# Temporal trends and hospital variation in the management of severe hyperglycemia among patients with acute myocardial infarction in the United States

**Lakshmi Venkitachalam, PhD,[a] Darren K. McGuire, MD, MHSc,[b] Kensey Gosch, MS,[c] Kasia Lipska, MD,[d] Silvio E. Inzucchi, MD,[d] Marcus Lind, MD,[e] Abhinav Goyal, MD, MHS,[f] John A. Spertus, MD, MPH,[a,c] Frederick A. Masoudi, MD, MSPH,[g] Philip G. Jones, MS,[c] and Mikhail Kosiborod, MD[a,c]** ***Kansas City, MO; Dallas, TX; New Haven, CT; Uddevalla, Sweden; Atlanta, GA; and Aurora, CO***

**Background** Elevated blood glucose is associated with higher mortality in patients with acute myocardial infarction (AMI). Although clinical guidelines recommend targeted glucose control in this group, clinical trials have yielded inconclusive results. Our objective was to understand how this lack of evidence impacts the management of severe hyperglycemia in routine practice.

**Methods** We examined insulin use among 4,297 AMI admissions with a mean hospitalization blood glucose of ≥200 mg/dL across 55 US hospitals from 2000 to 2008. Temporal trends and interhospital variation in 2 measures of insulin use during hospitalization—any (subcutaneous, intravenous [IV], short acting, long acting) and IV insulin—were examined using hierarchical Poisson regression models.

**Results** Of the 4,297 admissions, 2,618 (61%) received any insulin and 538 (13%) received IV insulin. After multivariable adjustment, a slight increase in insulin use was observed per admission year (relative risk [RR] 1.06, 95% CI 1.01-1.11). There was a modest (albeit nonsignificant) increase in IV insulin use seen before May 2004 (RR 1.18, 95% CI 0.96-1.47), with no significant change thereafter (RR 0.99, 95% CI 0.92-1.09). Marked variability in insulin use was observed across hospitals (median rate ratio 1.5 [any insulin] and 1.8 [IV insulin]), which did not change over time.

**Conclusions** Insulin use among patients with AMI and severe hyperglycemia has remained low over the past decade, with substantial and persistent interhospital variation. These observations reflect marked clinical uncertainty with regard to glucose management in AMI, underscoring the imperative for a definitive clinical trial in this field. (Am Heart J 2013;166:315-324.e1.)

Elevated blood glucose (BG) is common in patients hospitalized with acute myocardial infarction (AMI) and portends a poor prognosis both inhospital and long term.[1-7] Despite this inarguable epidemiologic association and numerous plausible mechanisms by which hyperglycemia may mediate excess cardiovascular risk in the setting of AMI,[8] it remains unclear whether elevated glucose is simply a marker of greater disease severity or a direct cause of harm (and thereby a target for therapeutic intervention).

Although cardiology and endocrinology professional society guidelines over the past decade have endorsed targeted glucose control for patients with AMI,[9-12] these recommendations were based principally on expert opinion and extrapolation of data from non-AMI cohorts because few data exist with regard to the clinical efficacy and safety of targeted glucose control in this setting. The clinical trials of this approach in patients with AMI are scarce and methodologically limited and offer inconclusive results,[13-15] with the data from trials in other selected intensive care unit populations being equally conflicting.[16-18]

Some studies examining the role of insulin in glucose control have highlighted improvement in myocardial blood flow, reduction in the generation of reactive oxygen species, and other beneficial effects with insulin

*From the [a]University of Missouri-Kansas City School of Medicine, Kansas City, MO, [b]University of Texas Southwestern Medical Center, Dallas, TX, [c]Saint Luke's Mid America Heart Institute, Kansas City, MO, [d]Yale University School of Medicine, New Haven, CT, [e]Department of Medicine, Uddevalla Hospital, Uddevalla, Sweden, [f]Emory Rollins School of Public Health and Emory School of Medicine, Atlanta, GA, and [g]Department of Medicine, Division of Cardiology, University of Colorado, Aurora, CO.*

*Raymond J. Gibbons, MD, served as guest editor for this article.*

*Submitted May 20, 2012; accepted May 13, 2013.*

*Reprint requests: Mikhail Kosiborod, MD, Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City School of Medicine, 4401 Wornall Road, Kansas City, MO 64111.*
*E-mails: mkosiborod@saint-lukes.org, mikhail.kosiborod@gmail.com*

*0002-8703/$ - see front matter*



*http://dx.doi.org/10.1016/j.ahj.2013.05.012*

use, and professional societies have endorsed insulin administration as the most effective current method for glucose control among hospitalized patients.[19] However, the complexities of insulin infusion for targeted glucose control, concerns about associated risk of hypoglycemia, and persistent questions about clinical efficacy and safety of this approach in patients with AMI have generated substantial uncertainty among clinicians about its application in practice. How this uncertainty has impacted the implementation of the guideline recommendations for treatment of hyperglycemia in patients with AMI is unknown. Addressing these gaps in knowledge is important because both "glucose neglect" and overly aggressive glucose control may adversely impact patient outcomes.

Accordingly, using data from a large US national database of consecutive patients with AMI, we sought to examine temporal trends in the frequency and interhospital variability of insulin use over the past decade among patients with AMI and severe, persistent hyperglycemia.

## Methods

### Study cohort

Details about the Cerner HealthFacts database have been previously described.[7,20-23] Briefly, deidentified information on consecutive patients treated between January 1, 2000, and December 31, 2008, was collected from participating hospitals. Rigorous quality assurance efforts and audits were conducted on a regular basis to ensure data accuracy. Data collected included patient demographics, comprehensive pharmacy, and laboratory data (including all venous and finger-stick BG measurements during hospitalization), inhospital procedures (including cardiac catheterization, coronary artery bypass surgery, and percutaneous coronary intervention), medical history and comorbidities (determined from *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] diagnostic codes), and hospital characteristics. A total of 78 hospitals contributed data to the Health Facts database; the median number of patients from each site was 219 (interquartile range [IQR] 48-1,030), and the median duration of hospitals' participation was 2.9 years (IQR 1.2-5.3 years). These hospitals were comparable in their characteristics with those reported in other national registries[24]: they were mostly urban (88.5%), were less frequently teaching (35.9%) hospitals, and represented all geographic regions of the United States (Northeast 38.5%, Midwest 25.6%, South 26.9%, and West 9%) and a broad range of sizes (bed size 1-99, 26.9%; 100-199, 20.5%; 200-299, 23.1%; 300-499, 17.9%; and ≥500 beds, 11.5%). All data were deidentified before they were provided to the investigators; accordingly, an exemption from review was granted by the Saint Luke's Hospital Institutional Review Board. Funding for research was provided by the American Heart Association Career Development Award in Implementation Research awarded to Dr Kosiborod. Dr Venkitachalam was supported by the American Heart Association Pharmaceutical Roundtable–David and Stevie Spina Outcomes Research Postdoctoral Fellowship. The Cerner Corporation provided the data but had no role in study funding, design, analyses, manuscript drafting, or review of the manuscript. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

We identified 42,204 admission encounters with the primary diagnosis of AMI between January 1, 2000, and December 31, 2008 (using *ICD-9-CM* codes 410.xx and excluding 410.x2, which represents readmission after AMI) and at least 1 documented abnormal troponin value (defined as greater than upper limit of normal according to each participating hospital's reference assay) or creatine kinase MB fraction (defined as greater than twice the upper limit of normal according to each participating hospital's assay). Subsequently, patients discharged within 24 hours of admission (unless died inhospital, n = 1,419), those missing glucose values (n = 1,235), those with hospital length of stay longer than 31 days (n = 407), and those admitted to hospitals that treated fewer than 20 AMI admissions between 2000 and 2008 (n = 58) were excluded from the analysis. Because our focus was on patients with severe, persistent hyperglycemia, only those encounters among the 39,085 admissions from 56 hospitals with mean hospitalization glucose of ≥200 mg/dL (or 11.1 mmol/L) were included in this analysis. Our final cohort thus comprised 4,297 hospitalizations with severe persistent hyperglycemia and biomarker-confirmed AMI from 55 US hospitals.

### Inpatient glucose assessment and diabetes

The HealthFacts database provided access to all patients' glucose levels (capillary and plasma assessments) during hospitalization. Mean hospitalization glucose level was calculated as the average of all capillary and plasma glucose readings during a particular hospitalization episode. Similar to prior analyses,[7,20,21] patients were classified as having recognized diabetes mellitus if they had a corresponding *ICD-9-CM* code or were treated with an oral antihyperglycemic agent during hospitalization.

### End point—use of insulin therapy

Two measures of insulin use during hospitalization—administration of any insulin (subcutaneous, intravenous [IV], short acting, or long acting) and specifically IV insulin—were examined.

### Statistical analysis

Baseline patient demographic and clinical as well as hospital characteristics were summarized in the overall cohort and across admission years. Temporal trends in patient demographic and clinical factors, as well as hospital characteristics, were examined using the Mantel-Haenzel trend test for categorical variables and the linear trend test for continuous variables.

**Variation in the use of insulin therapy.** Differences in baseline characteristics by insulin use were examined using the $\chi^2$ test for categorical variables and the Student $t$ test for continuous variables. Temporal trends in the crude rates of insulin use were examined, in the overall cohort as well as by diabetes status, using the Mantel-Haenzel trend test for categorical variables. Then, to calculate the risk-adjusted estimated probability and the relative risk (RR) of insulin use per admission year, we used hierarchical Poisson regression analysis that accounted for random site effects and select patient characteristics (mean age, sex, race, diabetes, mean hospitalization glucose, and length of stay). Evidence for