperglycemia at admission. To assess for this potential effect, we evaluated the association between hyperglycemia at admission and evidence of diabetes in patients after discharge, thus excluding all patients diagnosed with diabetes during the index hospitalization.

For all analyses, reported *P* values are two-sided, and *P* values $<0.05$ were considered significant. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC). Institutional review boards at the VA Puget Sound and VA Eastern Colorado Health Care Systems approved this study.

## RESULTS

### Patient and Treatment Characteristics at Baseline

Between 1 October 2005 and 29 March 2011, 68,242 admissions for ACS were recorded in the CCFCS data repository. After using the exclusion criteria listed above (*n* = 57,743 [84.6%]) (Fig. 1) 10,499 patients with AMI without known diabetes were included in our final study cohort.

In the study cohort 1,761 patients (16.8%) had hyperglycemia at admission. Table 1 compares various demographic, clinical, presentation, laboratory, and discharge medication variables by glycemic status at admission. Patients with hyperglycemia at admission were more likely to be >65 years old (52.4 vs. 44.5%; $P < 0.001$), present with a diagnosis of STEMI (29.0 vs. 18.9%; $P < 0.001$), and have a TIMI risk score >3 (26.2 vs. 20.8%; $P < 0.001$) compared with patients without hyperglycemia at admission. Rates of β-blocker use at admission (42.4 vs. 43.8%; *P* = 0.26), HCTZ use at admission (21.2 vs. 19.2%; *P* = 0.05), statin use at admission (74.8 vs. 76%; *P* = 0.32), β-blocker at discharge (91.5 vs. 90.6%; *P* = 0.22), and HCTZ at discharge (4.8 vs. 5.1%; *P* = 0.61) were statistically similar between groups. However, patients with hyperglycemia at admission were more likely to be discharged while using statins (77.5 vs. 71.5%; $P < 0.001$).

**Table 1—Baseline and in-hospital characteristics of the study cohort stratified by admission glycemic status**

| Characteristics | Hyperglycemia (glucose ≥140 mg/dL) present at admission (*n* = 1,761 [16.8%]) | Hyperglycemia (glucose <140 mg/dL) absent at admission (*n* = 8,738 [83.2%]) | *P* value |
|---|---|---|---|
| Demographic variables | | | |
| Age >65 years | 923 (52.4) | 3,889 (44.5) | <0.001 |
| Male sex | 1,725 (98) | 8,558 (97.9) | 0.97 |
| Caucasian race | 1,206 (68.5) | 6,016 (68.8) | 0.35 |
| Income >$45,000/year | 908 (51.6) | 4,597 (52.6) | 0.42 |
| Clinical variables (%) | | | |
| Prior MI | 241 (13.7) | 1,318 (15.1) | 0.13 |
| Prior CABG | 247 (14) | 1,302 (14.9) | 0.35 |
| Hypertension | 1,366 (77.6) | 6,620 (75.8) | 0.10 |
| Hypothyroidism | 107 (6.1) | 509 (5.8) | 0.68 |
| Obesity (BMI >30 kg/m$^2$) | 464 (26.3) | 2,114 (24.2) | 0.13 |
| Presentation variables | | | |
| STEMI | 510 (29) | 1,648 (18.9) | <0.001 |
| Cardiogenic shock | 11 (0.6) | 14 (0.2) | <0.001 |
| TIMI score >3* | 461 (26.2) | 1,815 (20.8) | <0.001 |
| β-Blocker before admission | 746 (42.4) | 3,828 (43.8) | 0.26 |
| HCTZ within 6 months before admission | 374 (21.2) | 1,680 (19.2) | 0.05 |
| Statins within 6 months before admission | 1,318 (74.8) | 6,637 (76.0) | 0.32 |
| Laboratory variables | | | |
| HDL cholesterol <40 mg/dL | 1,337 (75.9) | 6,534 (74.8) | 0.31 |
| TG >150 mg/dL | 342 (19.4) | 1,847 (21.1) | 0.11 |
| Treatment variables at discharge | | | |
| β-Blocker | 1,612 (91.5) | 7,918 (90.6) | 0.22 |
| HCTZ | 85 (4.8) | 447 (5.1) | 0.61 |
| Statins | 1,365 (77.5) | 6,247 (71.5) | <0.001 |

Data are *n* (%). MI, myocardial infarction; CABG, coronary artery bypass graft; TG, triglyceride. *TIMI score components for STEMI: age; Killip class; diabetes (absent, by definition, for our entire cohort); angina; hypertension; systolic blood pressure <100 mmHg; admission heart rate >100 bpm; weight; anterior MI or left bundle branch block. TIMI score components for non-STEMI: age, aspirin use in previous 7 days, ≥3 risk factors for coronary artery disease, known coronary stenosis >50%, ST segment deviation on presentation electrocardiogram, elevated troponin.

### Hyperglycemia at Admission and Evidence of Diabetes

Between presentation of AMI and the 6 months following hospital discharge, 651 patients (6.2%) in the entire study cohort had new evidence of diabetes. Among these patients, 208 (11.8%) had hyperglycemia at admission compared with 443 patients (5.1%) without hyperglycemia at admission ($P < 0.001$). Table 2 demonstrates the timing, glycemic status at admission, and modality of diagnosis in all patients with new evidence of diabetes in the study cohort. Among the 651 patients with new evidence of diabetes, 169 (26.0%) had evidence before their discharge, with the remaining occurring in the subsequent 6 months. Among those diagnosed before discharge, 71 (46.7%) had hyperglycemia at admission. Among these hyperglycemic patients, 64 (90.1%) had an elevated $HbA_{1c}$ without accompanying ICD-9-CM codes or prescriptions for glucose-lowering medications, whereas 87 patients (88.8%) without hyperglycemia at admission had elevated $HbA_{1c}$ without other evidence of diabetes (*P* = 0.78). This suggests that many patients,

regardless of their glycemic status at admission, have initial evidence of diabetes (i.e., elevated $HbA_{1c}$) before hospital discharge, but it is unclear whether it is sufficiently recognized and addressed by their treating clinicians.

In the 6 months following hospitalization, 10,235 patients (97.5%) had at least one outpatient visit after their index hospitalization. Among the 208 patients with hyperglycemia at admission and new evidence of diabetes between presentation of AMI and the 6 months following hospitalization, 84 (40.4%) had elevated $HbA_{1c}$ without accompanying ICD-9-CM codes or glucose-lowering medication prescriptions, whereas 183 patients (41.3%) without hyperglycemia at admission had elevated $HbA_{1c}$ without accompanying diagnostic codes or prescriptions ($P = 0.98$).

After multivariable adjustment, patients with hyperglycemia at admission were significantly more likely to have evidence of diabetes compared with those without hyperglycemia at admission (odds ratio [OR] 2.56 [95% CI 2.15–3.06]) (Fig. 2). The only demographic factor associated with evidence of diabetes was non-Caucasian race (OR 1.55 [95% CI 1.30–1.86]). Among clinical factors, hypertension (OR 1.29 [95% 1.04–1.59]) and obesity (OR 1.81 [95% CI 1.51–2.16]) were associated with a higher likelihood of diabetes. Among presentation and laboratory variables, presentation with a non-STEMI (OR 1.27 [95% 1.02–1.57]), triglycerides >150 mg/dL (OR 1.49 [95% CI 1.24–1.80]), and HDL cholesterol <40 mg/dL (OR 1.33 [95% CI 1.09–1.63]) were associated with higher likelihood of diabetes. None of the other covariates included in this analysis were significantly associated with new evidence of diabetes. This model demonstrated acceptable discrimination of hyperglycemia at admission for subsequent diabetes with a c-statistic of 0.66.

### Secondary Analyses

When mean in-hospital glucose ≥140 mg/dL (7.8 mmol/L), rather than glucose at admission ≥140 mg/dL (7.8 mmol/L), was used to define hyperglycemia, 611 patients (5.8%) in the entire study cohort were classified

**Table 2—Modality of assessing diabetes status stratified by follow-up duration and admission glycemic status**

| | | Modality of diabetes diagnosis | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Timing of diagnosis | Glycemic status at admission (mg/dL) | ICD-9-CM code only | Prescription* only | $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) only | ICD-9-CM code + prescription* | ICD-9-CM code + $HbA_{1c} > 6.5\%$ (48 mmol/mol) | $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) + prescription* | $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) + prescription* + ICD-9-CM code |
| During index hospitalization ($n$ = 169) | <140 ($n$ = 98) | 6 (6.1) | 3 (3.1) | 87 (88.8) | 2 (2.0) | 0 (0) | 0 (0) | 0 (0) |
| | ≥140 ($n$ = 71) | 2 (2.8) | 0 (0) | 64 (90.1) | 0 (0) | 2 (2.8) | 2 (2.8) | 1 (1.4) |
| During index hospitalization and 6 months after discharge ($n$ = 651) | <140 ($n$ = 443) | 132 (29.8) | 37 (8.4) | 183 (41.3) | 30 (6.8) | 28 (6.3) | 5 (1.1) | 28 (6.3) |
| | ≥140 ($n$ = 208) | 48 (23.1) | 5 (2.4) | 84 (40.4) | 8 (3.9) | 25 (12.0) | 3 (1.4) | 35 (16.8) |
| During index hospitalization and 12 months after discharge ($n$ = 964) | <140 ($n$ = 678) | 210 (31) | 42 (6.2) | 257 (37.9) | 45 (6.6) | 53 (7.8) | 11 (1.6) | 60 (8.9) |
| | ≥140 ($n$ = 286) | 63 (22.0) | 9 (3.2) | 104 (36.4) | 10 (3.5) | 31 (10.8) | 4 (1.4) | 65 (22.7) |

Data are $n$ (%). *Prescription indicates an outpatient prescription for glucose-lowering medications (insulin, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, or dipeptidyl peptidase-IV inhibitors).

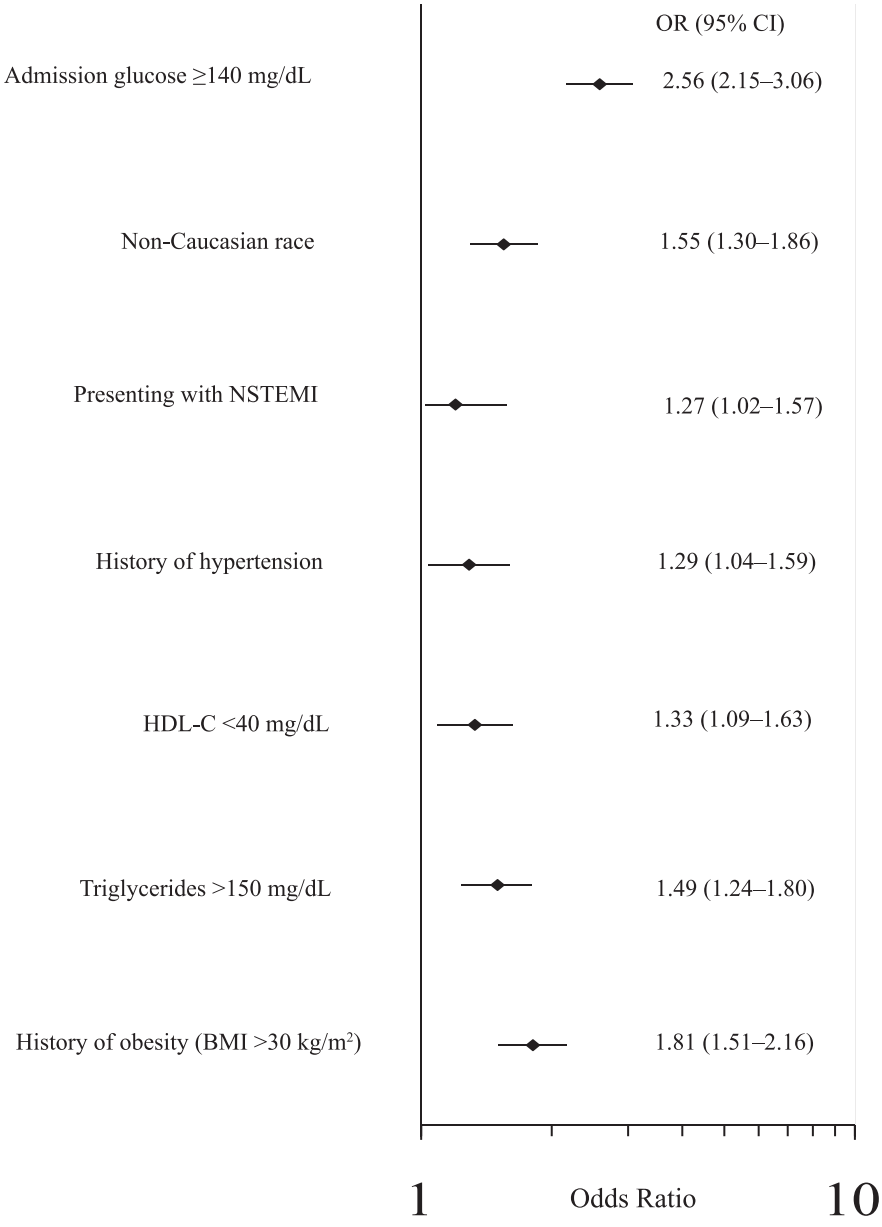


**Figure 2—**Forest plot showing variables significantly associated with evidence of diabetes in primary analysis. Vertical line represents no effect. All observations to the right of the vertical line signify a positive association with evidence of diabetes. NSTEMI, non-STEMI.

as hyperglycemic. Using this definition, 144 hyperglycemic patients (23.6%) had evidence of diabetes at 6 months compared with 507 patients (5.1%) without hyperglycemia ($P < 0.0001$). After multivariable adjustment, mean glucose ≥140 mg/dL (7.8 mmol/L) was significantly associated with evidence of diabetes at 6 months (OR 5.79 [95% CI 4.68–7.16]). The c-statistic for this model was 0.68. Other factors significantly associated with diabetes were similar to those in the primary analysis.

When peak in-hospital glucose ≥180 mg/dL (10 mmol/L) was used to define hyperglycemia, 1,608 patients (15.3%) in the entire study cohort were classified as hyperglycemic. Among these patients, 215 (13.4%) had evidence of diabetes at 6 months compared with 436 (4.9%) of those without hyperglycemia ($P < 0.0001$). After multivariable adjustment, peak in-hospital glucose ≥180 mg/dL (10 mmol/L) was associated with evidence of diabetes at 6 months (OR 3.07 [95% CI 2.57–3.66]). The c-statistic for this model was 0.68. Other factors significantly associated with diabetes were also similar to those in the primary analysis.

Twelve months after index hospitalization, 964 patients (9.2%) in the entire study cohort had evidence of diabetes. Of these, 286 patients (16.2%) with hyperglycemia at admission had evidence of diabetes compared with 678 patients (7.8%) without hyperglycemia at admission ($P < 0.0001$). After multivariable adjustment, patients with hyperglycemia at admission were more likely to have evidence of diabetes within 12 months

compared with those without hyperglycemia at admission (OR 2.36 [95% CI 2.02–2.74]).

When we stratified our study cohort into patients enrolled before and after June 2009 to account for changes in use of $HbA_{1c}$ as a diagnostic criterion for diabetes, results of our analyses remained unchanged. Among those enrolled before June 2009, the proportion of patients with elevated $HbA_{1c}$ without diagnostic codes and prescriptions was comparable to that of patients enrolled after June 2009, both during hospitalization (88.4 vs. 91.2%) and after discharge (41.3 vs. 40.3%) (Supplementary Table 1). For the cohort enrolled before June 2009, patients with hyperglycemia at admission had 2.4 times higher odds for developing subsequent diabetes (OR 2.40 [95% CI 1.93–2.98]). Among patients enrolled after June 2009, there was a three times higher odds of subsequent diabetes among those with hyperglycemia at admission compared with those without (OR 3.04 [95% CI 2.22–4.16]). Furthermore, results of our sensitivity analyses testing association between other measures of hyperglycemia and subsequent diabetes were unchanged after stratification of the study population by enrollment before or after June 2009 (Supplementary Table 2).

Last, the association between hyperglycemia at admission and evidence of diabetes at 6 months persisted when assessed among patients who had evidence of diabetes *after* their discharge (OR 2.07 [95% CI 1.68–2.55]). The association between other measures of hyperglycemia (mean glucose $\geq$140 mg/dL and peak glucose $\geq$180 mg/dL) and evidence of diabetes after discharge remained unmodified as well (Supplementary Table 2).

## CONCLUSIONS

Our study found that hyperglycemia at admission occurs in approximately one in six patients with AMI without known diabetes and is associated with a 2.5-fold higher odds of having evidence of diabetes in the 6 months following hospitalization, even after adjusting for a variety of demographic, clinical, presentation, and treatment factors. Among those with evidence of diabetes, 41% had elevated $HbA_{1c}$ without an accompanying ICD-9-CM code or glucose-lowering medication prescription, suggesting that these patients may have unrecognized diabetes. These findings remained consistent through a wide variety of secondary analyses to test their robustness. Overall, these findings demonstrate that acute hyperglycemia during AMI is common and strongly associated with subsequent evidence of diabetes. Accordingly, screening for diabetes among patients with in-hospital hyperglycemia, either during or shortly after their hospitalization for AMI, may be merited to identify diabetes and implement optimal care.

Prior studies have explored the prevalence of hyperglycemia at admission among patients with AMI without known diabetes and its association with adverse outcomes (1–3,20–22). The largest of these found hyperglycemia at admission in 45% of patients with AMI without known diabetes (2). Relative to their counterparts with prevalent diabetes, these patients had higher 30-day and 1-year mortality rates. Prior studies also have demonstrated higher rates of abnormal glucose metabolism and new-onset diabetes among patients with AMI. In a European survey of cardiac patients, 22% of patients with ACS without previously known diabetes were newly diagnosed with diabetes within 2 months of their hospitalization (4). Norhammar and colleagues (5) prospectively screened patients with AMI without known diabetes admitted at two hospitals in Sweden and found that 25% of patients had previously undiagnosed diabetes at 3 months. Similarly, using a hospitalized ACS population from two Kansas City hospitals, Conaway and colleagues (23) found that 14% of patients met criteria for new diagnosis of diabetes. Our overall hyperglycemia rate of 16.8% is lower than that in many of these studies. We believe that this variation is largely attributable to differences in population demographics and underlying comorbidities. For example, the Medicare population studied by Kosiborod and colleagues (2) is significantly older than our population, which may contribute to the higher rates of hyperglycemia at admission seen in their study. Furthermore, the difference in rates of diabetes between our study cohort and those of prior studies can be attributed to the selective, rather than systematic, detection that occurred in our cohort. This difference likely explains the higher rates of diabetes diagnosis noted in the study by Norhammar and colleagues (5).

Despite the known prevalence of newly diagnosed diabetes among patients with AMI, little evidence linking AMI-associated stress hyperglycemia and subsequent diabetes exists. Several studies have linked stress hyperglycemia and subsequent diabetes in pneumonia and critical illness (24,25), but efforts to determine a similar association between AMI hyperglycemia and diabetes have been few and conflicting (9,10). Our study addresses this gap in knowledge by demonstrating a strong association between hyperglycemia at admission and subsequent evidence of diabetes in a large, contemporary cohort using validated methods for diagnosing diabetes. Our results also provide important evidence to support the suggestion from the 2008 AHA Scientific Statement that diabetes screening occur among all ACS patients without known diabetes presenting with hyperglycemia at admission (14).

Our study also uncovered important insights in diabetes recognition. Among our study cohort, two of five patients with AMI had elevated $HbA_{1c}$ without either diabetes diagnosis codes or glucose-lowering medication prescription, suggesting that their diabetes was unrecognized by their health care providers. Moreover, the proportion of patients with unrecognized diabetes was similar between patients with and without hyperglycemia at admission for the index hospitalization, suggesting that providers may not recognize it as a marker of diabetes. However, this supposition should be made cautiously since elevated $HbA_{1c}$ values often require repeat testing for verification and many experts recommend further validation of diabetes using other forms of glucose

testing, such as fasting glucose values or oral glucose tolerance tests (26). In addition, use of $HbA_{1c}$ as a diagnostic test was approved by major society guidelines in June 2009, whereas the duration of our study ranges from 2005 to 2011. Nonetheless, our results remained unchanged when the proportion of patients with only elevated $HbA_{1c}$ was assessed among patients enrolled before and after June 2009. Moreover, our findings are consistent with previous studies and suggest that diabetes is often unrecognized in patients with AMI (4,23).

Early identification of diabetes has several implications for optimal care of patients with AMI. First, diabetes is known to be a marker of poorer prognosis in patients with AMI and can thus aid risk-stratification efforts (7,27). Second, diabetes affects revascularization decisions among patients with AMI and coronary artery disease, with many studies suggesting that these patients with multivessel disease benefit from coronary artery bypass grafting over percutaneous coronary intervention(8). Third, many diabetic patients benefit from additional secondary prevention medications such as ACE inhibitors. Finally, achieving early glycemic control has been shown to reduce the burden of microvascular disease in randomized trials of both patients with AMI and patients with diabetes in general (28–30), and sustained glycemic control with optimization of $HbA_{1c}$ levels continues to be recommended by major professional societies (31,32).

Our findings also suggest that the metric of hyperglycemia at admission, compared with other validated hyperglycemia metrics, may be the best blend of practicality and prediction in identifying patients with AMI who are at risk for diabetes. Hyperglycemia at admission is easily measured and rarely influenced by medical interventions such as insulin or dextrose infusions, enteral/parenteral nutrition, or use of vasopressors. It also has acceptable discriminatory power, with a c-statistic of 0.66. Although mean in-hospital glucose $\geq$140 mg/dL (7.8 mmol/L) had a higher c-statistic of 0.68, this modest increase in discriminatory performance is unlikely to offset the added difficulty in collecting and calculating this metric for clinical decision making. Furthermore, when we used admission glucose $\geq$140 mg/dL (7.8 mmol/L) to classify hyperglycemia, more patients were identified as hyperglycemic ($n$ = 1,761) compared with those identified using peak glucose $\geq$180 mg/dL (10 mmol/L; $n$ = 1,608), without a loss in discriminatory power (c-statistic for $\geq$140 mg/dL = 0.66; c-statistic for $\geq$180 mg/dL = 0.68). Since the value of glucose $\geq$140 mg/dL at admission is consistent with existing recommendations and identifies patients with AMI without known diabetes who are at higher risk of mortality, we believe this is an acceptable cutoff value. Accordingly, our analysis suggests that of the metrics we tested, hyperglycemia at admission is the best marker for identifying patients at higher risk of diabetes.

Our results should be interpreted in light of several potential limitations. First, this cohort comprises exclusively U.S. military veterans receiving care in the VA health system. This population is predominantly male (98% of our cohort), and the prevalence of diabetes and coronary artery disease in this population is higher compared with the general population. Therefore, our findings do not necessarily generalize to patient populations underrepresented in this cohort (e.g., women, children, non-U.S. populations). Second, the retrospective nature of our cohort and reliance on decision making by individual providers to detect diabetes may result in an underestimation of the prevalence of diabetes in our cohort. Future studies will need a more systematic approach to diabetes detection to fully appreciate the impact of screening programs. Third, since providers may incorrectly diagnose patients as having diabetes during the index hospitalization for AMI because of elevated glucose values secondary to stress—rather than relying on fasting glucose testing after discharge or other methods of diagnosis—our association between hyperglycemia at admission and subsequent diabetes could be spurious. However, our sensitivity analyses looking at the association between hyperglycemia at admission and evidence of diabetes in the 6 months *after* discharge found that the relationship between hyperglycemia at admission and evidence of diabetes after discharge remained unchanged. This suggests that the association between hyperglycemia at admission and evidence of diabetes is less likely to be due to physician diagnostic errors. Fourth, we defined patients with potentially unrecognized diabetes as those with only elevated $HbA_{1c}$ values in the absence of ICD-9-CM codes and glucose-lowering medication prescriptions. However, another explanation for this finding could be that providers recognized the presence of diabetes but both failed to document the diagnosis with an ICD-9-CM code and elected to treat with lifestyle modifications rather than pharmacotherapy. Accordingly, the rate of unrecognized diabetes reported in our cohort may be overestimated. Fifth, the utility of $HbA_{1c}$ as a screening tool in patients with AMI close to discharge is controversial because of the lack of standardization in several parts of the world and other factors that influence levels (e.g., red cell survival, renal dysfunction). Hence, screening programs will need to ensure the validity of their detection methods. Sixth, during our study there was a change in major society recommendations regarding the use of $HbA_{1c}$ as a diagnostic criterion for diabetes. However, the results of our sensitivity analyses based on date of enrollment revealed that the association between hyperglycemia at admission and evidence of diabetes persisted. Seventh, we observed high rates of subsequent diabetes in patients with AMI without stress hyperglycemia, underscoring the fact that stress hyperglycemia is not the only factor that predicts subsequent development of diabetes. However, our results show that hyperglycemia at admission is a strong factor associated with future diagnosis of diabetes, even after adjusting for other known confounders. Accordingly, given the strength of association we observed between stress hyperglycemia and subsequent diabetes, we believe that strong consideration should be given to diabetic screening programs for patients with stress hyperglycemia during or

shortly after hospitalization for AMI. Finally, as with all observational studies, residual confounding of the association between hyperglycemia and diabetes by unmeasured variables may remain. However, our accounting of covariates known to modify this association and robust modeling techniques likely reduced the source of this error.

In conclusion, we found that hyperglycemia at admission occurs in 16.8% of veterans without known diabetes who are hospitalized with AMI and is strongly associated with evidence of diabetes within 6 months after the AMI hospitalization. In addition, a significant number of these patients may have unrecognized diabetes and thus represent an important opportunity to appropriately identify and treat them. Accordingly, systematic screening for diabetes among hyperglycemic patients with AMI may provide opportunities for prompt identification, improved risk stratification, institution of optimal diabetes and AMI treatments, and improved outcomes.

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**Author Contributions.** S.S. wrote the manuscript, reviewed and edited the manuscript, and contributed to discussion. J.A.B., I.G.-C., and E.L. analyzed the data, reviewed and edited the manuscript, and contributed to discussion. K.M., P.M.H., M.N.T., D.K.M., J.M.S., S.V.A., and M.K. reviewed and edited the manuscript and contributed to discussion. T.M.M. conceived of and designed the study, wrote the manuscript, reviewed and edited the manuscript, and contributed to discussion. T.M.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## References

1. 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;117:1018–1027
2. 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;111:3078–3086
3. 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;355:773–778
4. Bartnik M, Rydén L, Ferrari R, et al.; Euro Heart Survey Investigators. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. Eur Heart J 2004;25:1880–1890
5. 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;359:2140–2144
6. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011;(6):CD008143
7. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. Circulation 1995;91:979–989
8. Farkouh ME, Domanski M, Sleeper LA, et al.; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–2384
9. Ishihara M, Inoue I, Kawagoe T, et al. Is admission hyperglycaemia in non-diabetic patients with acute myocardial infarction a surrogate for previously undiagnosed abnormal glucose tolerance? Eur Heart J 2006;27:2413–2419
10. Okosieme OE, Peter R, Usman M, et al. Can admission and fasting glucose reliably identify undiagnosed diabetes in patients with acute coronary syndrome? Diabetes Care 2008;31:1955–1959
11. Sohn MW, Zhang H, Arnold N, et al. Transition to the new race/ethnicity data collection standards in the Department of Veterans Affairs. Popul Health Metr 2006;4:7
12. Maynard C, Lowy E, Rumsfeld J, et al. The prevalence and outcomes of in-hospital acute myocardial infarction in the Department of Veterans Affairs Health System. Arch Intern Med 2006;166:1410–1416
13. Oswald GA, Smith CC, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction. Br Med J (Clin Res Ed) 1986;293:917–922
14. 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;117:1610–1619
15. Kashner TM. Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. Med Care 1998;36:1324–1336
16. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. Diabetes Care 2004;27(Suppl. 2):B10–B21
17. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835–842
18. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031–2037
19. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
20. Nordin C, Amiruddin R, Rucker L, Choi J, Kohli A, Marantz PR. Diabetes and stress hyperglycemia associated with myocardial infarctions at an urban municipal hospital: prevalence and effect on mortality. Cardiol Rev 2005;13:223–230
21. 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;40:1748–1754
22. 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;164:982–988
23. Conaway DG, O'Keefe JH, Reid KJ, Spertus J. Frequency of undiagnosed diabetes mellitus in patients with acute coronary syndrome. Am J Cardiol 2005;96:363–365
24. Gornik I, Vujaklija-Brajkovic A, Renar IP, Gasparovic V. A prospective observational

study of the relationship of critical illness associated hyperglycaemia in medical ICU patients and subsequent development of type 2 diabetes. Crit Care 2010;14:R130

25. Macintyre EJ, Majumdar SR, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Eurich DT. Stress hyperglycemia and newly diagnosed diabetes in 2124 patients hospitalized with pneumonia. Am J Med 2012;125:1036.e17–1036.e23
26. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
27. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1997;30:171–179
28. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–853
29. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
30. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
31. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011;17(Suppl. 2):1–53
32. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203