Published in final edited form as:
Am J Med. 2011 November ; 124(11): 1028–1035. doi:10.1016/j.amjmed.2011.07.011.

Hypoglycemia Associated Mortality is Not Drug-associated but Linked to Comorbidities

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Abstract

Objective—Although tight glucose control is widely used in hospitalized patients, there is concern that medication-induced hypoglycemia may worsen patient outcomes. We sought to determine if the mortality risk associated with hypoglycemia in hospitalized non-critically ill patients is linked to glucose-lowering medications (drug-associated hypoglycemia) or if it is merely an association mediated by comorbidities (spontaneous hypoglycemia).

Methods—Retrospective cohort of patients admitted to the general wards of an academic center during 2007. The in-hospital mortality risk of a hypoglycemic group (at least one blood glucose ≤ 70 mg/dl) was compared to that of a normoglycemic group using survival analysis. Stratification by subgroups of patients with spontaneous and drug-associated hypoglycemia was performed.

Results—Among 31,970 patients, 3,349 (10.5%) had at least one episode of hypoglycemia. Patients with hypoglycemia were older, had more comorbidities, and received more antidiabetic agents. Hypoglycemia was associated with increased in-hospital mortality (HR: 1.67, 95% CI, 1.33 to 2.09, p<0.001). However, this greater risk was limited to patients with spontaneous hypoglycemia (HR: 2.62, 95% CI, 1.97 to 3.47, p<0.001), not to those with drug-associated hypoglycemia (HR: 1.06, 95% CI, 0.74 to 1.52, p=0.749). After adjustment for patient comorbidities, the association between spontaneous hypoglycemia and mortality was eliminated (HR: 1.11, 95% CI, 0.76 to 1.64, p=0.582).

Conclusions—Drug-associated hypoglycemia was not associated with increased mortality risk in patients admitted to the general wards. The association between spontaneous hypoglycemia and

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Conflict of interest statement: LB, WNS, and JZ have not received any support from any organization for the submitted work; LB and WNS have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; JZ serves on an advisory panel for Takeda Pharmaceutical North America, and on the speakers bureau for Amylin Pharmaceuticals, Eli Lilly, Merck, Novo Nordisk, and Sanofi-Aventis.

Contribution from authors: LB, WNS, and JZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LB designed the study, researched the data, wrote, reviewed, and edited the manuscript. WNS contributed to data collection, researched the data, and contributed to writing, reviewing and editing the manuscript. JZ contributed to designing the study, writing, reviewing and editing the manuscript.

mortality was eliminated after adjustment for comorbidities, suggesting that hypoglycemia may be a marker of disease burden rather than a direct cause of death.

Keywords

Hypoglycemia; mortality; hypoglycemia in general ward patients

Hyperglycemia in hospitalized patients with and without diabetes is common and has been implicated as a risk factor for increased morbidity and mortality [1–5]. While a randomized controlled trial of "tight" glycemic control in critically ill patients has demonstrated decreased mortality[6], other studies have shown no benefits or even increased mortality with this therapeutic approach [7–11]. Despite these contradictory results in intensive care unit (ICU) patients, physicians have widely adopted tight glycemic control in hospitalized patients with hopes of improving outcomes. Enthusiasm for glucose-lowering interventions has been tempered by the concern that treatment-induced hypoglycemia may cause death. Although trials of intensive glucose control have shown higher rates of hypoglycemia than standard glucose management [9,12,13], and hypoglycemia has been associated with increased mortality [14–17], it is not clear whether hypoglycemia that occurs as a result of glucose-lowering therapy is associated with increased mortality.

Studies conducted in the outpatient setting usually serve to provide guidance in the management of hospitalized but not critically ill patients. In this regard, two multi-center outpatient clinical trials comparing the effects of intensive versus standard glycemic control in patients with advanced type 2 diabetes were recently completed and showed no significant reduction in cardiovascular disease outcomes nor any increased mortality with intensive glycemic control [18,19]. A third outpatient trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, was terminated because of increased mortality in participants randomized to receive intensive glycemic therapy [20]. However, a *post hoc* analysis of ACCORD was unable to attribute the excess mortality observed in the intensive therapy group to severe hypoglycemia [21]. Thus, it remains unclear whether hypoglycemia is responsible for increased mortality or it is just a marker of disease burden.

To address this important knowledge gap, we designed a retrospective observational study to determine first, whether hypoglycemia was associated with increased mortality in hospitalized but non-critically ill patients; and second, whether hypoglycemia associated with various illnesses that occurs in the absence of glucose-lowering therapy ("spontaneous hypoglycemia") and hypoglycemia that is associated with initiation of glucose-lowering therapy ("drug-associated hypoglycemia") carry similar prognostic implications. Specifically, we posited that if hypoglycemia *per se* were a direct cause of adverse outcomes, it would be expected to be associated with increased mortality regardless of its etiology. On the other hand, if hypoglycemia was a marker of disease burden, only spontaneous hypoglycemia would be associated with increased mortality.

RESEARCH DESIGN AND METHODS

Study Population

We examined a retrospective cohort of patients hospitalized at Montefiore Medical Center in Bronx, New York, from January 1st to December 31st, 2007. The data assembled were restricted to non-pregnant patients ages 21 years or greater, and included those with and without the concurrent diagnosis of diabetes, who were admitted to the general units. Patients admitted or transferred to medical or surgical intensive care units, and those discharged from the emergency room were excluded from this analysis. For patients with multiple admissions, only the earliest admission was considered as an index hospitalization.

Patients were included if their record had at least one blood glucose level performed during the period of hospitalization, which yielded a starting data set of 31,970 patients. The diabetes subgroup (n = 10,832) included patients with both type 1 and type 2 diabetes determined from *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes (ICD-9 codes) of inpatient and outpatient charts.

Data Source, hypoglycemia and comorbidities definition, and medications

All data was extracted from the hospital information system using Clinical Looking Glass™ (version 2.1.5, Bronx, NY). We defined the "hypoglycemia" group as those patients with at least one laboratory-documented blood glucose level ≤ 70 mg/dl. We used this threshold according to the definition provided by the American Diabetes Association[22]. We only used chemistry profiles and excluded patients with point of care (POC) glucose values < 70 mg/dl because 1) these are entered into the computer system manually by nurses and they are subject to more data entry errors than those values directly transmitted from the laboratory, 2) we thought we would encounter multiple short and trivial episodes of hypoglycemia evidenced by POC only in the group receiving anti-diabetic agents that would not necessarily be seen in the chemistry profiles and that would not be associated with increased mortality, thus favoring our hypothesis, and 3) we wanted to choose a more conservative approach of clearly documented hypoglycemia in a laboratory chemistry profile that would most likely represent a true episode of hypoglycemia. The "normoglycemia" group consisted of patients with all glucose levels > 70 mg/dl. "Spontaneous hypoglycemia" was defined as hypoglycemia occurring in the absence of glucose-lowering interventions; "drug-associated hypoglycemia" was hypoglycemia occurring in patients who were receiving glucose-lowering medications. Comorbidities were determined from ICD-9 codes and, whenever possible, enriched by including patients who met laboratory criteria for disease, and consisted of: body mass index, diabetes mellitus, congestive heart failure, myocardial infarction, cerebro-vascular accident, cancer, chronic obstructive pulmonary disease, shock, albumin level (as a surrogate for chronic illness, malnutrition, or liver disease when low), white blood cell count, and renal failure defined as a serum creatinine level ≥ 2 mg/dl. All medications were prescribed electronically and those administered during the patients' hospital stay were abstracted from the database. Anti-diabetic oral agents included sulfonylureas, metformin, thiazolidinediones (TZDs), glucagon-like peptide 1 (GLP-1) analogs, dipeptidyl peptidase 4 inhibitors (DPP-4i). Insulin therapy encompassed both human insulin and insulin analogs administered as basal (NPH-protamine insulin, or glargine), and/or bolus (regular insulin or rapid acting analogs).

Statistical analysis

All statistical analyses were performed using STATA/IC (version 10 for Windows; College Station, TX). Baseline demographic and clinical characteristics were compared between patients in the "hypoglycemia" group and patients in the "normoglycemia" group using Pearson X^2 test for categorical variables and Student t test or Mann-Whitney test for continuous variables.

To determine if hypoglycemia was associated with decreased survival, in-hospital mortality rates were compared between the hypoglycemia group and the normoglycemia group using logistic regression. Mortality analysis was repeated stratified by the presence or absence of diabetes. We further examined the relationship between glycemia and in-hospital mortality using Kaplan-Meier survival estimates in the hypoglycemic and normoglycemic groups and conducted the remaining univariate and multivariate analyses using survival analysis. Proportionality assumptions were tested with Schoenfeld residuals and log-log plots.

Because we hypothesized that there would be a differential effect of hypoglycemia resulting from treatment with antidiabetic medication (drug-associated hypoglycemia) vs. spontaneous hypoglycemia, we explored the interaction between antidiabetic medications and hypoglycemia and conducted separate analyses for subgroups of patients with drug-associated vs. spontaneous hypoglycemia. We also conducted sensitivity analyses using a glucose cut-off of 50mg/dl, and we performed sub-analyses by class of anti-diabetic agent to determine the specific effect of drugs known to cause hypoglycemia (i.e. sulfonylureas and insulin) on mortality. We examined the association between number of hypoglycemic episodes and mortality in the drug-associated and spontaneous hypoglycemic groups. Patients without hypoglycemic episodes (normoglycemia) served as the reference group and were compared with patients having one, two, and three or more hypoglycemic episodes.

Multivariate Cox proportional hazards models were constructed to examine the independent association between hypoglycemia and mortality. We conducted stratified analyses for patients with drug-associated and spontaneous hypoglycemia. Patient characteristics previously demonstrated to be prognostically significant or thought to be clinically important, and covariates identified in bivariate analyses as predictors of in-hospital mortality were entered into the models. Covariates included demographic factors: age, sex, self-reported race/ethnicity; comorbidities: body mass index, diabetes mellitus, congestive heart failure, myocardial infarction, cerebro-vascular accident, cancer, chronic obstructive pulmonary disease, shock, albumin level (as a surrogate for chronic illness, malnutrition, or liver disease when low), white blood cell count, and renal failure defined as a serum creatinine level ≥ 2 mg/dl; and number of glucose determinations.

The literature reports an increase of in-hospital mortality risk of hypoglycemic compared to normoglycemic patients ranging between 60% and 300%.[15–17,23] We performed a power calculation with the most conservative estimate of increased mortality risk in the hypoglycemic group. With our actual sample size, we calculated that we would have had 80% power to detect a 60% increase in mortality risk in hypoglycemic subjects compared to normoglycemic subjects using a two-tailed α of 0.05. All power determinations were calculated using PASS 11 2010 (version 11.0.2, 2010, http://www.ncss.com/pass.html).

RESULTS

Baseline characteristics

We identified 31,970 patients with at least one blood glucose determination during their hospitalization (mean age 61 ± 17.8 years, 58% females). Self-designated race/ethnicity was available in 92.6% of patients (Whites: 23.6%, Blacks: 32.2%, Hispanics: 36.8%, unknown: 7.4%). Table 1 presents baseline patient characteristics of those subjects who did (n= 3,349) and did not (n=28,621) develop hypoglycemia during their hospital stay. The proportion of females was similar between the two groups. There was a higher percentage of non-Hispanic Blacks in the hypoglycemic group. Compared with patients who did not develop hypoglycemia, those with hypoglycemic events were older, had a lower body mass index, had more co-morbidities including diabetes, and received more insulin, sulfonylureas, or a TZD. There were fewer patients in the hypoglycemia group receiving metformin.

Overall, 3,349 patients (10.5%) developed a total of 5,884 episodes of hypoglycemia. Spontaneous hypoglycemia occurred in 1,714 patients, drug-associated hypoglycemia happened in 1,635 individuals. Among patients with diabetes, those treated with insulin experienced higher rates of hypoglycemia compared with those who were not treated with insulin (23.7% [1,447/6,097 patients] vs 7.4% [1,902/25,873], p<0.001).

Unadjusted association between hypoglycemia and mortality

Figure 1 shows that patients with hypoglycemia had significantly higher in-hospital mortality than patients without hypoglycemia (4.39% [147/3,349] vs. 1.06% [304/28,621], p<0.001). Both diabetic and non-diabetic patients with hypoglycemia had significantly increased in-hospital mortality compared to patients without hypoglycemia. Non-diabetic patients with hypoglycemia had almost double the mortality rate than diabetic patients with hypoglycemia (5.88% vs 2.97%, p<0.001).

Patients with hypoglycemia had significantly higher mortality compared to normoglycemic patients (HR: 1.67, 95% CI, 1.33–2.09, p<0.001, Table 2). However, the association between hypoglycemia and mortality was markedly different among subjects who developed it spontaneously *vs.* those who developed it following glucose-lowering therapy [p=0.001 for hypoglycemia × antidiabetic medications interaction]. Among patients not treated with insulin or oral antidiabetic agents (spontaneous hypoglycemia), those with hypoglycemia had significantly higher mortality compared with those who did not develop hypoglycemia (HR: 2.62, 95% CI, 1.97–3.47, p<0.001). In contrast, among patients treated with insulin or oral antidiabetic agents (drug-associated hypoglycemia), mortality hazards were similar between those who did and did not develop hypoglycemia (HR: 1.06, 95% CI, 0.74–1.52, p=0.749). Sensitivity analyses using a glucose cut-off of 50 mg/dl showed similar results. Table 2a shows a sub-group analysis by drug class. The specific group who developed hypoglycemia associated with sulfonylureas and/or insulin did not have an increased mortality hazard compared to the normoglycemic group on the same drugs. The small number of deaths observed in patients receiving Metformin, TZDs, as well as sulfonylureas likely reflects the fact that oral drugs are discouraged during hospitalization and insulin is preferentially used.

Of the 3,349 patients with hypoglycemia, 64.3% had 1 episode, 19.1% had 2 episodes, and 16.6% had 3 or more episodes. We found an association between the number of spontaneous hypoglycemic episodes and in-hospital mortality (p for trend <0.001), but there was no significant association between the number of drug-associated hypoglycemic events and in-hospital mortality (p for trend = 0.562, Table 3).

Adjusted association between hypoglycemia and mortality

After multivariate adjustment for age, sex, race, and number of glucose determinations (Table 4, model 1), the association between hypoglycemia and mortality remained significantly different for patients with spontaneous hypoglycemia vs. those with drug-associated hypoglycemia (p<0.001 for adjusted interaction). Spontaneous hypoglycemia was significantly associated with higher risk of mortality (HR: 2.84, 95% CI, 2.14–3.76, p<0.001) while drug-associated hypoglycemia was not (HR: 0.95, 95% CI, 0.66–1.36, p=0.762). To determine if the association between hypoglycemia and mortality was attenuated after adjustment for comorbidities, we constructed serial regression models. In model 1, we adjusted for patient demographics and found a strong and significant association between spontaneous hypoglycemia and mortality (HR: 2.84, 95% CI, 2.14–3.76, p<0.001). In contrast, in model 2, after adjustment for patient demographics and comorbidities, the association between spontaneous hypoglycemia and mortality was eliminated (HR: 1.11, 95% CI, 0.76–1.64, p=0.582, Table 4, model 2). Among patients with drug-associated hypoglycemia, the relationship between hypoglycemia and mortality remained non-significant after adjustment for comorbidities (HR: 0.72, 95% CI, 0.45–1.13, p=0.155).

DISCUSSION

In this large group of patients hospitalized in the general wards, hypoglycemia was associated with greater risk of in-hospital mortality, but this association only occurred in those who developed it spontaneously. In contrast, hypoglycemia that occurred with initiation of antidiabetic medications was not associated with higher in-hospital mortality. These findings suggest that hypoglycemia in hospitalized patients may be a marker of disease burden rather than a direct cause of death, results that should reassure clinicians who manage glucose levels in hospitalized patients in the general wards.

Additional evidence that hypoglycemia may not cause mortality is provided in our multivariate analyses. While the unadjusted analyses suggested a strong and significant association between spontaneous hypoglycemia and mortality, this association disappeared after adjusting for patient comorbidities. This suggests that spontaneous hypoglycemia may be a marker of disease burden, and might be used to identify a susceptible host with multiple comorbidities, but it might not be a direct cause of mortality. Our findings contrast with epidemiologic studies conducted mainly in type 1 diabetes subjects which have rendered hypoglycemia responsible for increased mortality[24,25]. A recent report of a young type 1 diabetic subject wearing a retrospective (non-real-time) continuous subcutaneous glucose monitoring system documented the occurrence of hypoglycemia at the time of the patient's death[26]. Although drug-associated hypoglycemia is known to have deleterious effects on the central nervous system[27], we did not find an association between drug-associated hypoglycemia and mortality in either univariate or multivariate analyses.

Our results support many observational studies which found that hypoglycemia was common during hospitalization and it was strongly associated with in-hospital mortality [10,15–17,23,28–31]. Most studies, however, include critically ill patients. Two previous studies conducted among elderly patients (> 70 years of age) admitted to critical care and general ward units reported an association between hypoglycemia and in-hospital mortality[16,28]. Since elderly patients are at increased risk of developing comorbidities, the authors hypothesized that comorbidities, rather than hypoglycemia itself, would be responsible for the observed excess mortality. In these studies, as well as in others [29,30], it was not possible to determine if hypoglycemia was a direct cause of mortality. Our report extends these observations to a much younger population with less comorbidites as such found in the general hospital wards. One study excluded patients admitted to the ICU [23] and also showed an association between hypoglycemia and mortality. However, the authors could not distinguish between patients who developed hypoglycemia spontaneously vs. those who developed it as a consequence of glucose-lowering therapies[23]. Recently, Kosiborod et al. found increased mortality risk among patients with acute myocardial infarction developing hypoglycemia spontaneously, but not among those developing hypoglycemia as a consequence of glucose-lowering therapy[31]. Our results show a similar differential association but in non-critically ill patients. In addition, we provide further evidence that hypoglycemia behaves as a marker of disease rather than as a direct cause of death by showing that increase number of hypoglycemic episodes is associated with greater risk of hospital death only among patients developing hypoglycemia spontaneously. Moreover, when comorbidities are included in a multivariate model, the association between spontaneous hypoglycemia and mortality disappears.

Studies performed in outpatient populations are also pertinent when examining the role of hypoglycemia as a contributor to adverse outcomes versus a marker of disease burden. Two outpatient studies in individuals with type 2 diabetes showed no mortality benefit of tight glycemic control [18,19], while a third study, ACCORD, was prematurely stopped due to increased mortality in patients randomized to receive intensive glycemic therapy [20]. A *post-*

hoc analysis of ACCORD, however, could not attribute the excess mortality observed in the intensive therapy arm to severe hypoglycemia [21], suggesting that there are alternative explanations to the observed association between tight glycemic control and mortality independent of hypoglycemia. Some of the mechanisms contributing to increased mortality postulated by the ACCORD investigators include the magnitude or the speed of the reduction in glycated hemoglobin levels, or the development of adverse effects due to undetected interactions of various drug classes[20]. Recently, the authors from ADVANCE also studied the association between hypoglycemia and mortality and they concluded that while hypoglycemia may contribute to adverse outcomes, it is just as likely to be a marker of disease burden[32]. In our study, the fact that the association between spontaneous hypoglycemia and mortality disappeared after adjustment for comorbidities, and the fact that the number of hypoglycemic events was not associated with higher mortality risk in patients treated with antidiabetic agents (despite a much higher rate of hypoglycemic events in this group) suggest that hypoglycemia may not be a cause of mortality but rather a marker of poor prognosis in hospitalized patients.

Our study has several strengths. First, it was conducted in a highly diverse racial and ethnic patient base which should enhance the generalizability of our results. Second, we had a large data set that allowed us to perform sensitivity analyses using a lower glucose threshold (50mg/dl) and sub-analyses to examine the impact of different drug classes on hospital mortality. Finally, we designed a methodology that would allow us to distinguish mortality risks among hypoglycemic patients receiving and not receiving anti-diabetic drugs.

Despite its strengths, our study has several limitations. Because our analysis is retrospective and we were not able to document hypoglycemia at the time of death, we are not able to establish causality. However, prospective randomized trials are precluded for ethical reasons. In addition, we could not confirm a temporal relation between the administration of drugs and the occurrence of the hypoglycemic event. Despite the fact that drug-associated hypoglycemia was not associated with increased mortality, this study does not provide evidence that intensive therapy of hyperglycemia is beneficial in the general ward setting. An appropriately powered clinical trial of tight glycemic control in non-critically ill patients would be the adequate methodology to answer this question. Given the lack of randomization of our groups, we cannot exclude the possibility that antidiabetic agents might have been prescribed to an overall healthier population who tolerated hypoglycemia better and did not show evidence of increased mortality. Finally, the specific cause of hypoglycemia in patients who developed it spontaneously could not be established, and the specific cause of death could not be determined, so we considered all-cause mortality.

In conclusion, our study shows that while hypoglycemia is associated with increased in-hospital mortality among patients admitted to the general wards, this risk is confined to patients with spontaneous hypoglycemia. In contrast, drug-associated hypoglycemia is not associated with higher in-hospital mortality. While hypoglycemia remains an undesirable event and should be avoided when possible, these data suggest that hypoglycemia behaves as a marker of disease burden rather than as a direct cause of death.

Acknowledgments

Funding: This publication was made possible by the CTSA Grant UL1 RR025750 and KL2 RR025749 and TL1 RR025748 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessary represent the official view of the NCRR or NIH.

We thank Drs. Harry Shamoon, Norman Fleischer, and Martin I. Surks, Albert Einstein College of Medicine, for critically reading the manuscript and providing helpful suggestions.

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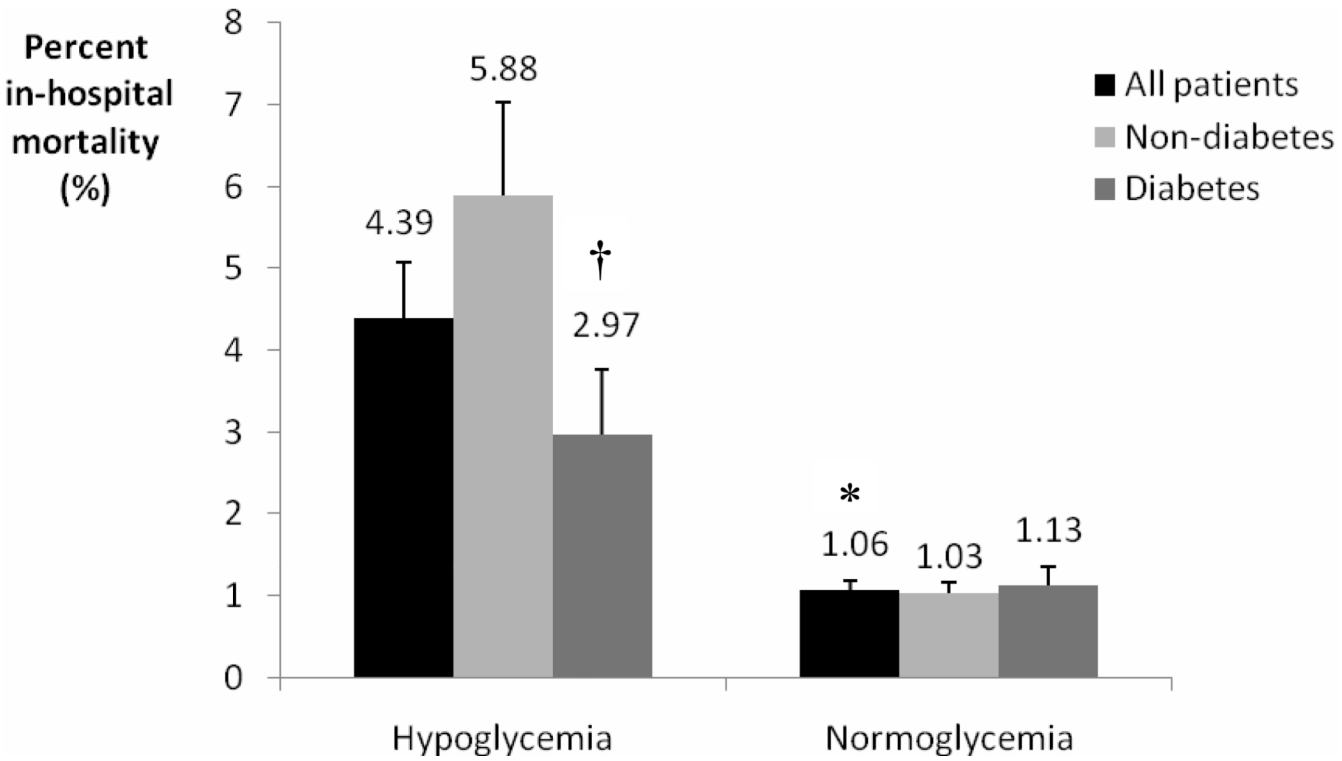

Figure 1.
Percent in-hospital mortality by glycemia status among all patients, patients with diabetes, and patients without diabetes.
* p <0.001 for all hypoglycemic versus normoglycemic patients.
† p <0.001 for non-diabetic hypoglycemic patients versus diabetic hypoglycemic patients.

Table 1

Patient Characteristics by Glycemia Status

	Hypoglycemia (n=3,349)	Normoglycemia (n=28,621)	p-value
Demographic data			
Age in years, mean (SD)	64.1 (17.3)	60.6 (17.9)	<.001
Female sex, *n*, (%)	1,918 (57.3)	16,765 (58.6)	0.15
Whites, *n*, (%)	732 (21.9)	6,829 (23.9)	0.01
Blacks, *n*, (%)	1,234 (36.9)	9,045 (31.6)	<.001
Hispanics, *n*, (%)	1,179 (35.2)	10,577 (36.9)	0.047
Clinical data			
Body mass index, mean(SD)	27.1 (7.5)	29.1 (7.8)	<.001
Diabetes *n*, (%)	1,717 (51.3)	9,115 (31.9)	<.001
Congestive heart failure *n*,(%)	944 (28.2)	3,984 (14.0)	<.001
Myocardial infarction *n*, (%)	311 (9.3)	2,005 (7.1)	<.001
Cerebro-vascular accident *n*, (%)	318 (9.5)	2,038 (7.2)	<.001
Cancer *n*, (%)	389 (11.6)	2,355 (8.3)	<.001
Shock *n*, (%)	75 (2.24)	134 (0.47)	<.001
Chronic obstructive pulmonary disease *n*, (%)	775 (23.2)	5,969 (21.0)	0.004
White blood cell count, median (iq range)	9.2 (6.8–12.8)	8.7 (6.7–11.7)	<.001
Albumin, mean (SD)	3.46 (0.71)	3.85 (0.56)	<.001
Renal failure *n*, (%)	804 (24.1)	1,968 (7.0)	<.001
In-hospital medications			
Sulfonylureas, *n*, (%)	342 (10.2)	1,570 (5.5)	<.001
Metformin, *n*, (%)	169 (5.1)	1,737 (6.1)	0.02
Thiazolidinediones, *n*, (%)	132 (3.9)	922 (3.22)	0.03
DPP-4i/GLP-1, *n*, (%)	4 (0.12)	33 (0.12)	0.95
Any insulin, *n*, (%)	1,447 (43.2)	4,650 (16.3)	<.001
Any oral, *n*, (%)	480 (14.3)	3,154 (11.0)	<.001
Any oral or insulin, *n*, (%)	1,635 (48.8)	6,670 (23.3)	<.001

Table 2

Unadjusted in-hospital mortality of all hypoglycemic patients, patients with spontaneous hypoglycemia, and patients with drug-associated hypoglycemia compared to normoglycemic patients.

	Hazard ratio	Number of deaths	p-value	95% CI
All hypoglycemic patients	1.67	451	<0.001	1.33 to 2.09
Spontaneous hypoglycemia	2.62	287	<0.001	1.97 to 3.47
Drug-associated hypoglycemia	1.06	164	0.749	0.74 to 1.52

2a – Sub-analysis of in-hospital mortality of patients who developed hypoglycemia compared to normoglycemic patients by class of anti-diabetic drug.

	Hazard ratio	Number of deaths	p-value	95% CI
Sulfonylureas	0.90	14	0.880	0.23 to 3.48
Metformin	1.28	5	0.855	0.09 to 17.7
Thiazolidinediones	0.01	4	1	-
Any insulin	0.98	158	0.907	0.68 to 1.40
Any sulfonylurea and/or insulin	0.97	163	0.867	0.68 to 1.39

Table 3

Number of hypoglycemic episodes and in-hospital mortality.

	Hazard ratio	p-value	95% CI
Spontaneous hypoglycemia*			
1 epsiode	1.73	0.006	1.17 to 2.57
2 episodes	3.78	<0.001	2.32 to 6.15
3 or more episodes	4.86	<0.001	3.11 to 7.60
Drug-associated hypoglycemia†			
1 episode	0.99	0.962	0.64 to 1.54
2 episodes	1.12	0.683	0.64 to 1.96
3 or more episodes	1.15	0.596	0.68 to 1.94

* p for trend <0.001

† p for trend= 0.562

Table 4

Adjusted in-hospital mortality of patients with spontaneous hypoglycemia and patients with drug-associated hypoglycemia compared to normoglycemic patients.

	Hazard ratio	Number of deaths	p-value	95% CI
Model 1				
Spontaneous hypoglycemia	2.84	287	<0.001	2.14 to 3.76
Drug-associated hypoglycemia	0.95	164	0.762	0.66 to 1.36
Model 2				
Spontaneous hypoglycemia	1.11	171	0.582	0.76 to 1.64
Drug-associated hypoglycemia	0.72	114	0.155	0.45 to 1.13

Model 1: hypoglycemia adjusted by age, sex, race, and number of glucose determinations.

Model 2: hypoglycemia adjusted by age, sex, race, body mass index, diabetes mellitus, congestive heart failure, myocardial infarction, cerebro-vascular accident, cancer, chronic obstructive pulmonary disease, shock, white blood cell count, albumin, creatinine, number of glucose determinations.