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Association of Continued Use of SGLT2 Inhibitors From the Ambulatory to Inpatient Setting With Hospital Outcomes in Patients With Diabetes: A Nationwide Cohort Study

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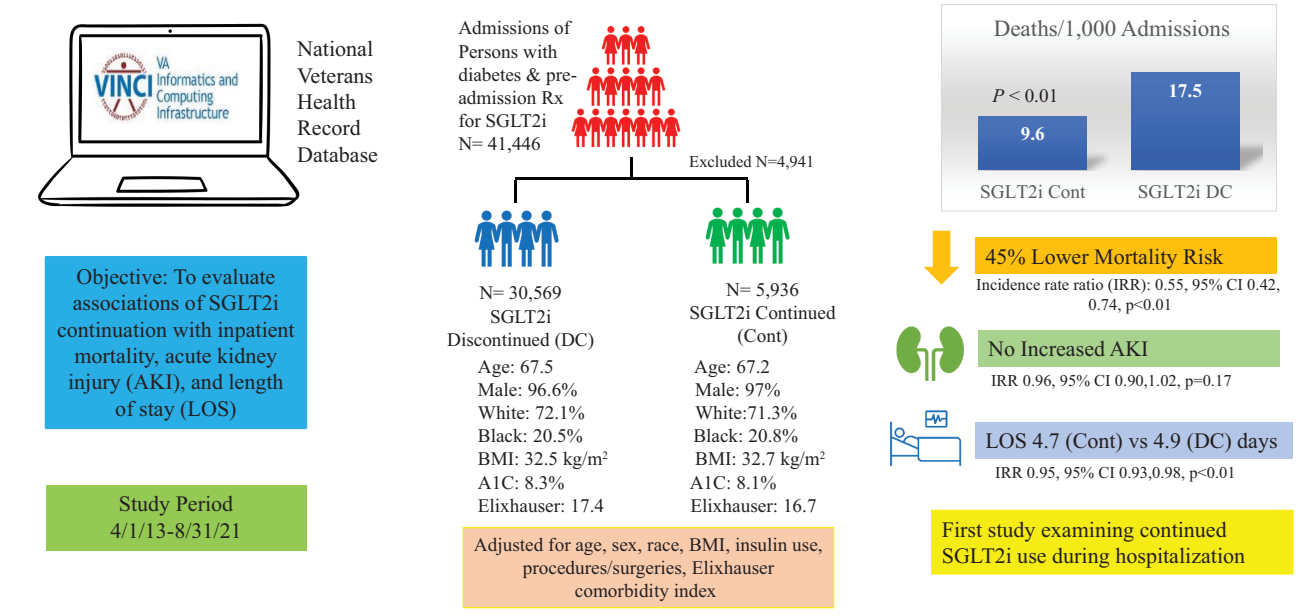

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Sodium glucose cotransporter 2 inhibitors (SGLT2is) have demonstrated nephro- and cardioprotective benefits in the outpatient setting, but less is known about continuation of SGLT2is in the inpatient setting.
- **What is the specific question we wanted to answer?**
  What is the association of continued use of SGLT2is in the inpatient setting with hospital outcomes?
- **What did we find?**
  Results revealed reduced mortality, no increased acute kidney injury, and modestly shorter length of stay.
- **What are the implications of our findings?**
  This study provides new evidence for continued SGLT2i use during hospitalization, and larger-scale randomized clinical trials are needed to evaluate the role of continued use of SGLT2is in the hospital.

Association of Continued Use of SGLT2 Inhibitors From the Ambulatory to Inpatient Setting With Hospital Outcomes in Patients With Diabetes: A Nationwide Cohort Study

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OBJECTIVE

Limited data are available on the continuation of outpatient sodium glucose cotransporter 2 inhibitors (SGLT2is) during hospitalization. The objective was to evaluate associations of SGLT2i continuation in the inpatient setting with hospital outcomes.

RESEARCH DESIGN AND METHODS

This nationwide cohort study used Veterans Affairs health care system data of acute care hospitalizations between 1 April 2013 and 31 August 2021. A total of 36,505 admissions of patients with diabetes with an outpatient prescription for an SGLT2i prior to hospitalization were included. The exposure was defined as SGLT2i continuation during hospitalization. Admissions where SGLT2i was continued were compared with admissions where it was discontinued. The primary outcome was in-hospital mortality. Secondary outcomes were acute kidney injury (AKI) and length of stay (LOS). Negative binomial propensity score–weighted and zero-truncated analyses were used to compare outcomes and adjusted for multiple covariates, including demographics and comorbidities.

RESULTS

Mean (SE) age was 67.2 (0.1) and 67.5 (0.1) years ($P = 0.03$), 97.0% and 96.6% were male ($P = 0.1$), 71.3% and 72.1% were White, and 20.8% and 20.5% were Black ($P = 0.52$) for the SGLT2i continued and discontinued groups, respectively. After adjustment for covariates (age, sex, race, BMI, Elixhauser comorbidity index, procedures/surgeries, and insulin use), the SGLT2i continued group had a 45% lower mortality rate (incidence rate ratio [IRR] 0.55, 95% CI 0.42–0.73, $P < 0.01$), no difference in AKI (IRR 0.96, 95% CI 0.90–1.02, $P = 0.17$), and decreased LOS (4.7 vs. 4.9 days) (IRR 0.95, 95% CI 0.93–0.98, $P < 0.01$) versus the SGLT2i discontinued group. Similar associations were observed across multiple sensitivity analyses.

CONCLUSIONS

Continued SGLT2i during hospitalization among patients with diabetes was associated with lower mortality, no increased AKI, and shorter LOS.

A higher risk of hospitalization has been observed in people living with diabetes. Approximately 8.25 million hospitalizations were reported among adults with diabetes

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(327.9 per 1,000) (1), signifying the immense burden of the disease. Reducing inpatient hyperglycemia is a critical therapeutic goal, as it has been associated with poor clinical outcomes such as increased risk of in-hospital mortality and increased length of stay (LOS) (2). The recommended pharmacologic approach for management of inpatient hyperglycemia for almost all hospitalized patients is insulin (2). This approach includes those who are treated with noninsulin medications preadmission, where these medications may be held and insulin is considered as initial therapy alternatively. In select individuals, dipeptidyl peptidase 4 inhibitors may be considered for inpatient use and have recently demonstrated potential effectiveness (2,3). Despite insulin's efficacy in this setting, reported barriers include risk of hypoglycemia, uncertainty with insulin regimen to use, fluctuating insulin requirements during stress, unpredictable procedure timings, and inconsistency in diet (4).

Alternatively, several noninsulin medications offer a lower risk of hypoglycemia and greater simplicity of administration compared with insulin. Despite these benefits, most of the noninsulin medications have a less established role in the hospital setting and are an area of research interest (2). Sodium glucose cotransporter 2 inhibitors (SGLT2is) inhibit renal glucose reabsorption, induce glycosuria, and carry a lower risk of hypoglycemia (5), an important benefit in the inpatient setting. In the outpatient setting, SGLT2is may be prioritized in type 2 diabetes, heart failure (HF), and/or chronic kidney disease (CKD) (6) because of benefits on cardiac and renal morbidity as well as reduction in mortality (7–9). In contrast, there are limited data about SGLT2i use in the inpatient setting (2). A few studies have evaluated the initiation of SGLT2is during hospitalization in patients with HF (with and without diabetes) and have demonstrated a postdischarge reduction in mortality, among other outcomes, with initiation of SGLT2is in the inpatient setting (10–12).

Compared with initiation during hospitalization, there is limited or no evidence on continuation of SGLT2is from the outpatient to the inpatient setting for management of hyperglycemia in the hospital. Because of limited information available, the most recent guidelines for the management of diabetes and hyperglycemia in the hospital setting do not recommend continuation of SGLT2is in the hospital among admitted patients with diabetes who are already treated with SGLT2is prior to hospitalization (2,3). Thus, the objective of our study was to evaluate the association of continuation of SGLT2is during hospitalization with mortality and other inpatient outcomes among patients with diabetes.

RESEARCH DESIGN AND METHODS

Study Cohort and Data Source

We conducted a nationwide observational study using data from Veterans Health Administration (VHA) electronic health records of patients with diabetes who were admitted for acute care hospitalization between 1 April 2013 and 31 August 2021. As patients with diabetes are at risk for recurrent hospitalizations (13), we included all admissions of patients with diabetes and treated each admission as the unit of analysis independently (14). The Veterans Affairs (VA) Informatics and Computing Infrastructure workspace and VA corporate data warehouse store all data entered into the VA electronic health record system along with all clinical, pharmacy, and health care utilization records. We used the VA Vital Status File to determine the vital status and date of death for patients included in this study (14). Our study was approved by the University of Maryland institutional review board and the VA Maryland Health Care System research and development committee.

Our study data set was created in several steps (Fig. 1). First, all patient admissions with a diagnosis of diabetes and one or more outpatient prescriptions for an SGLT2i issued during the study period were identified using outpatient VA pharmacy fill records (N = 270,873). Diabetes was defined by the presence of two or more ICD-9 or ICD-10 codes (assigned during an inpatient and/or outpatient visit) during the preceding 2 years on separate days and/or prescriptions for diabetes medications within the current year (15). We then excluded admissions that had an initial outpatient prescription for an SGLT2i issued after the hospitalization (n = 133,695). Next, we excluded hospitalizations to psychiatric, long-term-care, and rehabilitation settings or where the admitting service was not known (n = 95,732). Admissions with an LOS <1 day, ≥ 30 days, or not known were excluded (n = 1,674) (14). Admissions with less than two serum creatinine (SCr) values between 7 and 730 days before the hospitalization, less than one SCr value during the inpatient stay, and a baseline estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2 were excluded (n = 2,632). We excluded admissions where patients were transferred during hospitalization (n = 546). Finally, following imputation and statistical analyses, a small number of admissions were excluded (n = 89) because of invalid or biologically implausible imputed values for at least one of the covariates. After the above exclusions, there were 36,505 admissions (5,936 SGLT2i continued and 30,569 SGLT2i discontinued) from 112 VA hospitals.

Covariates

For each admission, the following data were obtained: age, sex, race, admission BMI, baseline A1C, glucose on admission, eGFR on admission, baseline systolic and diastolic blood pressure, insulin use, procedures and surgeries, and Elixhauser comorbidity index (14,16). Baseline demographic and medical condition data were collected up to 730 days before hospitalization. Demographic data used were that nearest to the hospital admission. The eGFR on admission was the first eGFR obtained during the hospitalization, baseline A1C was defined as the value nearest to admission, and baseline systolic and diastolic blood pressures were calculated as the mean of all blood pressures during the admission.

Exposure and Outcomes

The exposure of interest was continued use of SGLT2is in the hospital, defined by the receipt of one or more doses of an SGLT2i on the 1st or 2nd day of admission. The primary outcome was in-hospital mortality, defined as death during the hospitalization. Secondary outcomes were acute kidney injury (AKI) during the inpatient stay and LOS. AKI was defined as an increase of SCr $\geq$0.3 mg/dL from baseline within the initial 48 h after admission or a $>$50% increase from baseline to maximum SCr during the admission, as per consensus diagnostic guidelines (17). LOS was defined as the number of days between the admission and discharge date.

Statistical Methods

We used a fixed exposure based on initial continuation versus discontinuation of SGTL2is (defined by dosing on the 1st and/or 2nd hospital day) rather than a

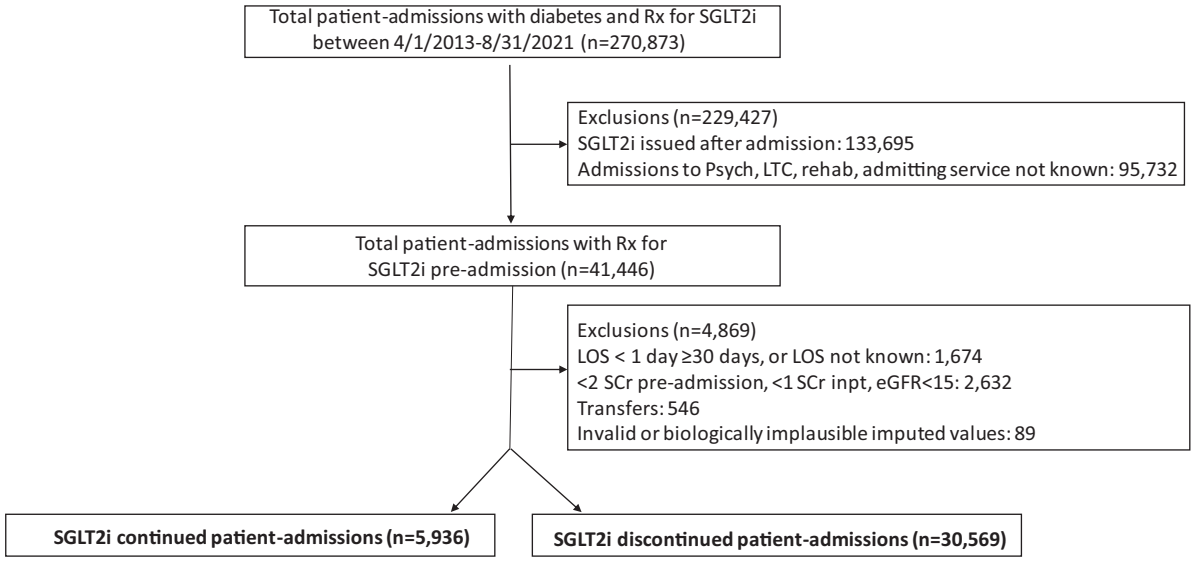

Figure 1—Study flow diagram. inpt, inpatient; LTC, long-term care; Psych, psychiatric; rehab, rehabilitation; Rx, prescription.

time-varying exposure variable. The latter approach may risk increasing confounding by indication because of acute changes in a patient's clinical status during hospitalization that may both trigger SGLT2i discontinuation and influence the risk of mortality, AKI, or longer LOS. In addition, the unit of analysis for this study was each individual hospital admission rather than each patient. As a result, for each admission, we determined whether SGLT2i therapy was continued or discontinued. An individual patient could have more than one hospital admission included in this analysis, and their exposure (SGLT2i continuation vs. discontinuation) was ascertained separately for each admission. We used general estimating equations (GEEs) to account for the serial autocorrelation resulting from studying a given patient more than once.

To obtain estimates of the average treatment effect (18) (i.e., the effect of SGLT2i therapy during admission) in which the risk of confounding by indication was minimized, each admission was weighted by the inverse of its probability (unstabilized inverse probability weighting) (19) of having SGLT2i continued at the time of admission. Baseline characteristics (see below) were used to compute the inverse probability weights.

Missing data (Supplementary Table 1) were imputed using multiple imputation (SAS PROC MI using the fully conditional specification method) (20). Following 20 burn-in iterations, a total of 25-imputed complete data sets were created. Nominal data (e.g., history of myocardial infarction) were imputed using discriminant analyses; continuous values (e.g., age, blood pressure) were imputed using linear regression. Following the imputation and after performing the statistical analysis, a small number of admissions were excluded from subsequent analyses (n = 89) because of invalid or biologically implausible imputed values for at least one of the covariates.

Four statistical analyses were conducted: two using the original nonimputed data and two using the imputed data. Regardless of whether the analyses were conducted using nonimputed data or imputed data, the analyses were weighted by the inverse of the patient's probability (unstabilized weights) of having an SGLT2i continued at the time of admission. Each of the four analyses used a different set of unstabilized propensity score weights.

Four distinct sets of inverse probability weights were created, one for each of the analyses described above. The weights were created using SAS PROC PSMatch, with a PSWEIGHT statement and a WEIGHT= ATEWGT option. The weights were computed as a function of age, race, BMI, date of admission (to account for changes in practice), Elixhauser comorbidity index, eGFR on admission, glucose value on admission, A1C nearest to the admission, use of insulin during the admission, and surgery or procedure during the admission.

Each of the four sets of weights were created using the data to which the weights would be applied, as follows: *1*) all imputed data, *2*) imputed data after dropping patients who died during their admission (for outcomes of AKI and LOS only), *3*) nonimputed data (i.e., patients remaining after casewise deletion of patient missing data), and *4*) nonimputed data after casewise deletion of patients missing data and patients who died during their admission (for outcomes of AKI and LOS). These weights reduced the standardized mean differences of the logits of the propensity score by ∼95% for all four analyses.

For AKI and death, the analyses of the association between exposure (continuing vs. not continuing SGLT2is) and outcome (mortality, AKI) were performed using negative binomial regression (SAS PROC GENMOD) with a negative binomial distribution and a log link. Estimate statements were used to compute estimates for predefined linear combinations of the independent variables (e.g., White race, male sex, age 67 years, BMI 32 kg/m^2, Elixhauser comorbidity index 17) and incidence rate ratios (IRRs) comparing patients differing only on group membership (SGLT2i continuation vs. discontinuation). As patients with diabetes commonly have multiple hospitalizations because of underlying comorbidities or diabetes-related complications (13), for these two outcome measures, the analyses used GEEs with an independent correlation structure to account for serial autocorrelation of repeated observations from the same patient (21,22). Because LOS cannot be 0, analyses of the association between

exposure and LOS were performed using zero-truncated Poisson regression (SAS PROC FMM with a truncated Poisson distribution) and a log link. The %NLEST macro was used to compute estimates of the predefined linear combinations of the independent variables and the IRRs because PROC FMM does not support estimate statements. GEE was not used for this outcome because PROC FMM does not support GEE.

Each set of analyses was composed of multiple models for each outcome measure. Model 1 was a crude model that included a single independent variable, group (SGLT2i continued vs. discontinued). In model 2, in addition to group, we adjusted for age, BMI, sex, race, insulin use, procedures and surgeries, and Elixhauser comorbidity index. Model 3 added an independent variable to model 2 that indicated whether the initial admission was to an intensive care unit (ICU) and an ICU × group interaction. Results for patients initially admitted to an ICU are reported as model 3a and for patients not initially admitted to an ICU, as model 3b. Model 4 was the same as model 2 but excluded patients who died during their admission. Model 5 was the same as model 3 but excluded admissions where patients died during hospitalization. For mortality, only models 1, 2, 3a, and 3b were conducted, given that in models 4, 5a, and 5b, admissions where patients died during hospitalization were excluded from the analyses.

Data and Resource Availability

Data that support the findings of this study are available within the VA Informatics and Computing Infrastructure database and are publicly available among VA investigators nationally. Data from the VHA cannot be shared without VA permission and collaborative agreement.

RESULTS

Baseline characteristics of the original cohort among the group of admissions where SGLT2i was continued and the group of admissions where SGLT2i was discontinued during hospitalization are presented in Table 1. In the SGLT2i continued versus discontinued group, respectively, mean (SE) age was 67.2 (0.1) and 67.5 (0.1) years (P = 0.03), 97% and 96.6% were male (P = 0.1), 71.3% and 72.1% were White and 20.8% and 20.5% Black (P = 0.52), and mean (SE) BMI was 32.7 (0.1) and 32.5 (0.04) kg/m^2 (P = 0.08). There was a high percentage of comorbidities among patients in the study cohort, including cardiovascular disease (CVD) (75.3% vs. 72.5%), cardiac arrythmias (69.5% vs. 68.3%), and congestive HF (60.0% vs. 56.2%) in the SGLT2i continued versus discontinued groups, respectively. Patients also exhibited diabetic neuropathy (73.1% vs. 76.1%), diabetic retinopathy (51.8% vs. 55.4%), and renal failure (42.9% vs. 45.7%), as well as a high percentage of hypertension (61.5% vs. 60.2%) and obesity (79.9% vs. 80.4%) in the SGLT2i continued versus discontinued groups, respectively. Reasons for hospitalizations are reported in Supplementary Table 2. Empagliflozin was the SGLT2i administered predominantly within this cohort (99.9%) as the main formulary SGLT2i used by the VHA during the study period (Supplementary Table 3). Among patients initially continued on SGLT2i on admission, SGLT2i was administered during 77% of total hospital days from admission to discharge.

There were 9.2 in-hospital deaths per 1,000 admissions in the SGLT2i continued group vs. 16.8 deaths per 1,000 admissions in the SGLT2i discontinued group, representing a 45% relatively lower mortality rate (IRR 0.55, 95% CI 0.41–0.72, $P < 0.01$) (Table 2, model 1). After adjusting for age, sex, BMI, race, insulin use, procedures and surgeries, and Elixhauser comorbidity index (model 2), the difference of in-hospital mortality was similar (IRR 0.55, 95% CI 0.42–0.73, $P < 0.01$). Likewise, estimated differences in mortality were similar among patients with a direct ICU admission (model 3a) (IRR 0.59, 95% CI 0.43–0.81, $P < 0.01$) and those whose admission was to a non-ICU bed (model 3b) (IRR 0.50, 95% CI 0.30–0.83, P = 0.01).

There were 201.9 in-hospital AKI events per 1,000 admissions in the SGLT2i continued group vs. 211.3 per 1,000 admissions in the SLGT2i discontinued group (Table 2). There was no significant difference in the AKI event rate between the two groups in either the unadjusted (IRR 0.96, 95% CI 0.90–1.02, P = 0.16) (model 1) or covariate-adjusted (IRR 0.96, 95% CI 0.90–1.02, P = 0.17) (model 2) analyses. No differences in results were observed among patients with and without direct ICU admission and after excluding those admissions with in-hospital death. Compared with the SGLT2i discontinued group, patients in the SGLT2i continued group experienced a shorter LOS in model 1 (unadjusted) of 4.7 vs. 4.9 days (IRR 0.95, 95% CI 0.93–0.98, $P < 0.01$), which was similar in all other analyses (Table 2, models 2–5).

Using complete-case sensitivity analysis (conducted without imputation of missing values but with unstabilized propensity score weighting), we repeated the analyses (Supplementary Table 4). Results from these analyses were similar to those obtained from the multiple imputation data (Table 2). There was a 39% lower mortality rate in the SGLT2i continued versus discontinued group (IRR 0.61, 95% CI 0.45–0.82, P = 0.01) in model 1 (unadjusted). After adjusting for age, sex, race, BMI, and Elixhauser comorbidity index (model 2), subsequent models 3–5 showed similar statistically significant reductions in mortality rate. Across secondary outcomes (AKI, LOS), similar associations as in the imputed data set were observed for the outcomes in the SGLT2i continued versus discontinued group.

CONCLUSIONS

In this study, we evaluated the continuation of SGLT2is from the outpatient to inpatient setting in patients with diabetes. Among patient admissions where SGLT2i was continued, there was at least a 40% lower rate of in-hospital death compared with those where SGLT2i was discontinued, after accounting for potential confounders, major comorbidity differences, and initial admission to the ICU versus not. Additionally, continuation of SGLT2i was associated with no increased risk of AKI and modestly shorter LOS, both representing important inpatient clinical outcomes. Current recommendations prioritize insulin as initial therapy during hospitalization, which represents a high-risk medication for hypoglycemia versus continuation of noninsulin-based medications. Insulin also has barriers of use, such as provider uncertainty with type of insulin regimen to use, difficulty with fluctuating insulin requirements, unpredictable meal or procedure timings, and inconsistency in diet (4). Our results shed light on potential benefits of continuation of a noninsulin medication used preadmission. Furthermore, to our knowledge, this study is the first to evaluate continuation of SGLT2i use from the ambulatory to inpatient setting.

Table 1—Characteristics of patient admissions at baseline

	SLGT2i continued (*n* = 5,936)	SGLT2i discontinued (*n* = 30,569)	*P*
Age (years), mean (SE)	67.2 (0.1)	67.5 (0.1)	0.03
Male sex	5,756 (97.0)	29,516 (96.6)	0.11
Race			0.52
White	4,235 (71.3)	22,032 (72.1)	
Black	1,232 (20.8)	6,272 (20.5)	
Other	168 (2.8)	788 (2.6)	
Unknown	301 (5.1)	1,478 (4.8)	
Admission BMI (kg/m^2), mean (SE)	32.7 (0.1)	32.5 (0.04)	0.08
Baseline A1C (%), mean (SE)	8.1 (0.02)	8.3 (0.01)	<0.01
Baseline eGFR (mL/min/1.73 m^2), mean (SE)	74.6 (0.3)	69.6 (0.2)	<0.01
Systolic blood pressure (mmHg), mean (SE)	128.0 (0.2)	130.7 (0.1)	<0.01
Diastolic blood pressure (mmHg), mean (SE)	72.1 (0.1)	72.5 (0.1)	<0.01
Elixhauser comorbidity index, mean (SE)	16.7 (0.2)	17.4 (0.1)	<0.01
Concurrent insulin use	5,046 (85.0)	27,696 (90.6)	<0.01
Procedures and/or surgeries	1,134 (19.1)	6,695 (21.9)	<0.01
Comorbid conditions			
Alcohol abuse	2,731 (46.0)	12,961 (42.4)	<0.01
Anemia blood loss	451 (7.6)	2,598 (8.5)	0.02
Cardiac arrythmias	4,126 (69.5)	20,879 (68.3)	0.06
Congestive HF	3,562 (60.0)	17,180 (56.2)	<0.01
Chronic pulmonary	3,829 (64.5)	19,320 (63.2)	0.04
Coagulopathy	1,015 (17.1)	5,411 (17.7)	0.20
CVD	4,470 (75.3)	22,163 (72.5)	<0.01
Deficiency anemia	1,656 (27.9)	9,171 (30.0)	<0.01
Depression	4,102 (69.1)	21,184 (69.6)	0.40
Diabetic neuropathy	4,339 (73.1)	23,263 (76.1)	<0.01
Diabetic retinopathy	3,075 (51.8)	16,935 (55.4)	<0.01
Drug abuse	1,579 (26.6)	7,795 (25.5)	0.07
Fluid and electrolyte disorder	3,763 (63.4)	20,145 (65.9)	<0.01
Hypertension, complicated	3,660 (61.5)	18,403 (60.2)	0.07
Liver disease	1,840 (30.5)	9,782 (32.3)	<0.01
Lymphoma	184 (3.1)	917 (3.0)	0.88
Metastatic cancer	232 (3.9)	1,834 (6.0)	<0.01
Obesity	4,749 (79.9)	24,455 (80.4)	0.35
Other neurological disorder	1,235 (20.8)	6,939 (22.7)	0.002
Paralysis	445 (7.5)	2,109 (6.9)	0.10
Peptic ulcer disease	540 (9.1)	3,057 (10.0)	0.04
Peripheral vascular disease	1,858 (31.3)	9,721 (31.8)	0.44
Pulmonary circulation disorder	1,253 (21.1)	6,114 (20.0)	0.05
Psychosis	2,642 (44.5)	13,909 (45.5)	0.16
Renal failure	2,547 (42.9)	13,970 (45.7)	<0.01
Rheumatoid arthritis	677 (11.4)	3,668 (12.0)	0.19
Solid tumor without metastasis	1,365 (23.0)	8,131 (26.6)	<0.01
Valvular disease	1,686 (28.4)	8,193 (26.8)	0.01
Weight loss	1,116 (18.8)	6,450 (21.1)	<0.01

Data are *n* (%) unless otherwise indicated and represent hospital admissions among the unweighted cohort. Individual patients may be represented in both subgroups if they had multiple hospitalizations with different SGLT2i use.

A key aspect of these analyses were methodological approaches to control for potential confounding that might bias estimated differences in outcomes between the two treatment groups. All analyses accounted for potential confounding via use of propensity score weighting, which equates the probability of continued SGLT2i in each of the two groups. In the main analyses, we further adjusted for pertinent characteristics such as age, sex, race, BMI, and a commonly used validated comorbidity index. Additionally, we accounted for admissions where the admitting service was an ICU (model 3) to account for the impact a greater acuity and severity of illness could have on use of SGLT2is and clinical outcomes. We also evaluated whether associations with AKI and LOS were affected after excluding admissions where patients died during their hospitalization (model 4). These adjustments would possibly account for patient admissions where individuals

Table 2—Associations of continued SGLT2i use with hospital outcomes (imputed)

Outcome	Model	Events (*n*)	SGLT2i continued, events per 1,000 admissions*	Events (*n*)	SGLT2i discontinued, events per 1,000 admissions*	IRR	95% CI	*P*
Mortality	1	57	9.2	514	16.8	0.55	0.41–0.72	<0.01
	2		9.6		17.5	0.55	0.42–0.73	<0.01
	3a		70.5		119.9	0.59	0.43–0.81	<0.01
	3b		2.7		5.5	0.50	0.30–0.83	0.01
AKI	1	1,123	201.9	6,646	211.3	0.96	0.90–1.02	0.16
	2		172.2		179.9	0.96	0.90–1.02	0.17
	3a		193.9		237.0	0.82	0.68–0.98	0.03
	3b		169.3		173.4	0.98	0.91–1.04	0.46
	4		167.1		172.9	0.97	0.91–1.03	0.29
	5a		159.0		184.9	0.86	0.69–1.07	0.18
	5b		167.7		171.8	0.98	0.91–1.04	0.47
LOS, days	1		4.7		4.9	0.95	0.93–0.98	<0.01
	2		3.9		4.1	0.94	0.92–0.97	<0.01
	3a		3.3		3.8	0.86	0.76–0.97	0.01
	3b		4.0		4.2	0.95	0.92–0.98	<0.01
	4		3.8		4.0	0.95	0.92–0.97	<0.01
	5a		2.7		3.1	0.86	0.77–0.96	0.01
	5b		3.9		4.1	0.95	0.93–0.98	<0.01

Model 1: crude, unadjusted. Model 2: adjusted for age, sex, race, BMI, Elixhauser comorbidity index, insulin use, and procedures and surgeries. Model 3a: model 2 plus initial admission to an ICU. Model 3b: model 2 plus initial admission not to an ICU. Model 4: model 2 plus exclusion of patients who died during hospitalization. Model 5a: model 3a plus exclusion of patients who died during hospitalization. Model 5b: model 3b plus exclusion of patients who died during hospitalization. Number of patients for models 4 and 5 was 5,879 for the SGLT2i continued group and 30,051 for the SGLT2i discontinued group. *Values for event rates and LOS are estimated from GEEs using values of 67 years for age, White for race/ethnicity, male for sex, 32 kg/m^2 for BMI, and 17 for Elixhauser comorbidity index, representing the average or most frequent values for these covariates.

were unstable and critically ill, predisposing them to a higher risk of death and poor clinical outcomes generally. Despite adjusting for these factors, we observed similar and consistent between-group differences in key outcomes. The adjustments did not change our inferences.

In the ambulatory setting, SGLT2is reduce the risk of mortality and morbidity in type 2 diabetes with atherosclerotic CVD (ASCVD) or CKD, CKD with or without diabetes, and HF with and without diabetes (7,23,24). In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG), there was a 32% reduction in death from any cause (hazard ratio [HR] 0.68, 95% CI 0.57–0.82, $P < 0.01$) with use of empagliflozin in type 2 diabetes and ASCVD (7). A meta-analysis including 21 trials reported a reduction in all-cause mortality with SGLT2is (odds ratio 0.86, 95% CI 0.81–0.91, $P < 0.01$) (25). Furthermore, dapagliflozin reduced all-cause death in HF (with and without diabetes) (HR 0.83, 95% CI 0.71–0.97) (24) and death from any cause in CKD (with or without diabetes) by 31% (HR 0.69, 95% CI 0.53–0.88, $P < 0.01$) (23). As our population exhibited extensive ASCVD, HF, and CKD (Table 1), it may be unsurprising to observe associations with reduced inpatient mortality and morbidity given that benefits have been previously shown with these comorbidities in the outpatient setting.

Studies evaluating inpatient SGLT2i use are limited. They were conducted mostly in HF (with and without diabetes) and evaluated SGLT2i initiation during hospitalization. The Empagliflozin in Patients Hospitalized With Acute Heart Failure (EMPULSE) trial evaluated empagliflozin initiated early in the hospitalization in acute de novo or decompensated HF (~45% of participants with diabetes) on a composite outcome of death of any cause, number and time to first HF events, and improvement of symptoms. Favorable effects were observed (win ratio of 1.36 in favor of empagliflozin vs. placebo, 95% CI 1.09–1.68, $P = 0.01$) (11). The Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure (EMPA-RESPONSE-AHF) randomized clinical trial demonstrated that initiation of empagliflozin for acute HF early in the admission of patients with or without diabetes reduced the composite end point of in-hospital worsening of HF, rehospitalization for HF, or death at 60 days versus placebo (4 [10%] vs. 13 [33%], $P = 0.01$). In this trial, ~45% of the population had diabetes (12). The Sotagliflozin in Patients With Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) trial revealed that sotagliflozin initiated prior to or within 3 days postdischarge for diabetes and recent worsening HF reduced cardiovascular deaths, hospitalizations, and urgent visits for HF (HR 0.67, 95% CI 0.52–0.85, $P < 0.01$) (10).

In addition to a high proportion of ASCVD, CKD, and HF in our cohort, there was also a significant percentage of patients with a history of arrythmia, which may represent another important comorbidity as SGLT2is have been proposed to have antiarrhythmic effects. The findings of reduced sudden cardiac death observed in SGLT2i cardiovascular outcomes trials suggest a potential benefit against ventricular arrythmias, an important cause of death in patients with HF (26). In a post hoc analysis of Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin reduced a composite outcome of serious ventricular arrhythmia, resuscitated cardiac arrest, and sudden death (27). Another key distinct demographic feature in our study is

the significantly higher number of Black patients (~21%) compared with other SGLT2i trials with a range of Black patients of 3–5% (7–9).

Mechanisms for the benefits of this class of medications are still not fully elucidated and extend beyond the glucose lowering effect. This glycemic effect is diminished in those with reduced eGFR (28), which indicates that cardiorenal benefits are independent of this mechanism of action. Patients may benefit from potential CVD and CKD risk reduction from ongoing use of SGLT2is in the hospital setting. Proposed mechanisms for other benefits of this class of medications include reduction of preload and afterload secondary to osmotic diuresis (29); reported minor increases in hemoglobin, hematocrit, and erythropoietin levels, which may improve oxygenation (30); and an ability to lower both systolic and diastolic blood pressure (29).

To our knowledge, this nationwide study is the largest to evaluate continuation of SGLT2i use in the hospital. Notably, we evaluated inpatient SGLT2i use in patients prescribed these mediations in the outpatient setting, which represents a population likely to have already been identified as optimal candidates for SGLT2i therapy in the ambulatory setting and presumably determined not to possess factors predisposing them to adverse effects or who had previous SGLT2i-related adverse events necessitating discontinuation. This differs from inpatient trials where SGLT2is are newly initiated amid acute changes in overall health. Our study included a larger proportion of minority patients (~21% Black) compared with other trials evaluating SGLT2is (7–9), in which the population was predominantly White. This is important as randomized clinical trials often underrepresent minority groups. Furthermore, our cohort possessed a high degree of comorbidities that have separately demonstrated benefits with SLGT2is, which may shed light on which patients could benefit from SGLT2i continuation in the hospital. Finally, the VHA is a closed health system where veterans receive care in both the ambulatory and inpatient setting, resulting in a robust population to evaluate research questions and accurately measure outcomes (14,31) and allowing for the evaluation of many covariates, as seen in Table 1.

There are a few limitations to consider for our study. While the VHA database allowed for a large population and extensive covariates, it can also be a potential limitation as it represents a single health care system (14). The population is also predominantly older and male and does not represent all racial or ethnic groups, which may reduce generalizability. Therefore, future studies in broader populations will be important. As this is a retrospective, cohort-based analysis, one cannot definitively infer causality between SGLT2i continuation and reduction of hospital outcomes in this study, and this study design can be susceptible to unmeasured confounders. For LOS, we used zero-truncated Poisson distribution as the LOS outcome has truncated zeros, but we were not able to use GEEs to account for the serial autocorrelation of data obtained from repeated measurements obtained from the same patient. In our analyses, we attempted to minimize potential confounding through robust statistical methods, including unstabilized propensity score weighting, covariate adjustment. We performed sensitivity analyses and obtained consistent findings across the three outcome measures of LOS, AKI, and mortality. Our findings are generally consistent with results observed in randomized trials conducted in ambulatory and inpatient settings evaluating SGLT2i use in patients with type 2 diabetes, ASCVD, CKD, and HF.

In conclusion, the results of this nationwide cohort study suggest associations of continued SGLT2i use in hospitalized patients with diabetes with a significantly lower rate of in-hospital mortality, no increased AKI, and modestly shorter LOS. This study adds to the body of literature that there may be a role for use of noninsulin-based pharmacotherapy to manage hyperglycemia in the inpatient setting. Further prospective, large-scale randomized clinical trials examining inpatient SGLT2i use are needed.

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