

## ECONOMIC AND CLINICAL IMPACT OF INPATIENT DIABETIC HYPOGLYCEMIA

Suellen M. Curkendall, PhD<sup>1\*</sup>; Jaime L. Natoli, MPH<sup>1</sup>; Charles M. Alexander, MD<sup>2</sup>; Brian H. Nathanson, PhD<sup>3</sup>; Tracy Haidar, PharmD<sup>1</sup>; Robert W. Dubois, MD, PhD<sup>1</sup>

### ABSTRACT

**Objective:** To assess the clinical and economic impact of hypoglycemia that develops during hospitalization of patients with diabetes.

**Methods:** In this retrospective cohort study, data from 70 hospitals were used to identify the first inpatient encounter for adult patients with diabetes. Patients were included if all blood glucose measurements were 70 mg/dL or higher during the first 24 hours and their primary discharge diagnosis was for a condition other than hypoglycemia. Those who developed laboratory evidence of hypoglycemia (blood glucose <70 mg/dL after 24 hours) were compared with patients whose blood glucose values were all 70 mg/dL or higher. An alternative definition of hypoglycemia (blood glucose <50 mg/dL after 24 hours) was also evaluated. We adjusted for potential confounders with multivariate models.

**Results:** Hypoglycemia had an adverse effect on all outcomes among more than 100 000 diabetic patients. After adjustment, patients with diabetes who developed hypoglycemia had higher charges (38.9%), longer lengths of stay (3.0 days), higher mortality (odds ratio, 1.07; 95% confidence interval, 1.02-1.11), and higher odds of being discharged to a skilled nursing facility (odds ratio, 1.58; 95% confidence interval, 1.48-1.69) than diabetic patients without hypoglycemia ( $P < .01$  for all). In all cases, using

the lower threshold (<50 mg/dL) to define hypoglycemia resulted in similar findings with a larger magnitude of differences.

**Conclusions:** Although a direct causal relationship cannot be inferred, these study findings suggest the importance of carefully maintaining euglycemia during hospitalizations. Whether the observed worse outcomes were due to hypoglycemia itself or whether they were a marker of worse outcomes due to other causes requires further research. (**Endocr Pract.** 2009;15:302-312)

### Abbreviations:

CI = confidence interval; ED = emergency department; EMR = electronic medical record; HIPAA = Health Insurance Portability and Accountability Act; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; OR = odds ratio; SNF = skilled nursing facility

### INTRODUCTION

Hypoglycemia is a common complication of diabetes and is associated with impaired quality of life, short-term work disability, and increased health care use, including hospitalization and emergency department (ED) visits (1-6).

Hypoglycemic events also have a substantial financial impact (3-5,7,8). A Scottish study using data from 1997-1998 demonstrated that the emergency treatment of diabetic hypoglycemia was associated with direct costs of £41 (US \$68) per case and hospital costs of £1593 (US \$2638) per day (5). When extrapolated to the entire UK population, the annual cost was approximately £13 million (US \$21.5 million). A small US study of data from 1992-1998 examined insulin-treated patients with diabetes and found that the mean cost of hypoglycemia requiring medical attention was \$1186 per episode (range: \$181 to \$4924), or \$7.04 per patient per month (7). Hospital costs (\$4924) exceeded costs for ED treatment (\$812). An analy-

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From <sup>1</sup>Cerner LifeSciences, Beverly Hills, California; <sup>2</sup>Merck & Co, Inc, Upper Gwynedd, Pennsylvania; and <sup>3</sup>OptiStatim, LLC, Longmeadow, Massachusetts.

\*Suellen Curkendall was an employee of Cerner LifeSciences at the time the research was conducted and is now employed by Thomson Reuters, Washington, DC.

Address correspondence and reprint requests to Jaime L. Natoli, Cerner LifeSciences, 9100 Wilshire Blvd, Suite 655 E, Beverly Hills, CA 90212. E-mail: jaime.natoli@cerner.com.

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sis of insurance claims from 5 large US employers during 1999-2001 found that diabetic patients with hypoglycemia had incrementally higher medical expenditures of \$3241 per patient compared with expenditures of patients without hypoglycemia (4). Studies addressing the incremental cost for diabetic patients of having hypoglycemia while hospitalized are unavailable.

Studies that have examined the association between diabetic hypoglycemia and death have provided mixed results (9-12). In a study of diabetic patients admitted for angina or acute myocardial infarction, the development of hypoglycemia during hospitalization was associated with an increased risk in short-term mortality (12). In contrast, a recent report from the DIGAMI 2 trial (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2) indicated that hypoglycemia was not associated with long-term mortality in diabetic patients with acute myocardial infarction after a median follow-up time of 2 years (11).

The primary objective of this study was to gain a better understanding of the clinical and economic impact of hypoglycemia that develops during hospitalization of patients with diabetes. A secondary objective was to analyze the effect of hypoglycemia occurring as a comorbidity at the time a patient with diabetes is admitted to the hospital or to the ED. This study was conducted among a large number of patients with diabetes who presented to the ED and/or were admitted to 1 of 70 hospitals in the United States.

## RESEARCH DESIGN AND METHODS

### Data Source

This retrospective cohort study used encounter-level data from a subset of 70 hospitals in the *Health Facts*® electronic medical record (EMR) database (Cerner Corporation, Kansas City, Missouri). Cerner Corporation has established Health Insurance Portability and Accountability Act (HIPAA)-compliant operating policies and procedures for extracting, translating, loading, and removing all personal health information (de-identifying) before depositing the EMR data in the *Health Facts* database. As such, the system and process are deemed to be HIPAA-exempt with regard to institutional review board oversight, although each participating institution's independent institutional review board has the right to make a determination based on their own interpretation of HIPAA regulations and enforcement. To date, no institution has determined that *Health Facts* is HIPAA-waivered instead of HIPAA-exempt, nor has any institution's institutional review board found that individual patient informed consent is required.

Hospital billing and encounter data are integrated with clinical information relating to drug orders and dispensing data, as well as to the results of diagnostic laboratory testing. Data used in this study included medication orders and dispensing information, serum blood glucose values and lab draw times, the patient's *International Classification*

*of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnoses for both the study encounter and previous encounters, and the patient's care setting (ED vs inpatient). Some blood glucose values from capillary whole blood samples (eg, fingerstick samples) were entered into the hospital database and were converted to a serum blood glucose equivalent by multiplying the whole blood value by 1.15.

### Inclusion Criteria and Study Group Definitions

Inpatient and ED encounters for nonpregnant adults ( $\geq 18$  years) with diabetes treated between January 1, 2000, and December 31, 2006, were identified. Patients presenting to the ED and subsequently admitted as inpatients were considered as having 1 hospital encounter. If a patient had more than 1 encounter during the study period, only the patient's first encounter was used.

Patients with diabetes were identified using a combination of ICD-9-CM codes and medication use. Patients with any of the following before or during the encounter were classified as having diabetes: (a) an ICD-9-CM code for diabetes (250.xx), (b) use of oral antihyperglycemic agents or noninsulin injectables, or (c) use of long-acting insulin, intermediate-acting insulin, or insulin mixtures.

To evaluate hypoglycemia that occurred exclusively during the inpatient hospital stay, encounters in which patients *developed* hypoglycemia only after the first 24 hours in the hospital or in the ED were identified using laboratory blood glucose measurements. In this group, patients initially presented with normal blood glucose levels, defined as a blood glucose concentration of 70 mg/dL or higher during the first 24 hours, and subsequently developed laboratory evidence of hypoglycemia (blood glucose  $< 70$  mg/dL). The comparison cohort consisted of patients who neither presented with nor developed hypoglycemia. These patients had blood glucose measurements of 70 mg/dL or greater within the first 24 hours *and* either no subsequent blood glucose measurements or all subsequent measurements 70 mg/dL or greater. A secondary analysis evaluated patients who presented with hypoglycemia as a comorbidity, defined as the first blood glucose value during the first 24 hours in the hospital or in the ED of less than 70 mg/dL.

Encounters with no blood glucose values during the first 24 hours were excluded because initial hypoglycemia status was unknown. Encounters with a primary inpatient diagnosis or any ED diagnosis of hypoglycemia (ICD-9-CM code 251.0, 251.1, or 251.2) were excluded because hypoglycemia was considered to be likely due to prescribed antihyperglycemic medications taken before the ED or hospital encounter.

### Outcomes and Statistical Analyses

Study outcomes were total hospital charges, length of hospital stay, hospital mortality, and discharge to a skilled

nursing facility (SNF). Charges were converted to 2006 US dollars using the US Consumer Price Index for medical care services (13). Both hospital mortality and discharge to a SNF were based on hospital discharge status. Patients who were originally admitted from a SNF were excluded from analyses of SNF discharge.

All analyses were restricted to encounters with an inpatient component (ie, patients whose hospital stays were confined to the ED were excluded). The comparison group for both hypoglycemia cohorts (ie, developed hypoglycemia, presented with hypoglycemia) consisted of patients without hypoglycemia. Comparisons were adjusted for potential confounders using general linear model multivariate regression and propensity scores. Statistical analyses were conducted using Stata/SE 10.0 (StataCorp, College Station, Texas).

Regression covariance adjustment, in which the propensity score for hypoglycemia is used as one of the covariates in each outcome model, was used to control for potential confounding caused by nonrandom cohort assignments (14). Propensity scores were estimated using nonparsimonious logistic regression models (15-17) with hypoglycemia status as the outcome variable and the other independent variables as predictors. This method is consistent with propensity score modeling in epidemiologic studies (15), and this nonparsimonious approach is better suited than more parsimonious models for bias reduction (16). The propensity score value was entered as a continuous variable in each model, which is appropriate given the very large size of the data set (14,15,17).

The hypoglycemia variable and the propensity score variables were included in all general linear models; other predictors entered the model based on their relationship with the relevant outcome as assessed by the bootstrapping stepwise approach of Austin and Tu (18). These predictors included age, sex, race, diagnoses of diabetes-specific complications, events and conditions during the hospitalization (ie, acute myocardial infarction, dialysis, ketoacidosis, high serum creatinine, gastrointestinal surgery, infection, sepsis, surgical vs medical), comorbid hypertension, heart failure, stroke, peripheral vascular disease, chronic kidney disease, chronic lung disease, gastrointestinal disease, cancer, adrenal/pituitary disorders, Charlson comorbidity index (19), insulin-use status, and hospital characteristics. Spline terms for age and clinically plausible interactions with age and other comorbidities were assessed. Models with main effects only (ie, no interactions) were compared with models with statistically significant interactions using the Bayesian Information Criterion statistic to determine the best model in terms of fit and parsimony (20). All general linear models used robust standard error estimates that adjusted for the hospital in which the patient was treated (21). The coefficients and standard errors for each final model were estimated from 500 bootstraps (with replacement) using a bias-correcting algorithm (22,23).

Sensitivity analyses (including unique propensity score models) based on an alternative definition of hypoglycemia (blood glucose <50 mg/dL) also were conducted.

## RESULTS

Of the 4 638 770 encounters in the data set, a total of 519 317 relevant encounters for 215 922 nonpregnant adults with diabetes were identified. Among these, 8234 hospitalized patients (19487 encounters) developed laboratory evidence of hypoglycemia after 24 hours, 3923 patients (8971 encounters) presented with laboratory evidence of hypoglycemia during the first 24 hours, and 95 579 patients (176 989 encounters) did not have evidence of hypoglycemia (Fig. 1).

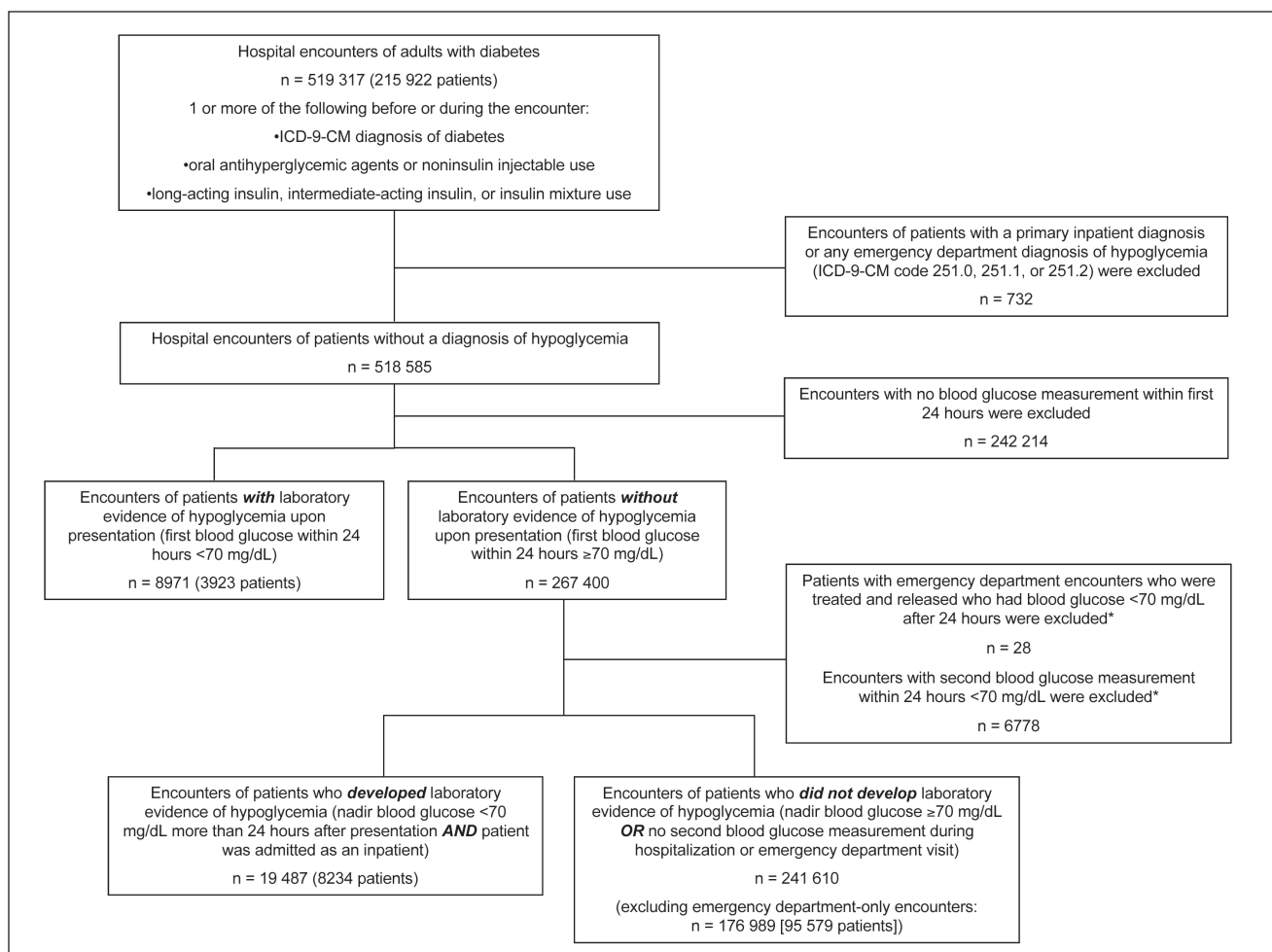
The demographics of patients who developed hypoglycemia differed from patients without hypoglycemia. Compared with patients without hypoglycemia, hypoglycemic patients were more likely to be female (53.1% vs 51.1%), African American (19.6% vs 14.6%), insulin-using (47.5% vs 23.9%), and to have type 1 diabetes (8.9% vs 4.7%) (all  $P < .01$ ) (Table 1). Patients who developed hypoglycemia also were slightly older, with a mean ( $\pm$  standard deviation) age of  $67.8 \pm 14.4$  years compared with  $65.7 \pm 14.5$  years for patients without hypoglycemia ( $P < .01$ ; inferences are from 2-sample  $t$  tests for proportions or continuous variables where applicable). Table 1 also shows the results of patients who presented with hypoglycemia. Both the patient groups who developed hypoglycemia and presented with hypoglycemia had a Charlson Comorbidity Score of  $2.6 \pm 1.6$  vs a score of  $2.1 \pm 1.5$  for patients without hypoglycemia ( $P < .001$ ).

With the exception of diabetes, the most common primary diagnoses were cardiac disorders including heart failure, myocardial infarction, and ischemic heart disease (Table 2). Most patients were hospitalized for medical rather than surgical care (Table 1).

Table 2 shows that patients who developed hypoglycemia were more likely to have a given comorbid condition than patients without hypoglycemia. Exceptions for which a condition was less prevalent among patients with hypoglycemia were hypertension (59.6% vs 64.6%,  $P < .001$ ) and gastrointestinal disease (14.4% vs 15.5%,  $P = .014$ ). Conversely, among patients who presented with hypoglycemia, only 9 of the 19 comorbidities were more common among patients with hypoglycemia than among those without hypoglycemia.

### Development of Hypoglycemia

Results of analyses for patients who developed hypoglycemia after being in the hospital or ED for 24 hours are presented in Table 3. At the univariate level, the development of hypoglycemia was associated with worse outcomes in hospitalized patients with diabetes. More importantly, this remained true after adjusting for differences in patient



**Fig. 1.** Hospital encounters of adult patients with diabetes: base-case analysis (hypoglycemia cut-off <70 mg/dL). The patient population excluded pregnant patients. The asterisks indicate that these 2 groups were not mutually exclusive. ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*.

characteristics and disease severity. Total charges were higher for patients who developed hypoglycemia (mean, \$85 905; median, \$33 446) than for those without evidence of hypoglycemia (mean, \$54 038; median, \$17 609;  $P < .001$ ). Due to the skewed distribution of charges, the best-fitting general linear model had a logarithmic link. The interpretation of the model's results indicates that development of hypoglycemia was associated with 38.9% higher total charges (95% confidence interval [CI], 35.6%-42.1%;  $P < .001$ ).

Length of hospital stay was significantly longer for patients who developed hypoglycemia (mean, 11.7 days; median, 8.0 days) than for patients without hypoglycemia (mean, 5.1 days; median, 3.8 days;  $P < .001$ ). The adjusted results indicate that hypoglycemia was associated with an increase in the average length of stay by 3.0 days (95% CI, 2.8-3.2;  $P < .001$ ).

Hypoglycemia was significantly associated with hospital mortality at the univariate level (4.79% mortality vs

2.26%,  $P < .001$ ). After adjustment for confounders, hypoglycemia was associated with a 7% increased odds of death (odds ratio [OR], 1.07; 95% CI, 1.02-1.11;  $P = .007$ ).

We excluded a small number of patients admitted from a SNF (<1% of all patients) when analyzing those who were discharged to a SNF. Patients who developed hypoglycemia during hospitalization were more likely to be discharged to a SNF than those without hypoglycemia (26.5% vs 14.5% at the univariate level,  $P < .001$ ). After adjustment, patients not originally from a SNF who had hypoglycemia were significantly more likely to be discharged to a SNF (OR, 1.58; 95% CI, 1.48-1.69;  $P < .001$ ).

For all outcomes, using a lower threshold to define hypoglycemia (<50 mg/dL) resulted in similar findings, with greater differences between the groups (Table 3).

### Presentation With Hypoglycemia

Findings of patients who presented with hypoglycemia were somewhat similar to those of patients who developed

**Table 1**  
**Characteristics of Hospitalized Diabetic Patients With Hypoglycemia**  
**(Blood Glucose <70 mg/dL) vs Hospitalized Diabetic Patients Without Hypoglycemia<sup>a</sup>**

Variable	Developed hypoglycemia after 24 hours (n = 8234)	Presented with hypoglycemia during first 24 hours (n = 3923)	No hypoglycemia during ED visit or hospitalization (n = 95 579)
Age, y			
Mean (SD)	67.8 (14.4)	67.6 (15.2)	65.7 (14.5)
Median (interquartile range)	70 (59-79)	71 (58-79)	67 (56-77)
Blood glucose, baseline, mg/dL			
Mean (SD)	207.7 (137.9)	53.3 (13.0)	187.5 (102.8)
Median (interquartile range)	170.2 (120-250)	57 (45-64)	160 (122-222)
Blood glucose, nadir after ≥24 h, mg/dL			
Mean (SD)	54.2 (11.9)	...	133.2 (52.8)
Median (interquartile range)	57 (47-64)	...	120 (97-154)
Blood glucose, maximum, mg/dL			
Mean (SD)	314.4 (161.4)	168.9 (136.1)	234.2 (138.1)
Median (interquartile range)	288 (199-400)	131 (63-235)	205 (148-288)
Charlson Comorbidity Index (score) <sup>b</sup>			
Mean (SD)	2.6 (1.6)	2.6 (1.6)	2.1 (1.5)
Median (interquartile range)	2 (1-3)	2 (1-3)	2 (1-3)
Sex			
Female, No. (%)	4372 (53.1)	2004 (51.1)	48 781 (51.1)
95% CI	52.0-54.2	49.5-52.7	50.7-51.4
Male, No. (%)	3860 (46.9)	1917 (48.9)	46 770 (48.9)
95% CI	45.8-48.0	47.3-50.4	48.6-49.3
Race			
White, No. (%)	5846 (71.0)	2863 (73.0)	72 075 (75.4)
95% CI	70.0-72.0	71.6-74.4	75.1-75.7
African American, No. (%)	1611 (19.6)	672 (17.1)	13 933 (14.6)
95% CI	18.7-20.4	16.0-18.3	14.4-14.8
Other known (eg, Asian) and unknown, No. (%)	777 (9.4)	388 (9.9)	9571 (10.0)
95% CI	8.8-10.1	9.0-10.9	9.8-10.2
Insulin use <sup>c</sup>			
No evidence of long- or intermediate-acting insulin use or type 1 diabetes, No. (%)	4321 (52.5)	2677 (68.2)	72 786 (76.2)
95% CI	51.4-53.6	67.8-69.7	75.8-76.4
Evidence of long- or intermediate-acting insulin use or type 1 diabetes, No. (%)	3913 (47.5)	1246 (31.8)	22 793 (23.8)
95% CI	46.4-48.6	30.3-33.2	23.6-24.1
Diabetes type <sup>d</sup>			
Type 1, No. (%)	731 (8.9)	349 (8.9)	4530 (4.7)
95% CI	8.3-9.5	8.0-9.8	4.6-4.9
Type 2, No. (%)	6109 (74.2)	2897 (73.9)	81 051 (84.8)
95% CI	73.2-75.1	72.4-75.2	84.6-85.0
Unknown, No. (%)	1394 (16.9)	677 (17.3)	9998 (10.5)
95% CI	16.1-17.8	16.1-18.5	10.3-10.7
Hospitalization type <sup>e</sup>			
Medical hospitalization, No. (%)	5188 (63.0)	2280 (58.1)	65 218 (68.2)
95% CI	62.0-64.1	56.6-60.0	67.9-68.5
Surgical hospitalization, No. (%)	2898 (35.2)	613 (15.6)	29 261 (30.6)
95% CI	34.2-36.2	14.5-16.8	30.3-30.9

Abbreviations: CI, confidence interval; ED, emergency department.

<sup>a</sup> The first encounter was used for patients who had more than 1 encounter.

<sup>b</sup> The Charlson Comorbidity Index is a method of scoring comorbidities according to the 1-year mortality risk for each condition. Each comorbidity is assigned a score of 1, 2, 3, or 6. The overall index reflects both the number and the severity of comorbid diseases.

<sup>c</sup> Evidence of insulin use was based on (a) patients with a type 1 diabetes *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis code during or before any encounter used in the study or (b) patients with long-acting insulin, intermediate-acting insulin, or insulin mixture use during or before any encounter used in the study. Remaining patients were classified as having no evidence of insulin use.

<sup>d</sup> Diabetes type was based on ICD-9 codes (type 1 diabetes: 250.x1, 250.x3; type 2 diabetes: 250.x0, 250.x2) before or during the encounter, including primary or secondary diagnoses. Patients with both type 1 and type 2 codes (as well as patients without a code) were classified as unknown.

<sup>e</sup> Hospitalization type was based on diagnosis-related group codes.

**Table 2**  
**Primary Diagnosis and Comorbidities of Hospitalized Diabetic Patients With Hypoglycemia (Blood Glucose <70 mg/dL) vs Hospitalized Diabetic Patients Without Hypoglycemia<sup>a</sup>**

Diagnosis or comorbidity	Developed hypoglycemia after 24 hours (n = 8234)		Presented with hypoglycemia during first 24 hours (n = 3923)		No hypoglycemia during ED visit or hospitalization (n = 95 579)	
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
Primary diagnosis (ICD-9 3-digit code) <sup>b</sup>						
Diabetes mellitus (250.x)	894 (10.9)	10.2-11.5	914 (23.3)	22.0-24.7	6423 (6.7)	6.6-6.9
Heart failure (428.x)	732 (8.9)	8.3-9.5	280 (7.1)	6.4-8.0	5416 (5.7)	5.5-5.8
Acute myocardial infarction (410.x)	502 (6.1)	5.6-6.6	74 (1.9)	1.5-2.4	4787 (5.0)	4.9-5.1
Other forms of chronic ischemic heart disease (414.x)	467 (5.7)	5.2-6.2	144 (3.7)	3.1-4.3	8196 (8.6)	8.4-8.8
Pneumonia, organism unspecified (486.x)	369 (4.5)	4.0-5.0	134 (3.4)	2.9-4.0	3142 (3.3)	3.2-3.4
Septicemia (038.x)	288 (3.5)	3.1-3.9	66 (1.7)	1.3-2.1	1483 (1.6)	1.5-1.6
Acute renal failure (584.x)	225 (2.7)	2.4-3.1	138 (3.5)	3.0-4.1	1159 (1.2)	1.1-1.3
Complications peculiar to certain specified procedures (996.x)	180 (2.2)	1.9-2.5	61 (1.6)	1.2-2.0	1626 (1.7)	1.6-1.8
Other diseases of lung (518.x)	173 (2.1)	1.8-2.4	38 (1.0)	0.7-1.3	948 (1.0)	0.9-1.1
Comorbidities during encounter <sup>c</sup>						
Infection	3847 (46.7)	45.6-47.8	1152 (29.4)	27.9-30.8	27 160 (28.4)	28.1-28.7
Gastrointestinal surgery	1508 (18.3)	17.5-19.2	389 (9.9)	9.0-10.9	12 432 (13.0)	12.8-13.2
Dialysis during encounter	883 (10.7)	10.1-11.4	304 (7.7)	7.0-8.6	3398 (3.6)	3.4-3.7
Bacteremia/sepsis	566 (6.9)	6.3-7.4	90 (2.3)	1.8-2.8	2092 (2.2)	2.1-2.3
Seizure (nonepileptic)	248 (3.0)	2.7-3.4	81 (2.1)	1.6-2.6	2060 (2.2)	2.1-2.2
Diabetes with ketoacidosis	128 (1.6)	1.3-1.8	4 (0.1)	0.0-0.3	500 (0.5)	0.5-0.6
Adrenal and pituitary disorders	61 (0.7)	0.6-1.0	24 (0.6)	0.4-0.9	440 (0.5)	0.4-0.5
Coma (nonhepatic)	28 (0.3)	0.2-0.5	5 (0.1)	0.0-0.3	129 (0.1)	0.1-0.2
Comorbidities during encounter or in previous 12 months <sup>d</sup>						
Hypertension	4910 (59.6)	58.6-60.7	2235 (57.0)	55.4-58.5	61 714 (64.6)	64.3-64.8
Heart disease, other	4441 (53.9)	52.9-55.0	1731 (44.1)	42.6-45.7	46 643 (48.8)	48.5-49.1
Infection	4356 (52.9)	51.8-54.0	1499 (38.2)	36.7-39.7	33 993 (35.6)	35.3-35.9
Heart failure	2523 (30.6)	29.6-31.6	914 (23.3)	22.0-24.7	16 930 (17.7)	17.5-18.0
Chronic kidney disease	2336 (28.4)	27.4-29.4	886 (22.6)	21.3-23.9	11 031 (11.5)	11.3-11.7
Chronic lung disease	1850 (22.5)	21.6-23.4	664 (16.9)	15.8-18.1	17 902 (18.7)	18.5-19.0
Gastrointestinal surgery	1808 (22.0)	21.1-22.9	569 (14.5)	13.4-15.6	16 250 (17.0)	16.8-17.2
Gastrointestinal disease	1188 (14.4)	13.7-15.2	514 (13.1)	12.1-14.2	14 763 (15.4)	15.2-15.7
Diabetes with neurologic manifestations	910 (11.1)	10.4-11.7	295 (7.5)	6.7-8.4	6175 (6.5)	6.3-6.6
Peripheral vascular disease	841 (10.2)	9.6-10.9	282 (7.2)	6.4-8.0	7182 (7.5)	7.3-7.7
Stroke/transient ischemic attack/cerebrovascular disease	638 (7.7)	7.2-8.3	257 (6.6)	5.8-7.4	6807 (7.1)	7.0-7.3
Cancer (malignant neoplasms)	634 (7.7)	7.1-8.3	275 (7.0)	6.2-7.9	6448 (6.7)	6.6-6.9
Diabetes with retinopathy or ophthalmic manifestations	552 (6.7)	6.2-7.3	166 (4.2)	3.6-4.9	2540 (2.7)	2.6-2.8
Acute myocardial infarction	361 (4.4)	4.0-4.8	94 (2.4)	1.9-2.9	2408 (2.5)	2.4-2.6
Diabetes with circulatory disorders	207 (2.5)	2.2-2.9	45 (1.2)	0.8-1.5	972 (1.0)	1.0-1.1
Liver disease	173 (2.1)	1.8-2.4	86 (2.2)	1.8-2.7	1911 (2.0)	1.9-2.1
Diabetes with ketoacidosis	146 (1.8)	1.5-2.1	8 (0.2)	0.1-0.4	635 (0.7)	0.6-0.7
Adrenal and pituitary disorders	70 (0.9)	0.7-1.1	29 (0.7)	0.5-1.1	606 (0.6)	0.6-0.7
Diabetes with hyperosmolarity	31 (0.4)	0.3-0.5	4 (0.1)	0.0-0.3	161 (0.2)	0.1-0.2

Abbreviations: CI, confidence interval; ED, emergency department; ICD-9, *International Classification of Diseases, Ninth Revision*.

<sup>a</sup> The first encounter was used for patients who had more than 1 encounter.

<sup>b</sup> Results are presented for codes present in at least 2.0% of patients in the developed-hypoglycemia group.

<sup>c</sup> Comorbidities during encounter defined based on any ICD-9 code listed as a secondary diagnosis during the encounter.

<sup>d</sup> Comorbidities defined based on any ICD-9 code listed as a secondary diagnosis during the encounter or any diagnosis at any time during the 12 months before the encounter.

**Table 3**  
**Comparison of Outcomes for Patients Who Developed Hypoglycemia After 24 Hours in the Hospital With Outcomes of Hospitalized Patients Without Hypoglycemia**

Outcome	Patients who developed hypoglycemia			Patients without hypoglycemia			Unadjusted comparison		Multivariate model results		
	No.	Mean or %	Median	No.	Mean or %	Median	Difference or OR <sup>a</sup>	P value	Difference or OR <sup>a</sup>	95% CI	P value
<b>Base-case analysis (blood glucose &lt;70 mg/dL)</b>											
Total charges, 2006 \$	6020	85 905	33 446	72 681	54 038	17 609	59%	<.001	39%	36-42	<.001
Length of stay, days	8234	11.7 days	8.0 days	95 579	5.1 days	3.8 days	6.6 days	<.001	3.0 days	2.8-3.2	<.001
Hospital mortality	7994	4.8%	...	93 012	2.3%	...	2.12	<.001	1.07	1.02-1.11	.007
Discharge to SNF <sup>b</sup>	7787	26.5%	...	93 134	14.5%	...	1.83	<.001	1.58	1.48-1.69	<.001
<b>Sensitivity analysis (blood glucose &lt;50 mg/dL)</b>											
Total charges, 2006 \$	2088	98 304	25 401	72 681	54 038	17 609	82%	<.001	50%	43-55	<.001
Length of stay, days	2896	13.6 days	9.1 days	95 579	5.1 days	3.8 days	8.6 days	<.001	4.2 days	3.8-4.6	<.001
Hospital mortality	2783	6.3%	...	93 012	2.3%	...	2.80	<.001	1.16	1.09-1.30	<.001
Discharge to SNF <sup>b</sup>	2699	30.1%	...	93 134	14.5%	...	2.07	<.001	1.84	1.65-2.04	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; SNF, skilled nursing facility.

<sup>a</sup> Difference is shown as the percentage difference for charges, mean difference in days for length of stay, odds ratio for hospital mortality, and odds ratio for discharge to SNF.

<sup>b</sup> Patients who were admitted to the hospital from a SNF were excluded from this analysis.

hypoglycemia, but the differences were smaller and sometimes did not reach statistical significance (Table 4). After adjustment, hypoglycemia within the first 24 hours was associated with higher total charges (coefficient, 0.300; 95% CI, 0.052-0.557;  $P = .019$ ), but not significantly longer length of stay (coefficient, 0.2 days; 95% CI, 0.0-0.3;  $P = .054$ ). Although patients who presented with hypoglycemia had higher in-hospital mortality rates than patients without hypoglycemia (3.6% compared with 2.3% [ $P < .001$ ]), the difference was not significant after multivariate adjustment for confounders (OR, 1.01; 95% CI, 0.94-1.08;  $P = .868$ ).

Among hospitalized patients who were not in a SNF before hospital admission, 20.2% of those who presented with hypoglycemia were discharged to a SNF compared with 14.5% of patients who did not have hypoglycemia during their hospital stay ( $P < .001$ ). After adjustment, patients with hypoglycemia not originally from a SNF were significantly more likely to be discharged to a SNF (OR, 1.14; 95% CI, 1.03-1.28;  $P = .033$ ).

For both hospital length of stay and mortality, using a lower threshold to define hypoglycemia (<50 mg/dL) resulted in similar findings (Table 4). For total charges, however, the magnitude decreased and was not statistically significant. In contrast, the odds of being discharged to a SNF remained significant and increased slightly.

## DISCUSSION

We found that laboratory-documented hypoglycemia was associated with worse outcomes among a large number of hospitalized patients with diabetes in the United States. After multivariate adjustment, patients with diabetes who developed hypoglycemia during their hospitalization had higher charges, longer lengths of stay, higher odds of not surviving their hospitalization, and higher odds of being discharged to a SNF than hospitalized patients with diabetes who did not have hypoglycemia. Patients who presented with hypoglycemia followed similar trends, particularly among patients discharged to a SNF, although the

**Table 4**  
**Comparison of Outcomes for Patients Who Presented With Hypoglycemia**  
**(Determined by Blood Glucose Concentration During the First 24 Hours in the Hospital)**  
**With Outcomes of Hospitalized Patients Without Hypoglycemia**

Outcome	Patients who presented with hypoglycemia			Patients without hypoglycemia			Unadjusted comparison		Multivariate model results		
	No.	Mean or %	Median	No.	Mean or %	Median	Difference or OR <sup>a</sup>	P value	Difference or OR <sup>a</sup>	95% CI	P value
<b>Base-case analysis (blood glucose &lt;70 mg/dL)</b>											
Total charges, 2006 \$	2218	58 364	16 193	72 681	54 038	17 609	8%	.600	30% <sup>c</sup>	5-56	.019
Length of stay, days	2916	6.3 days	4.2 days	95 579	5.1 days	3.8 days	1.2 days	<.001	0.2 days	0-0.3	.054
Hospital mortality	2819	3.6%	...	93 012	2.3%	...	1.57	<.001	1.01	0.94-1.08	.868
Discharge to SNF <sup>b</sup>	2794	20.2%	...	93 134	14.5%	...	1.39	<.001	1.14	1.03-1.28	.033
<b>Sensitivity analysis (blood glucose &lt;50 mg/dL)</b>											
Total charges, 2006 \$	654	68 851	16 310	72 681	54 038	17 609	27%	.326	5%	-5 to 14	.298
Length of stay, days	848	6.2 days	4.2 days	95 579	5.1 days	3.8 days	1.1 days	<.001	0.2 days	-0.1 to 0.6	.147
Hospital mortality	811	4.8%	...	93 012	2.3%	...	2.09	<.001	1.08	0.96-1.27	.266
Discharge to SNF <sup>b</sup>	803	22.7%	...	93 134	14.5%	...	1.56	<.001	1.28	1.02-1.53	.015

Abbreviations: CI, confidence interval; OR, odds ratio; SNF, skilled nursing facility.

<sup>a</sup> Difference is shown as the percentage difference for charges, mean difference in days for length of stay, odds ratio for hospital mortality, and odds ratio for discharge to SNF.

<sup>b</sup> Patients who were admitted to the hospital from a SNF were excluded from this analysis.

<sup>c</sup> This model included an interaction between hypoglycemia and age, meaning that the effect of hypoglycemia was not constant over age. The coefficient on age (in years) was 0.008, the coefficient on hypoglycemia was 0.300, and the interaction term coefficient was -0.004. All else equal, this implies a 62% increase in charges for hypoglycemia for an 80-year-old patient and a 40% increase for a 25-year-old patient. However, the CI for the hypoglycemia coefficient was very wide.

differences were not as large and often not statistically significant after adjustment for potential confounders.

These potential consequences of hypoglycemia, especially the development of hypoglycemia in the hospital setting, may be underrecognized. According to a review of inpatient diabetes management by Clement and colleagues, institutions are more likely to have nursing protocols for treatment of hypoglycemia rather than for its prevention (24). A prospective study in a French geriatric hospital found that 24% of diabetic patients had a hypoglycemic episode (fingerstick glucose <4 mmol/L [72 mg/dL]) within the first 24 hours in the hospital (25). With the implementation of hospital protocols to attain the glycemic targets recommended by the consensus conference of the American Association of Clinical Endocrinologists (26), it is important to recognize the potential consequences of hypoglycemia and to monitor blood glucose levels accordingly (24,27).

Our analyses found that 4.8% of patients with diabetes who developed hypoglycemia and 3.6% who presented with hypoglycemia died in the hospital, whereas the crude mortality rate of the comparison group was 2.3%. This rate is higher than that from a French study that found that 1.9% of patients who were hospitalized due to hypoglycemia died despite inpatient treatment (28). After adjusting for severity, development of hypoglycemia in the hospital increased the odds of in-hospital mortality by 7% (OR, 1.07; 95% CI, 1.02-1.11) in our study. However, we did not find a statistically significant increase in the likelihood of death for patients who presented with hypoglycemia. An analysis of patients who had acute myocardial infarction who were part of the DIGAMI 2 trial also found higher long-term mortality rates among patients with hypoglycemia, but found that these differences were not significant after adjustment (11). A 2003 case-control study in Israel of elderly hospitalized patients with and without diabetes

found that hypoglycemia was not an independent predictor of death (9).

Our study was retrospective and was limited by the available data. In particular, since the source of blood glucose values was hospital laboratory data, we did not have results for bedside capillary (fingerstick) blood tests unless they were entered into the hospital's laboratory system. Also, diagnostic data that were used to identify patient comorbidities were from hospital billing data, which are limited in the number of recorded diagnoses. Total charges per patient, from the hospital billing system, were used as a way to compare the intensity of resource use among patient cohorts because cost data were not available. Charges reported on hospital billing data are usually higher than the amount actually paid after the implementation of discounts that insurers have negotiated with hospitals. However, the use of charges in this study is reasonable since our purpose was to compare costs between the different groups of patients rather than to estimate actual costs of hospital care.

As in any retrospective study, multivariate adjustment for the differences between the comparison groups is needed. Our nonparsimonious propensity score technique adjusted for possible differences in severity between patients with and without hypoglycemia, using a large number of variables (approximately 40, depending on the model). However, the variables were limited to the data available and mainly included conditions, comorbidities, and treatments that could be determined using laboratory results, diagnoses, procedures, or medications given during the hospitalization. We did not have data to identify the timing and dosage of insulin, duration of diabetes, or glucose control (hemoglobin A<sub>1c</sub> results) before hospitalization. However, we were able to create a variable indicating whether the patient's diabetes required insulin by identifying diagnoses of type 1 diabetes and inpatient treatment with long-acting or intermediate-acting insulin. This variable was highly significant in our model of the propensity for hypoglycemia.

Another limitation of this study is that we could not adjust for hyperglycemia, which is both a common indication for treatment with insulin or other antihyperglycemic agents that could result in hypoglycemia, as well as a consequence of treatment for hypoglycemia (eg, rebound hyperglycemia) (3). Hyperglycemia is associated with negative outcomes among hospitalized patients with diabetes (24,29). A prospective study conducted in 1 hospital in Sweden found that development of hypoglycemia in the hospital had an independent effect on mortality. That study enrolled patients with diabetes who were admitted for unstable angina or non-Q-wave myocardial infarction and captured hyperglycemia at admission and development of hypoglycemia during hospitalization. Using a model that adjusted for high blood glucose upon hospital admission, hypoglycemia during hospitalization

(<55 mg/dL) was found to have an adjusted hazard ratio for 2-year mortality of 1.93 (12).

We have found that, all else equal, hospital length of stay is associated with hypoglycemia. Our research design did not separate the patients for whom hypoglycemia was the probable cause of the longer length of stay from those whose longer time in the hospital provided the opportunity for hypoglycemia to occur. These things may, in fact, be simultaneous and difficult to separate. However, the results suggest that some of the clinical benefit of reducing the occurrence of hypoglycemic episodes may take place through decreasing the length of stay.

In addition to finding that hypoglycemia is associated with worse outcomes among patients with diabetes, this study reveals differences in outcomes between patients who develop hypoglycemia in the inpatient setting and those who present with hypoglycemia. Patients may develop hypoglycemia as a result of inpatient treatment, per se, or it may be due to failure to defend against hypoglycemia resulting from loss of glucagon response to falling blood glucose levels. Hypoglycemia also may be a secondary consequence of impaired ability to synthesize glucose (ie, gluconeogenesis) and may signal a more acutely ill or unstable patient. Patients who present with hypoglycemia may be more likely to have hypoglycemia due to inadequate caloric intake, excess alcohol consumption, or excessive dosages of their antihyperglycemic medications. These causes may be more readily treated in a controlled hospital setting and may explain, in part, why hypoglycemia on presentation is less predictive of a negative outcome.

An association between hypoglycemia and worse outcomes is supported by accumulating evidence from an increasing number of studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD), where reported hypoglycemic episodes were associated with increased mortality (30,31). However, whether this association is a result of hypoglycemia, per se, the adverse consequences of metabolic compensation to hypoglycemia, or some other cause associated with hypoglycemia is unclear. Although there was 3 times the number of hypoglycemic events in the ACCORD intensive group, the investigators compared mortality associated with reported episodes of hypoglycemia and concluded that there was no evidence that hypoglycemic episodes, per se, were associated with increased observed mortality. However, it is known from accumulated data including continuous glucose monitoring that patient reports underestimate the total number of hypoglycemic episodes, especially nocturnal hypoglycemia (32). Under the circumstances, the difficulty in ascertaining all hypoglycemic episodes is a serious issue. Compensation for hypoglycemia involves many different hormones and metabolic pathways (33). In nondiabetic individuals, glucagon is the main hormone secreted when circulating plasma glucose levels fall. However, the ability

to secrete glucagon is commonly lost in those with diabetes of long duration. At that point, release of the catecholamines epinephrine and norepinephrine is needed to raise plasma glucose concentrations. It has been reported that catecholamine levels may remain elevated for prolonged periods following hypoglycemic episodes. It is also clear that diabetic patients with heart disease do not tolerate the rise in circulating catecholamines well (34,35).

The Veterans Administration Diabetes Treatment (VADT) study investigators found that benefits of intensive glycemic control varied by duration of diabetes; those with a longer duration of diabetes did not benefit, while those with a shorter duration appeared to benefit from intensive treatment (36,37). The duration of diabetes when the treatment switched from benefit to harm was approximately 10 years. Of note, the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) study participants had a duration of diabetes approximately 2 years shorter than that of ACCORD participants (8 vs 10 years, respectively) (38). Although that may seem like a relatively small difference, the VADT findings suggest that it may have been an important one. The ACCORD study investigators have not yet reported a formal analysis of mortality results by duration of diabetes. Although the cause for the lost benefit with increased duration of diabetes is not known, it is an intriguing possibility that the explanation may be the combination of loss of glucagon response to hypoglycemia and increasing intolerance to catecholamines.

## CONCLUSION

Whether the observed worse outcomes in our study were due to hypoglycemia itself or whether they were just a marker of those worse outcomes due to other unmeasured causes requires further research. Nevertheless, this study does show that hypoglycemia among hospitalized patients with diabetes has serious implications. Although a direct causal relationship cannot be inferred, these findings suggest the importance of carefully maintaining euglycemia during hospitalizations without either hypoglycemia or hyperglycemia.

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## DISCLOSURE

Dr. Alexander is employed by Merck & Co, Inc. Dr. Haidar, Dr. Dubois, and Ms. Natoli are employed by Cerner LifeSciences, which provides research and consulting services to the pharmaceutical industry, as well as to other clients. Dr. Curkendall was employed by Cerner LifeSciences

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