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No Association between Hemoglobin A1c and In-Hospital Mortality in Patients with Diabetes and Acute Myocardial Infarction

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Abstract

Background—Patients with diabetes have increased in-hospital mortality following acute myocardial infarction (AMI), with studies suggesting higher risk with both hypoglycemia and hyperglycemia. We assessed whether a J-shaped relation exists between hemoglobin A1C (A1C) in patients with diabetes and AMI.

Methods—We assessed the associations between A1C and in-hospital mortality using data from a nationwide sample of AMI patients who had both prior diabetes and measurement of A1C (n=15,337).

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Results—When evaluated continuously, we observed no evidence of a J-shaped relation between A1C and in-hospital mortality in multivariable analysis (test for linearity $p=0.89$). Patients with lowest ($<5.5\%$) and highest A1C ($\geq 9.5\%$) had a crude mortality rate of 4.6% and 2.8%, respectively, compared with 3.8% among those in the referent A1C category (6.5 to $<7\%$). In multivariable regression, we observed no association between low A1C ($<5.5\%$, odds ratio [OR] 0.81, 95% CI 0.47-1.39) or high A1C (A1C ≥ 9.5 , OR 1.31, 95% CI 0.94-1.83) with mortality as compared to the referent group.

Conclusion—In this large contemporary cohort of patients with diabetes presenting with AMI, we did not observe a J-shaped association between A1C and mortality.

Introduction

Observational studies have consistently demonstrated an association between higher levels of hemoglobin A1C (A1C) and adverse cardiovascular disease (CVD) outcomes and mortality among patients with diabetes in the outpatient setting.¹⁻³ Similarly, a recent study has shown an association between low values of A1C and all-cause mortality among outpatients with diabetes treated with either oral agents or insulin therapy.⁴

In the acute myocardial infarction (AMI) setting, multiple studies have examined the association between glucose levels and mortality, and a J-shaped relationship has been demonstrated between glucose and mortality among both patients with and without diabetes.⁵ However, it has been postulated that the association between both hyperglycemia and hypoglycemia and mortality may be explained by glucose levels serving as a marker of illness severity.⁶ Thus, glucose may be less useful in providing insight into the actual association of glycemic control and outcomes in AMI.

A1C reflects longer-term glycemic control, and is less influenced by acute stress. Therefore, A1C levels may provide insight into the relation between chronic glucose control and patient outcomes. However, available studies that have assessed the relationship between A1C and mortality in the acute MI setting have not explicitly examined the association between low A1C levels and mortality.^{8,9} The Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With The Guidelines (GWTG) provides a large sample of patients with diabetes presenting with MI. The present analyses were designed to assess whether a J-shaped relationship exists between categories of A1C and hospital mortality among patients with diabetes and MI. We hypothesized that low, in addition to high A1C levels, would be associated with higher in-hospital mortality in the AMI setting.

Methods

Study Sample

The National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry- Get with the Guidelines (GWTG) (AR-G) is a nationwide, outcomes-based, voluntary, observational registry of ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI). The registry was instituted in January 2007, and the present analyses include data from patients registered between January 1, 2007 and June 30, 2009 at 360 AR-G hospitals. Of the entire MI population ($n=131,980$), 80,000 presented with NSTEMI and 51,980 presented with STEMI. Patients with missing status on A1C collection ($n=980$), missing A1C values ($n=185$), and those who did not have diabetes ($n=91,560$) or with missing diabetes status ($n=348$) were excluded sequentially, resulting in a total of 38,907 patients with a reported diagnosis of diabetes. We further restricted our analysis population on those with A1C collected, resulting in a sample size of 16,004 with 322 hospitals. For our mortality analyses, we

additionally excluded patients who were transferred out of an AR-G hospital (n=667), resulting in a final sample size of 15,337. In secondary analyses, we further excluded patients not known to be receiving either oral hypoglycemic or insulin treatment for diabetes (n=2,621), resulting in a sample of 12,716.

Participating hospitals submit data to the AR-G registry for all patients presenting within 24 hours of the onset of a coronary ischemic syndrome with an ultimate primary diagnosis of MI. NSTEMI was defined as ischemic symptoms at rest, lasting 10 minutes or longer occurring within 24 hours before admission and with elevated cardiac markers of necrosis (CK-MB or Troponin). STEMI was defined as ischemic symptoms at rest lasting 10 minutes or more within 72 hours from admission and ECG changes associated with STEMI (new left bundle-branch block [LBBB] or persistent ST segment elevation >1 mm in 2 or more contiguous electrocardiographic leads).¹⁰ Laboratory values including initial serum troponin and creatinine values were obtained from the medical record and troponin levels varied by assay type and reference ranges across different hospital sites. Initial troponin values were reported as troponin ratio, defined as the laboratory value divided by the hospital assay's upper limit of normal. All participating centers are required to abide by local institutional review or ethical review standards. Patient characteristics and key outcome data are extracted to a web-based case record form from existing medical records using a trained data collector at each hospital using standard definitions, and do not require direct contact with individual patients. Data quality and completeness are monitored by the NCDR Data Quality Program. The NCDR AR-G is administered by the American College of Cardiology Foundation (ACCF) and sponsored by Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Genentech, and Schering-Plough Corporation who provide material support for the operation of the data collection and infrastructure. The sponsors had no additional role in the present analyses, including the selection of topic, analyses of data, decision to publish, or approval of the manuscript prior to publication. Data analyses were performed by a statistician independent of the sponsors (AYC) at the Duke Clinical Research Institute.

Assessment of Diabetes and Hemoglobin A1C

Patients were classified as having diabetes if their medical record reported diabetes on admission or contained documentation of a prior diagnosis. Glucose-lowering therapy was defined according to diabetes treatment recorded at the time of admission. Laboratory analysis of A1C was performed at the individual hospital laboratory. A1C was collected a median of 14.2 hours after hospital arrival. In-hospital glucose data was not available.

Outcome Variable

The primary outcome of interest was all-cause in-hospital death. All outcomes were ascertained from the AR-G data collection form based on medical record abstraction at each participating hospital using standard definitions.

Covariate Assessment

Demographic information, medical history, and in-hospital clinical characteristics were abstracted from the medical record. A listing of specific data fields and definitions is available at <http://www.ncdr.com/WebNCDR/ACTION/Elements.aspx>.¹⁰

Statistical Methods

Patient demographics, in-hospital clinical, and hospital characteristics were summarized by the presence of A1C (collected/not collected). In addition, baseline patient characteristics were presented across A1C category. A1C categories were defined as <5.5%, 5.5 to <6%, 6 to <6.5%, 6.5 to <7%, 7 to <7.5%, 7.5 to <8%, 8 to <8.5%, 8.5 to <9%, 9 to <9.5%, and

$\geq 9.5\%$. Mean $\pm$ standard deviation were reported for continuous variables, and percentages (number) were reported for categorical variables. Continuous variables were compared using Wilcoxon rank-sum tests, and categorical variables were compared using chi-square tests.

We assessed the relationship between A1C and in-hospital mortality using the logistic generalized estimating equations (GEE) method with exchangeable working correlation matrix to account for within-hospital clustering, because patients at the same hospital are more likely to be similar and have similar responses relative to patients at other hospitals (i.e., within-center correlation for responses).¹² A1C was first modeled as a categorical variable using the groupings stated above with A1C 6.5 to $<7\%$ as the referent. We chose A1C of 6.5 to $<7\%$ as the referent because this is a standard A1C target in clinical practice among patients on therapy for diabetes.¹³ We then tested for the evidence of a non-linear association between A1C and mortality by fitting the Stone and Koo additive spline transformation of the logistic model to analyze the relation between initial continuous A1C measurements and in-hospital mortality with multivariable adjustment.¹⁴⁻¹⁶ Covariates in the multivariable models included initial serum creatinine, age, systolic blood pressure on presentation, initial troponin ratio, heart failure (HF) or shock on admission (HF only, shock only or HF with shock, versus none), electrocardiographic findings (ST elevations, ST changes (ST depression or transient ST elevation) versus no ST changes (T-wave inversion or No electrocardiographic changes), heart rate on presentation, and prior peripheral arterial disease based on the ACTION in-hospital mortality model.¹⁷

We also examined the relationship between A1C and in-hospital mortality in patients receiving either oral hypoglycemic or insulin treatment for diabetes. These analyses were then stratified by type of MI (STEMI and NSTEMI). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each independent variable in the models. All comparisons were 2-tailed and $p < 0.05$ was considered statistically significant. The entire analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC).

All authors had access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Sample Characteristics

Overall, 29.5% ($n=38,907$) of the AR-G sample had a diagnosis of diabetes, of which 41.1% ($n=16,004$) had an A1C value available. Patients with A1C measured were younger, more likely to present with STEMI, and tended to have lower in-hospital rates of heart failure, shock, and death (Table I). All further analyses were limited to those with A1C; patients comprising the analysis cohort were on average 65 years of age, 38.8% were women, and 32.5% presented with STEMI. At higher A1C levels, patients tended to be younger, had higher initial troponin values, and were more likely to have experienced a STEMI and be on insulin therapy (Supplemental Table I).

Categories of Hemoglobin A1C and In-Hospital Mortality

Patients with A1C $<5.5\%$ had a crude mortality rate of 4.6% compared to 3.8% among those with A1C of 6.5 to $<7\%$ and 2.8% among those with A1C $\geq 9.5\%$ (Table II). We observed no significant association between A1C categories and in-hospital mortality in either crude or multivariable adjusted models (Table II).

When analyses were repeated limiting the analysis to patients that were on pharmacologic therapy for diabetes ($n=12,716$), we observed an increased mortality risk among those with A1C 5.5- $<6\%$ (OR 1.53, 95% CI 1.05-2.23), which was attenuated with multivariable

adjustment (OR 1.27, 95% CI 0.88-1.85). Results were not otherwise materially different (Table III).

Continuous Analyses of Hemoglobin A1C and In-Hospital Mortality

We tested for evidence of a non-linear trend in A1C and in-hospital mortality, thus allowing for a potential J-shaped relationship. Non-linearity was not observed ($p=0.89$). Subsequent analyses focused on the linear relationship between A1C and in-hospital mortality; the multivariable-adjusted OR, per 1% increase in A1C, was 1.06 (95% CI 1.00-1.11, $p=0.048$). The association between continuous initial A1C level and in-hospital mortality after additive spline transformation of the logistic model and multivariable adjustment is shown in Figure I.

Secondary Analyses Stratified by NSTEMI versus STEMI

We performed secondary analyses stratified by MI type since patients with higher A1C levels were more likely to present with STEMI. In these analyses, the association between A1C and in-hospital mortality differed in NSTEMI as compared to STEMI patients ($p_{\text{interaction}}=0.03$). In NSTEMI, we observed no association in multivariable regression between either low A1C (A1C <5.5%, OR 1.06, 95% CI 0.50-2.27) or high A1C (A1C $\geq$ 9.5%, OR 0.83, 95% CI 0.52-1.33) and mortality as compared to patients in the referent group (A1C 6.5-<7%) (Table III). Similarly, in STEMI, low A1C was not associated with in-hospital mortality as compared to the referent group (A1C <5.5%, OR 0.59, 95% CI 0.16-1.56, Table III). However, STEMI patients with A1C $\geq$ 9.5% had excess mortality as compared to the referent group (OR 1.99, 95% CI 1.06-3.73, Table III).

Discussion

Contrary to our hypothesis, we observed no evidence for a J-shaped relationship between A1C and mortality in patients with diabetes presenting with acute MI. There was no association between low A1C and in-hospital mortality even in analyses restricted to patients receiving pharmacologic therapy for diabetes. We did observe a modest association between increasing A1C and mortality when analyzing A1C as a continuous variable.

While three prior studies have assessed the association between A1C and mortality in acute MI and found no association,^{8, 9, 18} these studies were limited to single centers and had small sample sizes (largest $n=521$ patients). Importantly, the association between low A1C and mortality was not examined. In contrast, our study uses a large, nationally representative registry and is the largest analysis reported of data assessing the associations between A1C and mortality among patients with diabetes and acute MI. The large sample size allowed us to examine the entire range of A1C values.

Our findings also provide further insight into the relation between glucose metabolism and mortality in the acute MI setting. Hypoglycemia during AMI has been shown to be associated with increased mortality,^{5, 19} but several studies provide evidence that low glucose may serve primarily as a marker rather than a mediator of adverse events.^{6, 20-23} An analysis of STEMI patients pooled from three large clinical trials demonstrated that admission hypoglycemia was most strongly associated with mortality in those patients with other features known to be associated with increased risk.²⁰ In addition, a large registry of acute MI patients demonstrated that only spontaneous, and not iatrogenic, hypoglycemia was associated with more adverse outcomes.²¹ Similarly, a post-hoc analysis of clinical trials of insulin therapy in acute MI found only admission and not post-admission hypoglycemia to be a predictor of mortality.²² Finally, a separate post-hoc analysis of another trial of insulin therapy in acute MI found that although hypoglycemia was more

prevalent in patients with high-risk features, it was not an independent risk factor for mortality.²³ We found that low A1C was not associated with in-hospital mortality in patients with diabetes and AMI. These findings are consistent with glucose serving as a risk-marker. Low A1C, which reflects longer term low glucose levels, should not be associated with increased mortality if glucose is primarily serving as a marker of acute illness severity.

The results of our stratified analysis A1C and mortality may differ by type of MI. The findings in our study of a significant crude association between low A1C and mortality in patients with NSTEMI, which was attenuated upon multivariable adjustment, suggests that shared risk factors between low A1C and in-hospital mortality in NSTEMI may account for our observations. Consistent with this, patients with diabetes and NSTEMI tend to be older and have more severe co-morbidities,²⁷ including chronic renal insufficiency and anemia, known to be associated with low A1C.²⁸ In contrast, the findings of a significant association between A1C and mortality in the highest A1C category in STEMI patients suggests that long-term glucose control has an association with in-hospital mortality in these patients independent of those factors known to be associated with mortality in the MI setting. In these patients with severe long-term dysglycemia, glucose may be potentially serving both as a marker and mediator of adverse effects.

A strength of the present study is the use of a nationally representative registry, which increases the generalizability of our findings and reduces the selection bias that is inherent in clinical trials. In addition, the large number of patients allowed for classification of A1C into multiple categories as well as for stratification of analyses by MI type. Some limitations warrant discussion. Patients not surviving to hospital presentation are not registered, and associations between A1C and mortality may be different in that subset. The substantial proportion of patients with diabetes who did not have A1C reported and the difference in patients with regard to A1C collection status with regard to demographic, clinical and hospital level characteristics limits the generalizability of our findings. In addition, these differences may have lead to ascertainment bias, as only 41% of patients with diabetes had A1C measured. Our analysis only examined in-hospital mortality and precludes generalization to longer-term survival considerations. Furthermore, we only examined mortality and not other CV outcomes such as recurrent MI, stroke, heart failure, and arrhythmia.

In this large contemporary cohort of patients with diabetes presenting with acute MI, we did not observe a J-shaped association between A1C and in-hospital mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Adjusted in-hospital mortality by continuous initial hemoglobin A1C level

Table I

Characteristics of 38, 907 subjects with diabetes according to hemoglobin A1C collection status

Baseline Characteristics	Not Collected	Collected
<u>N</u>	22,903	16,004
Age, years *	68.2±13	64.7±13
Female Gender, % (n)	41.9 (9594)	38.8 (6213)
White race, % (n)	80.8 (18,500)	77.6 (12,426)
Hypertension, % (n)	86.0 (19,702)	84.7 (13,560)
Dyslipidemia, % (n)	70.1 (16,061)	70.0 (11,201)
Current/recent smoker, % (n)	23.2 (5317)	29.2 (4679)
Prior MI, % (n)	35.8 (8201)	30.6 (4890)
Peripheral arterial disease, % (n)	16.9 (3860)	13.7(2198)
Clinical and hospital characteristics		
In-hospital death, % (n)	7.8 (1625)	3.7 (561)
ST elevation MI, % (n)	28.2 (6458)	32.5 (5205)
Heart failure on presentation, % (n)	28.1 (6433)	23.7 (3791)
Shock on presentation , % (n)	3.9 (885)	2.7 (430)
Heart rate on presentation (bpm) *	88±24	88±23
Systolic blood pressure on presentation (mmHg) *	143±34	146±34
Peak troponin, % (n) †	79.6 (13,890)	82.6 (10,526)
Initial creatinine value (mg/dL) * ‡	1.4±0.8	1.3±0.8
Initial hemoglobin (g/dL) *	12.9±2	13.3±2
Academic medical center, % (n) §	22.5 (5158)	30.4 (4860)
Cardiothoracic surgery available, % (n)	83.1 (19,042)	90.5 (14,491)
Hospital Region, % (n)		
West	15.7 (3601)	11.7 (1867)
Northeast	11.4 (2617)	9.7 (1560)
Midwest	33.9 (7763)	34.8 (5577)

Baseline Characteristics	Not Collected	Collected
South	39 (8922)	43.7 (7000)

* means $\pm$ standard deviation

[†] defined as % of subjects with peak troponin > 5 times the upper limit of normal (xULN); troponin levels vary by assay type and reference ranges across different hospital sites.

[‡] non-dialysis patients

[§] Academic affiliation reflects listing in Council of Teaching Hospitals

Table II

Crude mortality rates and crude and multivariable adjusted odds ratios with 95% CI of in-hospital mortality according to hemoglobin A1C category

Hemoglobin A1C Category (%)	Overall N	Death, % (n)	Crude Odds Ratio (95% CI)	Multivariable Adjusted Odds Ratio* (95% CI)
<5.5	388	4.6 (18)	1.24 (0.75-2.03)	0.81 (0.47-1.39)
5.5-<6	1154	4.8 (55)	1.26 (0.90-1.78)	1.12 (0.80-1.56)
6-<6.5	2136	3.9 (83)	1.03 (0.76-1.39)	0.94 (0.69-1.28)
6.5-<7	2293	3.8 (87)	1.0 (Referent)	1.0 (Referent)
7-<7.5	2025	4.1 (83)	1.09 (0.79-1.50)	1.08 (0.79-1.47)
7.5-<8	1559	3.1 (49)	0.81 (0.56-1.19)	0.91 (0.63-1.34)
8-<8.5	1130	4.0 (45)	1.05 (0.73-1.50)	1.18 (0.79-1.76)
8.5-<9	929	3.2 (30)	0.84 (0.55-1.3)	1.17 (0.77-1.78)
9-<9.5	688	3.9 (27)	1.03 (0.65-1.63)	1.45 (0.90-2.33)
≥9.5	3035	2.8 (84)	0.72 (0.53-0.98)	1.31 (0.94-1.83)

* Multivariable model adjusted for age, initial serum creatinine, systolic blood pressure on presentation, initial troponin ratio, heart failure or shock on admission (none, heart failure only, shock only, or heart failure with shock), electrocardiographic findings (ST elevations, ST segment changes, no ST segment changes), heart rate on presentation, prior history of peripheral arterial disease

Table III

Crude and multivariable adjusted odds ratios with 95% CI of mortality according to hemoglobin A1C category in subjects receiving therapy for diabetes and stratified by MI type

Hemoglobin A1C Category (%)	Overall (n=12,716)		NSTEMI (n=8,704)		STEMI (n=4,012)	
	Crude Odds Ratio (95% CI)	Multivariable Adjusted Odds Ratio* (95% CI)	Crude Odds Ratio (95% CI)	Multivariable Adjusted Odds Ratio* (95% CI)	Crude Odds Ratio (95% CI)	Multivariable Adjusted Odds Ratio* (95% CI)
<5.5	1.39 (0.79-2.46)	0.85 (0.45-1.62)	1.44 (0.76-2.76)	1.06 (0.50-2.27)	1.34 (0.45-4.03)	0.49 (0.16-1.56)
5.5-<6	1.53 (1.05-2.23)	1.27 (0.88-1.85)	1.82 (1.17-2.83)	1.42 (0.91-2.23)	1.03 (0.48-2.21)	0.96 (0.46-2.00)
6-<6.5	1.04 (0.73-1.50)	0.92 (0.64-1.33)	1.15 (0.73-1.82)	0.96 (0.60-1.54)	0.85 (0.42-1.71)	0.76 (0.37-1.57)
6.5-<7	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
7-<7.5	1.10 (0.77-1.57)	1.10 (0.77-1.57)	1.11 (0.75-1.65)	1.01 (0.67-1.52)	1.06 (0.55-2.06)	1.32 (0.68-2.56)
7.5-<8	0.81 (0.52-1.24)	0.90 (0.58-1.39)	0.88 (0.55-1.41)	0.92 (0.58-1.48)	0.68 (0.30-1.52)	0.85 (0.35-2.06)
8-<8.5	1.07 (0.69-1.65)	1.23 (0.77-1.95)	1.31 (0.79-2.16)	1.51 (0.88-2.57)	0.65 (0.30-1.39)	0.76 (0.33-1.77)
8.5-<9	0.86 (0.55-1.34)	1.20 (0.78-1.86)	0.84 (0.46-1.52)	0.96 (0.51-1.80)	0.87 (0.41-1.87)	1.85 (0.82-4.17)
9-<9.5	1.11 (0.67-1.82)	1.55 (0.93-2.58)	1.00 (0.54-1.86)	1.38 (0.72-2.63)	1.26 (0.52-3.02)	1.94 (0.81-4.62)
≥9.5	0.71 (0.50-1.00)	1.25 (0.87-1.79)	0.52 (0.33-0.81)	0.83 (0.52-1.33)	0.87 (0.48-1.57)	1.99 (1.06-3.73)

* Multivariable model adjusted for age, initial serum creatinine, systolic blood pressure on presentation, initial troponin ratio, heart failure or shock on admission (none, heart failure only, shock only, or heart failure with shock), electrocardiographic findings (ST elevations, ST segment changes, no ST segment changes), heart rate on presentation, prior history of peripheral arterial disease