Risk of Hypoglycemia Following Hospital Discharge in Patients With Diabetes and Acute Kidney Injury

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OBJECTIVE

Hypoglycemia is common in patients with diabetes. The risk of hypoglycemia after acute kidney injury (AKI) is not well defined. The purpose of this study was to compare the risk for postdischarge hypoglycemia among hospitalized patients with diabetes who do and do not experience AKI.

RESEARCH DESIGN AND METHODS

We performed a propensity-matched analysis of patients with diabetes, with and without AKI, using a retrospective national cohort of veterans hospitalized between 2004 and 2012. AKI was defined as a 0.3 mg/dL or 50% increase in serum creatinine from baseline to peak serum creatinine during hospitalization. Hypoglycemia was defined as hospital admission or an emergency department visit for hypoglycemia or as an outpatient blood glucose <60 mg/dL. Time to incident hypoglycemia within 90 days postdischarge was examined using Cox proportional hazards models. Prespecified subgroup analyses by renal recovery, baseline chronic kidney disease, preadmission drug regimen, and HbA$_{1c}$ were performed.

RESULTS

We identified 65,151 propensity score–matched pairs with and without AKI. The incidence of hypoglycemia was 29.6 (95% CI 28.9–30.4) and 23.5 (95% CI 22.9–24.2) per 100 person-years for patients with and without AKI, respectively. After adjustment, AKI was associated with a 27% increased risk of hypoglycemia (hazard ratio [HR] 1.27 [95% CI 1.22–1.33]). For patients with full recovery, the HR was 1.18 (95% CI 1.12–1.25); for partial recovery, the HR was 1.30 (95% CI 1.23–1.37); and for no recovery, the HR was 1.48 (95% CI 1.36–1.60) compared with patients without AKI. Across all antidiabetes drug regimens, patients with AKI experienced hypoglycemia more frequently than patients without AKI, though the incidence of hypoglycemia was highest among insulin users, followed by glyburide and glipizide users, respectively.

CONCLUSIONS

AKI is a risk factor for hypoglycemia in the postdischarge period. Studies to identify risk-reduction strategies in this population are warranted.

Patients who experience hypoglycemia are at an increased risk of major adverse clinical outcomes, such as poor quality of life, acute and long-term neurological impairment, acute cardiovascular events, and death (1–3). Hypoglycemia is also one of the leading causes of hospital admissions and emergency department visits in patients with diabetes (4).

Patients with chronic kidney disease (CKD) have a higher risk of hypoglycemia and related complications (1–5). The latter is related to several factors including decreased renal gluconeogenesis, decreased clearance of insulin, and decreased clearance of antidiabetes drugs (6). Acute kidney injury (AKI) is also a strong risk factor for hypoglycemia during critical illness (7). However, it is not known whether the risk for hypoglycemia in patients with AKI extends beyond hospitalization and after apparent partial and/or full recovery of renal clearance. As the incidence of AKI is increasing rapidly in the U.S. (8,9) and occurs most commonly in patients with diabetes and CKD (10–13), understanding the risk for hypoglycemia in this population is important to improving outcomes in the growing population of survivors with this condition.

In this study, we hypothesized that hospitalized patients who experienced AKI would be at increased risk for post-hospitalization hypoglycemia compared with well-matched patients hospitalized without AKI. To test this hypothesis, we used a national Veterans Health Administration cohort to evaluate the risk of hypoglycemia in the 90 days after hospital discharge among patients with diabetes who experienced AKI compared with hospitalized patients with diabetes without AKI. We also examined how the risk of hypoglycemia varied with the degree of renal recovery at discharge, CKD status, and baseline HbA$_{1c}$.

RESEARCH DESIGN AND METHODS

Study Setting and Design

The Veterans Affairs (VA) uses an electronic health record, the Veterans Health Information Systems and Technology Architecture (VistA) and Computerized Patient Record System (CPRS), with nationally reliable data for the domains required for this study since 2002. This study involved a national retrospective cohort comprised of veterans 18 years of age and older with diabetes who filled a prescription for an antidiabetes medication (excluding metformin monotherapy and thiazolidinedione [TZD] users) in the 180 days prior to index hospitalization. The outcome of interest was time to hypoglycemia after hospital discharge. The exposure of interest was AKI that occurred during hospitalization. This study was approved by the institutional review board and the research and development committee of the Tennessee Valley Healthcare System VA.

Data Collection

Data were collected from 1 January 2002 to 31 December 2013 from the national Corporate Data Warehouse, which aggregates data from all VA facilities (14). Data were obtained from 730 days prior to hospital admission to 90 days after discharge in order to establish medical conditions and exposures prior to admission and to monitor for outcomes after discharge. Detailed references for data domains and data field availability can be obtained from www.hsrd.research.va .gov/for_researchers/vinci/default.cfm. All VA laboratory data were obtained for each patient and linked to their hospitalization. Diagnoses were obtained from ICD-9, ICD-9 Procedure, and Current Procedural Terminology codes. Medications were obtained from outpatient VA pharmacy fill records and inpatient bar-coded medication administration.

Cohort Exclusion Criteria

We assembled a national retrospective cohort of 5,666,604 adult admissions to 120 VA hospitals between 1 January 2004 and 31 December 2012. We excluded patients without at least one outpatient visit in each of the 2 years prior to admission to enrich for continuity of care within the system. We excluded patient hospitalizations with lengths of stay <48 h and >30 days because these patients were systematically different from the standard-length-of-stay population. Patients were required to have a preadmission creatinine value and one creatinine during hospitalization because these elements were required to ascertain AKI. We excluded patients with a history of end-stage renal disease, defined as a baseline estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, a history of kidney transplantation, or any dialysis prior to admission. Information regarding end-stage renal disease was obtained from the United States Renal Data System, the fee basis care files, and the VA dialysis units' ICD-9 and Current Procedural Terminology codes. Patients on metformin monotherapy were also excluded, as metformin is usually stopped during an AKI episode and not historically associated with hypoglycemia. We also excluded TZD users, as they were not formulary in the VA system and TZD users represent a small elective group of the population. We excluded patients who were receiving hospice services from 30 days before to 48 h after admission and patients who received palliative care or died during hospitalization. Finally, we excluded VA hospitals with <100 hospital admissions per year (Fig. 1).

Study Definition of AKI

The exposure of interest, AKI, was determined using creatinine laboratory value data and dialysis procedure codes collected during hospitalization. AKI was calculated as a 0.3 mg/dL or 50% increase in serum creatinine from baseline to the maximum serum creatinine during hospitalization and staged according to the Kidney Disease: Improving Global Outcomes classification scheme, with stage II AKI denoted by a 2.0–2.9 times increase in serum creatinine from baseline and stage III AKI denoted by a >3.0 times increase from baseline or receipt of acute dialysis (15). Baseline serum creatinine was defined as the mean outpatient serum creatinine value from 7 to 365 days before admission as per our previously validated approach (16). Acute dialysis was defined using procedure codes for dialysis without the prior occurrence of dialysis before admission.

Primary Outcome: Hypoglycemia

Hypoglycemia was defined as an outpatient blood glucose measurement of <60 mg/dL or occurrence of relevant administrative codes associated with a hospitalization or an emergency department visit due to hypoglycemia between discharge and 90 days. For hospitalizations, we included those only with a primary discharge diagnosis for hypoglycemia with ICD-9-CM 251.0, 251.1, 251.2, 962.3, and 270.3. This was done to exclude events that may have occurred during a concurrent hospitalization in relation to other illness. For emergency department visits, hypoglycemia was defined as ICD-9-CM codes 251.0–251.2, 270.3, 962.3, or 250.8 but excluding codes 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1–707.9, 730.0–730.2, 731.8, and 250.3 (17,18).

Covariates

Baseline risk factors and inclusion/exclusion criteria were collected in the 730 days before admission. Hospital care–related risk factors for AKI were collected during hospitalization.
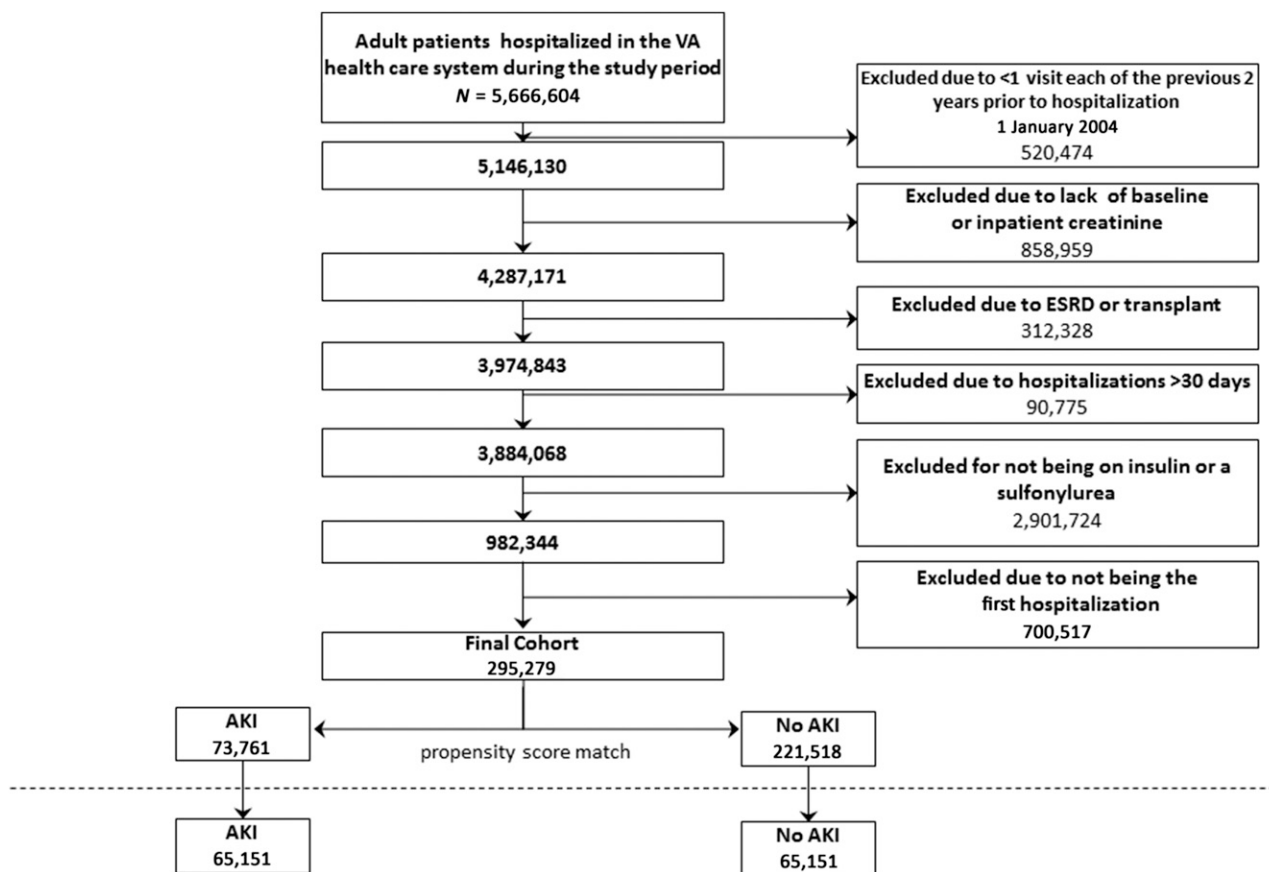
Figure 1—Flow of eligible hospitalizations and patients. ESRD, end-stage renal disease.

AKI risk factors were based on established risk factors from the literature review (19) (Supplementary Table 1). Medications and vital signs including blood pressure were recorded in both the preadmission and admission windows. Preadmission medication exposures were calculated using fill dates and pill counts allowing fill gaps of 90 days, which approximates 80% adherence (20). Admission medications were recorded from the bar-coded medication administration records during the admission window. The medication regimens included glipizide only; glipizide and insulin; glipizide and metformin; glipizide, insulin, and metformin; glyburide only; glyburide and insulin; glyburide and metformin; glyburide, insulin, and metformin; insulin only; and insulin and metformin. For contrast studies, we were able to ascertain the order by radiology without confirming delivery. All covariates and their definitions are listed in Supplementary Table 2. eGFR was calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation (21). Also, CKD defined by ICD-9 code 585.x was recorded as a separate variable.

Statistical Analysis

The primary analysis compared time to first hypoglycemic episode within 90 days postdischarge between patients hospitalized with and patients hospitalized without AKI. To account for measured confounding, we executed a two-stage approach that included 1) propensity score (PS) matching and 2) applying Cox proportional hazards (PH) with and without additional variable adjustment.

A PS was developed for the exposure of AKI and matched AKI patients to non-AKI patients stratified by the antidiabetes medication profiles and including other variables that are known to increase the risk for hypoglycemia such as baseline HbA$_{1c}$, history of prior hypoglycemia, and concomitant medication exposures of fluoroquinolones, indomethacin, and quinine. The PS score used a 1:1 matching with a caliper of 0.2 of the SD of the logit (22,23). Stratified matching by medication regimen was used to optimize matching within the medication regimens and reduced the variance. This often improves the representativeness of the sample by reducing sampling error. The overlapping

histogram for each medication regimen is shown in Supplementary Fig. 1. Standardized mean differences were used to assess covariate balance after matching. To address potential ascertainment bias, i.e., AKI patients getting more glucose measurements taken and thus being more likely to have a low measure observed, we included in the model the number of days with glucose measurements in the baseline year. As a sensitivity analysis to address potential remaining ascertainment bias, the percentage of days with glucose measures between discharge and 90 days or the day before a hypoglycemic event—whichever came first—was added for this sensitivity analysis to the PS model. This postdischarge rate of measurement is a postexposure variable, so it would have been inappropriate to include it in the primary analysis. Missing values for baseline HbA$_{1c}$, 1-year preadmission mean systolic blood pressure (SBP), and admission mean SBP were imputed using global mean imputation. The PS model included indicator variables for missing values and all variables noted above. Multiple imputation for PS

Table 1—Baseline characteristics

	Prematched			Matched		
Variables	Non-AKI (N = 221,518)	AKI (N = 73,761)	Standardized differences	Non-AKI (N = 65,151)	AKI (N = 65,151)	Standardized differences
Demographics						
Age, mean (SD)	65.67 (11.06)	67.69 (11.06)	0.183*	67.29 (11.06)	67.49 (11.12)	0.018*
Female, n (%)	6,935 (3.1)	1,657 (2.2)	0.055*	1,516 (2.3)	1,511 (2.3)	0.001
Race, n (%)						
Unknown	7,283 (3.3)	2,460 (3.3)	0.003	2,170 (3.3)	2,037 (3.1)	0.012*
African American	44,264 (20.0)	16,419 (22.3)	0.056*	14,464 (22.2)	14,572 (22.4)	0.004
Other	5,142 (2.3)	1,676 (2.3)	0.003	1,488 (2.3)	1,496 (2.3)	0.001
White	164,829 (74.4)	53,206 (72.1)	0.051*	47,029 (72.2)	47,046 (72.2)	0.001
Preadmission outpatient medications, n (%)						
Diuretics	102,538 (46.3)	43,521 (59.0)	0.257*	37,446 (57.5)	37,475 (57.5)	0.001
RAAS inhibitors	156,113 (70.5)	55,813 (75.7)	0.117*	49,187 (75.5)	49,040 (75.3)	0.005
Aminoglycosides	2,406 (1.1)	916 (1.2)	0.015*	807 (1.2)	788 (1.2)	0.003
NSAIDs	20,264 (9.1)	4,759 (6.5)	0.101*	4,491 (6.9)	4,484 (6.9)	<0.001
Indomethacin	2,068 (0.9)	759 (1.0)	0.010*	711 (1.1)	675 (1.0)	0.005
Quinine	1,213 (0.5)	478 (0.6)	0.013*	423 (0.6)	437 (0.7)	0.003
Preadmission laboratory/vitals						
HbA$_{1c}$ %, mean (SD)	7.62 (1.74)	7.65 (1.80)	0.021*	7.70 (1.81)	7.64 (1.78)	0.032*
HbA$_{1c}$ mmol/mol, mean	59.79	60.11		60.70	60.00	
HbA$_{1c}$ nonmissing, n (%)	157,367 (71.0)	52,880 (71.7)	0.014*	46,466 (71.3)	46,590 (71.5)	0.004
eGFR, mean (SD)	72.90 (21.91)	63.71 (23.30)	0.406*	65.32 (23.08)	65.17 (23.08)	0.007
SBP, mean (SD)	134.00 (14.11)	136.05 (15.54)	0.138*	135.72 (15.40)	135.79 (15.31)	0.005
Mean SBP nonmissing, n (%)	221,107 (99.8)	73,601 (99.8)	0.007	65,012 (99.8)	65,007 (99.8)	0.002
Glucose measurements prior year, mean (SD)	5.41 (12.10)	5.93 (14.59)	0.039*	5.86 (14.41)	5.81 (14.03)	0.003
History of hypoglycemia, n (%)	15,286 (6.9)	6,913 (9.4)	0.09*	5,987 (9.2)	5,814 (8.9)	0.009
Preadmission chronic conditions/utilization						
No. of encounters (1 year), mean (SD)	33.25 (25.98)	32.53 (25.57)	0.028*	32.79 (25.82)	32.58 (25.64)	0.008
CKD, n (%)	17,630 (8.0)	11,895 (16.1)	0.253*	9,263 (14.2)	9,341 (14.3)	0.003
Heart failure, n (%)	33,428 (15.1)	16,133 (21.9)	0.175*	13,599 (20.9)	13,685 (21.0)	0.003
Peripheral vascular disease, n (%)	37,172 (16.8)	13,957 (18.9)	0.056*	12,253 (18.8)	12,168 (18.7)	0.003
Valvular heart disease, n (%)	11,491 (5.2)	4,478 (6.1)	0.038*	3,843 (5.9)	3,953 (6.1)	0.007
Prior cardiac surgery, n (%)	7,299 (3.3)	2,380 (3.2)	0.004	2,160 (3.3)	2,153 (3.3)	0.001
Type 2 diabetes (ICD-9), n (%)	217,618 (98.2)	72,483 (98.3)	0.002	64,066 (98.3)	64,026 (98.3)	0.005
Coronary artery disease, n (%)	92,155 (41.6)	30,945 (42.0)	0.007	27,338 (42.0)	27,473 (42.2)	0.004
Hypertension, n (%)	190,925 (86.2)	66,692 (90.4)	0.132*	58,533 (89.8)	58,645 (90.0)	0.006
Advanced liver disease, n (%)	5,737 (2.6)	2,004 (2.7)	0.008	1,798 (2.8)	1,781 (2.7)	0.002
Cancer (ICD-9), n (%)	37,194 (16.8)	12,996 (17.6)	0.022*	11,362 (17.4)	11,500 (17.7)	0.006
Inpatient conditions/laboratory/vitals						
Admission SBP, mean (SD)	134.22 (16.81)	130.45 (18.91)	0.211*	131.53 (18.27)	131.45 (18.40)	0.005
Admission mean SBP nonmissing, n (%)	216,289 (97.6)	72,249 (98.0)	0.021*	63,797 (97.9)	63,773 (97.9)	0.003
ICU stay, n (%)	30,115 (13.6)	13,887 (18.8)	0.142*	11,342 (17.4)	11,491 (17.6)	0.006

Table 1—Continued

Variables	Prematched			Matched		
	Non-AKI (N = 221,518)	AKI (N = 73,761)	Standardized differences	Non-AKI (N = 65,151)	AKI (N = 65,151)	Standardized differences
Mechanical ventilation, n (%)	3,823 (1.7)	3,030 (4.1)	0.142*	1,995 (3.1)	2,092 (3.2)	0.009
Sepsis, n (%)	2,802 (1.3)	8,487 (11.5)	0.428*	2,726 (4.2)	3,179 (4.9)	0.033*
Acute coronary syndrome, n (%)	18,616 (8.4)	5,798 (7.9)	0.02*	4,876 (7.5)	5,100 (7.8)	0.013*
Cardiac surgery, n (%)	2,573 (1.2)	1,361 (1.8)	0.056*	1,276 (2.0)	1,226 (1.9)	0.006
Major vascular surgery, n (%)	9,416 (4.3)	6,365 (8.6)	0.179*	4,600 (7.1)	4,666 (7.2)	0.004
Abdominal surgery, n (%)	5,590 (2.5)	1,863 (2.5)	<0.001	1,653 (2.5)	1,675 (2.6)	0.002
Gastrointestinal bleed, n (%)	4,570 (2.1)	2,195 (3.0)	0.058*	1,752 (2.7)	1,815 (2.8)	0.006
Advanced liver disease, n (%)	5,050 (2.3)	1,976 (2.7)	0.026*	1,718 (2.6)	1,717 (2.6)	<0.001
Radiology IV contrast, n (%)	10,784 (4.9)	2,307 (3.1)	0.089*	2,200 (3.4)	2,130 (3.3)	0.006
Fluoroquinolone use 48 h prior to discharge, n (%)	13,221 (6.0)	7,444 (10.1)	0.152*	5,868 (9.0)	5,836 (9.0)	0.002

NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system. Standardized differences are the absolute difference in means or percentage divided by an evenly weighted pooled SD or difference between groups in number of SDs. In the PS-matched cohort, all standardized differences were <10% (or 0.1), indicating good balance. *$P < 0.05$.

is not required because the PS does not use the error estimates in its calculation, and inclusion of indicator variables for missing values can correct adjustment of the intercept (24).

Cox PH models with restricted cubic splines for continuous variables were used to compare time to first hypoglycemia within 90 days postdischarge between AKI and non-AKI patients in the matched cohort censored on death. The primary analysis was the PS-matched cohort with covariate adjustment in the Cox model. For the covariate-adjusted Cox PH analysis, missing values for baseline HbA$_{1c}$ (28.6%), 1-year preadmission mean SBP (0.2%), and admission mean SBP (2.1%) were imputed with multiple imputation using additive regression, bootstrapping, and predictive mean matching (25). A secondary analysis was performed using the PS-matched cohort in the Cox model without additional covariate adjustment (unadjusted). The PH assumption was verified using a plot of raw and spline-smoothed scaled Schoenfeld residuals for AKI, nonlinearly coded from the Cox model fit. All analyses were conducted using R software, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Preplanned subgroup analyses were performed by stratifying on *1*) degree of renal recovery defined as full recovery (20% of baseline), partial recovery (defined as 50% to 20% of baseline), and no recovery (defined as 50% of baseline or more) with non-AKI as the reference group; *2*) baseline HbA$_{1c}$ <7% (53 mmol/mol), 7–9% (53–75 mmol/mol), >9% (75 mmol/mol), and missing, and *3*) baseline eGFR <60 vs. ≥60 mL/min/1.73 m^2 and preadmission antidiabetes drug regimen.

RESULTS

Of 295,279 eligible patients with diabetes with an index hospitalization during the study period (1 January 2004 to 31 December 2012), 73,761 (25%) experienced hospital-acquired AKI. Compared with patients who did not experience AKI, at time of hospitalization, those with AKI were older (67.69 vs. 65.67 years old), had lower baseline eGFR (63.71 vs. 72.90 mL/min/1.73 m^2), and a higher frequency of heart failure (21.9 vs. 15.1%) and use of diuretics (59.0 vs. 46.3%) and renin-angiotensin-aldosterone system inhibitors (75.7 vs. 70.5%). During hospitalization, patients

experiencing AKI were more likely to be treated in the intensive care unit (ICU), diagnosed with severe sepsis, and undergo vascular surgery. After PS matching, our study cohort included 65,151 patients who experienced an AKI hospitalization and 65,151 with a non-AKI hospitalization. In the matched cohort, all baseline characteristics were similar between groups, as noted by absolute standardized mean differences <0.10. In both groups, 98% of patients were male and 72% were white, median age was 66 years (interquartile range [IQR] 60–76), baseline eGFR was 63.6 mL/min/1.73 m^2 (IQR 47.6–82.1), preadmission HbA$_{1c}$ levels were 7.3% (IQR 6.5–8.4) (56 mmol/mol [IQR 47–68]), the average number of glucose measurements in the prior year was 5.8, and 9% of patients had a hypoglycemic episode in the prior year (26) (Table 1). Baseline medication regimen proportions were as follows: 15% on glipizide monotherapy; 4% glipizide and insulin; 11% glipizide and metformin; 3% glipizide, insulin, and metformin; 12% glyburide monotherapy; 3% glyburide and insulin; 11% glyburide and metformin; 3% glyburide, insulin, and metformin; 27% insulin only; and 10% insulin and metformin. Of the 65,151 patients with an AKI hospitalization, 45% had full recovery, 41% had partial recovery, and 14% did not recover. The baseline characteristics per group for the prematched cohort and the PS-matched cohort are shown in Table 1.

Risk of Hypoglycemia for the Overall Cohort

In the 90 days after hospital discharge, 4,341 (7%) vs. 3,519 (5%) patients with and patients without AKI during their hospitalization, respectively, had a hypoglycemic event, corresponding to 29.6 vs. 23.5 events per 100 person-years (Table 2 and Fig. 2). In the unadjusted Cox PH model of the PS-matched cohort, the hazard ratio (HR) for hypoglycemia within 90 days of discharge for a patient with AKI compared with an otherwise similar patient without AKI was 1.25 (95% CI 1.20–1.31). Similar results were obtained in the Cox PH model of the matched cohort with adjustment for the variables included in the PS model (HR 1.27 [95% CI 1.22–1.33]) (Table 2). For both AKI and non-AKI hospitalizations, 86% of the hypoglycemic events were identified via outpatient glucose measures, with 13% from emergency department visits and 1% from hospitalizations due to hypoglycemia.

Subgroup Analyses by Renal Recovery, History of CKD, Baseline HbA$_{1c}$, and Preadmission Antidiabetes Drug Regimen

A dose-response relationship was observed with stratification by the degree of AKI recovery. The HR for hypoglycemia within 90 days of discharge for AKI patients with full renal recovery compared with patients without AKI was 1.18 (95% CI 1.12–1.25). The HRs for hypoglycemia within 90 days of discharge for AKI patients with partial renal recovery and no recovery compared with patients without AKI were 1.30 (95% CI 1.23–1.37) and 1.48 (95% CI 1.36–1.60), respectively (Fig. 3). In subgroup analyses that evaluated the risk of hypoglycemia post-AKI, no differences were observed in the risk by the presence of previous CKD or by different HbA$_{1c}$ subgroups (preadmission baseline HbA$_{1c}$ <7% [53 mmol/mol], 7–9% [53–75 mmol/mol], and >9% [75 mmol/mol]) (Table 3).

A subgroup analysis by drug regimen showed that the higher risk of hypoglycemia persisted for AKI compared with non-AKI for patients for all drug regimens (Table 4). However, overall, the incidence rate of hypoglycemia was the highest for insulin users with AKI (43.70 per 100 person-years [95% CI 42.15–45.26]), followed by glyburide plus insulin combo users with AKI (39.03 per 100 person-years [95% CI 34.39–43.88]). In general, any regimen with insulin had a higher incidence rate of hypoglycemia. Regimens with glipizide or glipizide plus metformin had the lowest rates of hypoglycemia. The incidence rates for each drug regimen are presented in Table 4.

Hypoglycemia Event Defined as an Outpatient Glucose <50 mg/dL in the 90 Days Postdischarge

When a hypoglycemic event was defined using a more strict definition as a glucose level <50 mg/dL, the number of events was reduced substantially. However, the results of this sensitivity analysis were similar to those from the primary analysis. AKI was associated with a higher risk for hypoglycemia (HR 1.29 [95% CI 1.21–1.39]) compared with patients who did not experience AKI.

Other Sensitivity Analyses

Two other sensitivity analyses were conducted. First, to account for potential ascertainment bias during the follow-up period, we included the percentage of days with glucose measurements in the PS model. Results were consistent with
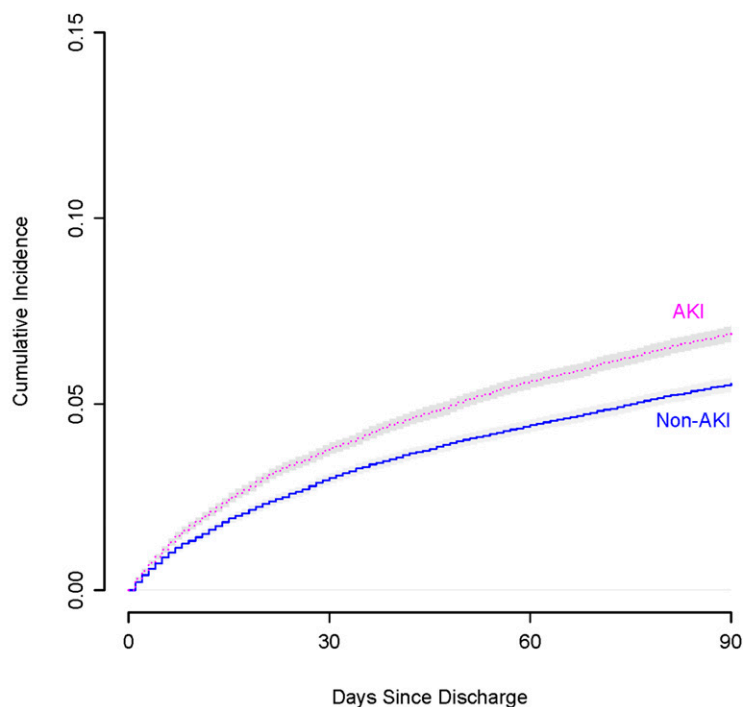
Table 2—Risk of hypoglycemic events among patients who experienced AKI during hospitalization within 90 days postdischarge

	Non-AKI	AKI
A) Summary characteristics		
Patients	65,151	65,151
Composite hypoglycemic events	3,519	4,341
Follow-up time (person-years)	14,953.85	14,648.28
Unadjusted rate per 100 person-years (95% CI)	23.5 (22.9–24.2)	29.6 (28.9–30.4)
B) Primary analyses		
PS-matched unadjusted Cox PH, HR (95% CI)	Ref.	1.25 (1.20–1.31)
PS-matched adjusted Cox PH, HR (95% CI)	Ref.	1.27 (1.22–1.33)
C) Sensitivity analyses		
Outcome defined as a glucose value <50 mg/dL		
Hypoglycemia events of glucose <50 mg/dL	1,517	1,909
Follow-up time (person-years)	15,253.82	15,020.53
Unadjusted rate per 100 person-years (95% CI)	9.95 (9.48–10.43)	12.71 (12.19–13.25)
PS-matched unadjusted Cox PH, HR (95% CI)	Ref.	1.27 (1.19–1.36)
PS-matched adjusted Cox PH, HR (95% CI)	Ref.	1.29 (1.21–1.39)

A) Summary of patients, outcomes, and follow-up time for all analyses; *B*) risk of hypoglycemic event among patients who experienced an AKI episode during a hospitalization vs. those who did not experience an AKI episode within 90 days postdischarge; and *C*) sensitivity analysis using a more strict definition for the outcome, where hypoglycemia was defined as a glucose blood value <50 mg/dL in the outpatient setting. Composite hypoglycemia event was defined as hospital admission, an emergency department visit for hypoglycemia, or an outpatient blood glucose value of <60 mg/dL. PS-matched unadjusted Cox PH analysis controlled for confounding via matching only; PS-matched adjusted Cox PH analysis additionally controlled for confounding via direct covariate adjustment. Sensitivity analysis was performed using a more strict definition for the outcome, where hypoglycemia was defined as a glucose blood value <50 mg/dL in the outpatient setting.

Figure 2—Cumulative incidence of hypoglycemic events by AKI status. Cumulative incidence of hypoglycemic events (hospital admission, an emergency department visit for hypoglycemia, or an outpatient blood glucose value <60 mg/dL) among a PS-matched cohort on the likelihood of AKI in the 90 days postdischarge between patients hospitalized with or without AKI between 2004 and 2012.

and similar to those from the primary analysis. In the adjusted Cox PH model of the PS-matched cohort, with adjustment for the variables included in the PS model, the HR was 1.26 (95% CI 1.21–1.32). The last sensitivity analysis was done restricting the analysis to individuals who had CKD at baseline, defined as two eGFR levels <60 mL/min/1.73 m^2 more than 3 months apart (HR 1.23 [1.15–1.31], which was consistent with the HR for the primary analysis).

CONCLUSIONS

In this large national cohort of patients with diabetes on insulin or sulfonylurea monotherapy or in combination therapy, which could have included metformin, we demonstrate that patients with AKI are at significant risk for developing hypoglycemia in the postdischarge period (~7% in 90 days), with a relative increase in risk of 27% compared with similarly ill patients who did not experience AKI. Our findings remained robust after matching for several risk factors that could affect the risk of both hypoglycemia and AKI, and we

demonstrated that the risk of hypoglycemia incrementally increases in a dose-responsive manner with less renal recovery at discharge.

The kidneys play an important role in glucose metabolism and insulin degradation. Isotopic dilution studies have demonstrated the renal cortex to be responsible for between 15 and 30% of total body gluconeogenesis (27–29), and <1% of the filtered insulin is freely excreted in the urine, with the catabolism of insulin and its precursors occurring primarily via peritubular uptake. Many of the medications used to treat diabetes, including insulin and sulfonylureas, are also at least partially cleared by the kidneys. Given these metabolic and care implications, it is no surprise that several randomized control trials have highlighted that the risk of serious hypoglycemia with tight glucose control in the outpatient setting is highest among patients with CKD (2,3). Hence, glycemic targets for CKD have already been modified to be less stringent to avoid the risk of this potentially life-threatening complication in the stable outpatient setting (30–33).

However, little is known about the risk of hypoglycemia after a hospitalization in patients with CKD or after an episode of AKI.

We hypothesized that patients with AKI may be at especially high risk for hypoglycemia after discharge. Patients with CKD and diabetes are at a higher risk of experiencing AKI (13), recurrent AKI (11), and delayed recovery compared with those without both conditions (13,34). During hospitalization, the risk of hypoglycemia in these patients may increase owing to variability in the timing and amount of nutrient intake, acute illness itself, a lack of counterregulatory mechanisms, and further decrements in kidney function that may not be appreciated (35). Our results suggest that the risk for hypoglycemia, particularly among patients who have experienced AKI, are significant, extend beyond hospitalization, and place AKI survivors also at increased risk for potentially severe adverse events.

The number of patients with AKI are growing rapidly, with an estimated 10–11% increase in the annual population-based incidence of this disease, with a recent study estimating a hospital-based incidence rate of 21.6% using current definitions (8,9,36). Simultaneously, incremental improvements in in-hospital mortality have translated to a growing population of survivors (37). With 21 million adult with diabetes and an estimated hospitalization rate of 267/1,000 patient-years in the U.S. according to Centers for Disease Control and Prevention estimates, this translates to an estimated 1.2 million AKI-related hospitalizations and potentially >20,000 AKI-associated hypoglycemic episodes per year. The American Society of Nephrology and other organizations have highlighted the transition of care between hospitalization and the outpatient setting as a potential opportunity to improve outcomes for a population for whom optimal care has yet to be defined (38). Although the absolute risk and overall relative risk increase of hypoglycemia with AKI observed was modest, given the high incidence of AKI in hospitalized patients with diabetes, delineating the complications after AKI in patients with diabetes and identifying management strategies for minimizing the risk for hypoglycemia in this patient population should be a health care priority.

One potential contributor to our findings may be that the impact of AKI on diabetes drug metabolism or direct
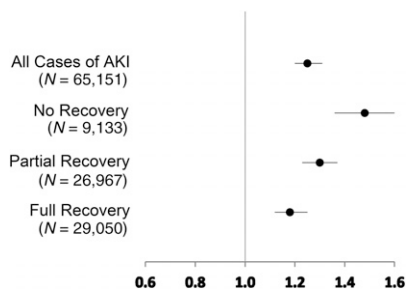
Figure 3—Adjusted HR for risk of first hypoglycemic event after a hospitalization complicated vs. not complicated by AKI, by degree of renal recovery. Degree of renal recovery stratified into full recovery (defined as 20% of baseline), partial recovery (defined as 20–50% of baseline), and no recovery (defined as 50% or more of baseline). Adjusted hazards were derived using Cox PH models. Models were adjusted for age, sex, race, physiologic variables (eGFR, HbA$_{1c}$, and SBP), history of prior hypoglycemia, number of encounters in the year prior to hospitalization, use of medications known to affect creatinine values (ACE inhibitors or angiotensin receptor blocker, loop diuretics, nonsteroidal anti-inflammatory drugs, and aminoglycosides) or known to potentially affect the risk of hypoglycemia (indomethacin, quinine, and fluoroquinolones), exposure to potential nephrotoxins such as contrast, type of surgery, sepsis, ICU stay and length of stay, and the presence of other comorbidities. All continuous variables were modeled as third- or fourth-degree polynomials. Non-AKI hospitalizations represented the reference group.

biochemical or filtration changes during AKI may have not been fully recognized. The stepwise increase in risk that we observed with lesser degrees of recovery also is consistent with this hypothesis. We did not have information available in our database on formal or informal (verbalized) changes to dosing of medication in the postdischarge period to examine in detail how practice patterns may have contributed to risk. However, we did observe that the highest rates of hypoglycemia were observed in patients with AKI on insulin-containing regimens, followed by glyburide-containing regimens, which are cleared to a greater degree by the kidneys. This, coupled with the stepwise increase in risk that we observed with lesser degrees of recovery, suggests that an appropriate review of medication choice and dosing is warranted among survivors of AKI on these medications. At minimum, these findings suggest that a careful assessment of hypoglycemic risk in patients with AKI, particularly among patients with prior hypoglycemia, underlying CKD, or AKI

who have not recovered by discharge, is warranted. It also suggests that immediate reinstitution of a strategy toward tight control may not be appropriate for all patients immediately after AKI.

Our study had numerous strengths. We used a large national database that reflects the population of U.S. veterans. We had extensive preadmission data available to comprehensively define preadmission comorbidities. We had serial outpatient serum creatinine measures available to adequately define baseline eGFR prior to the index hospitalization. We used rigorous matching of AKI and non-AKI patients with a comprehensive list of potential confounders in addition to the adjusted analyses. We used a validated algorithm base on ICD-9 codes to define hypoglycemia (17) and performed a sensitivity analysis of the outcome defined as glucose value <50 mg/dL, with very similar results. Limitations of our study include the use of a predominately male population and an inability to generalize to patients not on sulfonylureas or insulin. Our matched study design also raises the possibility that our matched populations differ from the wider population of hospitalized patients. Hypoglycemic episodes frequently also happen in the outpatient setting, and many patients have been trained to self-

treat; hence, we may have underestimated the incidence of hypoglycemic events in the 90 days after an AKI episode. However, this poor sensitivity for the outcome should not be differential and would have biased our results toward the null. Newer methods of continuous glucose monitoring will improve capturing of outpatient hypoglycemia events that are self-treated, which are not currently available in the VA system. In addition, newer oral antidiabetes agents, particularly dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium–glucose cotransporter 2 inhibitors, which have lower hypoglycemic risk compared with other medications, were not included in this study, as most of them are nonformulary in the VA system. Lastly, although we applied an extensive set of strategies to address confounding and our postmatch risk estimates remained similar with and without adjustment, residual confounding remains possible and causality cannot be implied.

Conclusion

The risk of hypoglycemia, a complication that is associated with poor outcomes and death in patients with diabetes, is increased after an AKI episode and varies with the degree of renal recovery. This increase in risk compared with similarly

Table 3—Risk of hypoglycemic event among patients who experienced an AKI episode during a hospitalization vs. those who did not experience an AKI episode within 90 days postdischarge, by CKD status and preadmission HBA$_{1c}$ subgroups

Subgroup analyses	Non-AKI	AKI
Mean preadmission outpatient eGFR <60 mL/min/1.73 m^2		
PS-matched inadjusted Cox PH	Ref.	1.22 (1.14–1.29)
PS-matched adjusted Cox PH	Ref.	1.22 (1.15–1.30)
Mean preadmission outpatient eGFR ≥60 mL/min/1.73 m^2		
PS-matched unadjusted Cox PH	Ref.	1.30 (1.22–1.38)
PS-matched adjusted Cox PH	Ref.	1.32 (1.24–1.41)
Baseline HbA$_{1c}$ <7%		
PS-matched unadjusted Cox PH	Ref.	1.23 (1.13–1.34)
PS-matched adjusted Cox PH	Ref.	1.24 (1.14–1.35)
Baseline HbA$_{1c}$ 7–9%		
PS-matched unadjusted Cox PH	Ref.	1.23 (1.13–1.33)
PS-matched adjusted Cox PH	Ref.	1.24 (1.14–1.34)
Baseline HbA$_{1c}$ >9%		
PS-matched unadjusted Cox PH	Ref.	1.20 (1.06–1.36)
PS-matched adjusted Cox PH	Ref.	1.27 (1.13–1.44)
Baseline HbA$_{1c}$ missing		
PS-matched unadjusted Cox PH	Ref.	1.34 (1.23–1.45)
PS-matched adjusted Cox PH	Ref.	1.36 (1.25–1.47)

Hypoglycemia was defined as hospital admission, an emergency department visit for hypoglycemia, or an outpatient blood glucose value of <60 mg/dL. PS-matched unadjusted Cox PH analysis controlled for confounding via matching only; PS-matched adjusted Cox PH analysis additionally controlled for confounding via direct covariate adjustment.

Table 4—Incidence rates of hypoglycemia in patients with AKI compared with patients without AKI by specific drug regimen

Regimen	Incidence rate* (95% CI) of hypoglycemia in AKI hospitalizations	Incidence rate* (95% CI) of hypoglycemia in non-AKI hospitalizations	HR (95% CI)
Glipizide only	20.47 (18.85–22.19)	16.18 (14.73–17.75)	1.26 (1.10–1.44)
Glyburide only	24.69 (22.71–26.78)	18.02 (16.31–19.88)	1.33 (1.15–1.54)
Insulin only	43.70 (42.15–45.26)	35.31 (33.84–36.80)	1.25 (1.17–1.34)
Glipizide + insulin	33.00 (29.44–36.76)	27.81 (24.49–31.39)	1.22 (0.99–1.49)
Glyburide + insulin	39.03 (34.39–43.88)	32.99 (28.61–37.68)	1.21 (0.95–1.53)
Glipizide + metformin	17.60 (15.86–19.47)	12.20 (10.74–13.83)	1.44 (1.20–1.72)
Glyburide + metformin	22.29 (20.32–24.40)	16.41 (14.69–18.28)	1.35 (1.15–1.59)
Insulin + metformin	31.19 (28.89–33.58)	25.77 (23.63–28.03)	1.22 (1.06–1.39)
Glipizide + insulin + metformin	25.26 (21.67–29.22)	21.70 (18.36–25.45)	1.18 (0.91–1.52)
Glyburide + insulin + metformin	30.08 (25.95–34.56)	26.91 (22.97–31.25)	1.15 (0.89–1.50)

*Incidence rate per 100 person-years.

ill individuals without AKI is anywhere between 18 and 48% depending in the degree of renal recovery. Further studies to identify AKI survivors at highest risk and modifiable risk factors, including evaluating the choice and dose of antidiabetes drug regimens, to reduce these risks may constitute an important contribution to improving outcomes for this growing population.

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