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Risk of ICU Admission and Related Mortality in Patients With Sodium-Glucose Cotransporter 2 Inhibitors and Dipeptidyl Peptidase-4 Inhibitors: A Territory-Wide Retrospective Cohort Study

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OBJECTIVES: The benefit of sodium-glucose cotransporter 2 (SGLT2) inhibitors in reducing the occurrence rate of adverse cardiac and renal outcomes in patients with type 2 diabetes has been well described in randomized trials. Whether this benefit extends to patients at the most severe end of the disease spectrum requiring admission to the ICU remains to be examined.

DESIGN: Retrospective observational study.

SETTING: Data were obtained from a territory-wide clinical registry in Hong Kong (Clinical Data Analysis and Reporting System).

PATIENTS: All adult patients (age ≥ 18 yr) with type 2 diabetes and newly prescribed SGLT2 inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors between January 1, 2015, and December 31, 2019.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: After 1:2 propensity score matching, a total of 27,972 patients (10,308 SGLT2 inhibitors vs 17,664 DPP-4 inhibitors) were included in the final analysis. The mean age was 59 ± 11 years, and 17,416 (62.3%) were male. The median follow-up period was 2.9 years. The use of SGLT2 inhibitors was associated with decreased ICU admission (286 [2.8%] vs 645 [3.7%]; hazard ratio [HR], 0.79; 95% CI, 0.69–0.91; $p = 0.001$) and lower risks of all-cause mortality (315 [3.1%] vs 1,327 [7.5%]; HR, 0.44; 95% CI, 0.38–0.49; $p < 0.001$), compared with DPP-4 inhibitors. The severity of illness upon ICU admission by Acute Physiology and Chronic Health Evaluation IV-predicted risk of death was also lower in SGLT2 inhibitors users. Admissions and mortality due to sepsis were lower in SGLT2 inhibitor users compared with DPP-4 inhibitor users (admissions for sepsis: 45 [0.4%] vs 134 [0.8%]; $p = 0.001$ and mortality: 59 [0.6%] vs 414 [2.3%]; $p < 0.001$, respectively).

CONCLUSIONS: In patients with type 2 diabetes, SGLT2 inhibitors were independently associated with lower rates of ICU admission and all-cause mortality across various disease categories.

KEY WORDS: all-cause mortality; diabetes; dipeptidyl peptidase-4 inhibitor; intensive care unit; sodium-glucose cotransporter 2 inhibitor

The global burden of critical illness has steadily increased especially with an aging population in the developed world (1). Despite modern advances in life support, mortality rates in the ICU has remained persistently high at over 15%, and even higher for patients admitted with sepsis (2, 3). However, recent clinical trials have failed to identify therapies that effectively moderate overall ICU and sepsis-related mortality (4, 5). In large cohort studies, patients with diabetes contribute more than 15% of intensive care

DOI: 10.1097/CCM.0000000000005869

KEY POINTS

Questions: The efficacy of sodium-glucose cotransporter 2 (SGLT2) inhibitors on clinical outcomes related to burden of critical illness has not been examined.

Findings: In this retrospective cohort study, 10,308 SGLT2 inhibitors users and 17,664 dipeptidyl peptidase-4 (DPP-4) inhibitors users were included in analysis after 1:2 propensity score matching. The use of SGLT2 inhibitors compared with DPP-4 inhibitors was significantly associated with lower rates of ICU admission (286 [2.8%] vs 645 [3.7%]) and all-cause mortality (315 [3.1%] vs 1,327 [7.5%]).

Meanings: SGLT2 inhibitors may be associated with benefits in clinical efficacy and cost-benefit ratios in the critical care setting that remains to be confirmed in prospective trials.

admissions and are at increased risks of adverse outcomes after intensive care (6).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the occurrence rate of major adverse cardiovascular events (MACE) and adverse renal events among patients with type 2 diabetes in randomized controlled trials (7–11). At the same time, certain safety endpoints were more frequently observed in the groups assigned to SGLT2 inhibitors, including urinary tract infection, diabetic ketoacidosis (DKA), hypotension, volume depletion, and amputation (7–9, 12). While there have been preliminary data on the reduced risks of pneumonia and sepsis-related morbidities with use of SGLT2 inhibitors (13, 14), the effect on the overall burden of critical illnesses and their efficacy in reducing ICU-related mortality have not been studied.

The objective of the study was to determine whether SGLT2 inhibitors had any benefit to the overall burden of critical illness. We hypothesized that the use of SGLT2 inhibitors is associated with decreased risks of ICU admission and all-cause mortality. We compared the risks and causes of admission to the ICU, severity of illness, and mortality associated with the incidental use of SGLT2 inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors among patients with type 2 diabetes.

METHODS

Study Population and Design

Data on new users of SGLT2 inhibitors or DPP-4 inhibitors between January 1, 2015, and December 31, 2019, from all public hospitals in Hong Kong were reviewed. Patients' baseline characteristics, clinical information, and outcomes were retrieved from the Clinical Data and Analysis Reporting System of the Hospital Authority in Hong Kong. We included all adult patients (18 yr old or older) with type 2 diabetes who received SGLT2 inhibitors or DPP-4 inhibitors for the first time or had not received these drugs within 12 months prior to the index date. Type 2 diabetes was defined as having an *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) code starting with 250, except those indicating type 1 diabetes; or having baseline hemoglobin A1c (HbA1c) greater than or equal to 6.5%; or using any anti-diabetic medications (i.e., insulins, glucagon-like peptide-1 [GLP-1] agonists, or oral hypoglycemic agents). Patients who received SGLT2 inhibitors or DPP-4 inhibitors for other indications and did not have diabetes were not included. Exclusion criteria were patients with estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m^2 or patients who were started on both SGLT2 inhibitors and DPP-4 inhibitors on the index date. This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority of Hong Kong West Cluster with a waiver of informed consent on July 28, 2022 (Institutional Review Board reference number: UW 22-561, study title "Association of SGLT2 Inhibitors and ICU Outcomes In a Territory Wide Longitudinal Cohort"). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration of 1975 and its later amendments.

Definition of Exposure Variables

We defined the index date as the first date of dispensing SGLT2 inhibitors or DPP-4 inhibitors. SGLT2 inhibitors included canagliflozin, dapagliflozin, and empagliflozin. DPP-4 inhibitors included alogliptin, linagliptin, linagliptin/metformin, saxagliptin, sitagliptin, sitagliptin/metformin, vildagliptin, and vildagliptin/metformin.

Patients were assigned to either the "SGLT2 inhibitors" group or "DPP-4 inhibitors" group and followed up according to their assigned drug group. Patients who were prescribed medication from the alternative drug group were censored on the dispense date of the alternative drug.

Definition of Outcome Variables

The co-primary outcomes were any admission to the ICU and all-cause mortality. Secondary outcomes were duration of ICU stay, severity of illness upon ICU admission, mortality due to cardiovascular, renal, and infectious causes, any emergent ICU admission, and any nonoperative ICU admission. The severity of illness upon ICU admission was measured by the Acute Physiology and Chronic Health Evaluation (APACHE) IV-predicted mortality (15). Safety outcomes including DKA, lower limb amputation, new requirement for dialysis, acute pulmonary edema, and urinary tract infection were also examined. DKA was defined using ICD-9-CM code or an elevated beta-hydroxybutyrate level. All outcome events were recorded until the date of censoring or death, or the data cutoff date of March 31, 2022, whichever occurred first. Detailed ICD-9-CM codes for clinical outcomes are listed in **eTable 1** (http://links.lww.com/CCM/H330).

Definitions of Covariables

Patient's baseline characteristics including age, sex, HbA1c, eGFR, comorbidities, and previous ICU admissions were collected. Detailed ICD-9-CM codes for comorbidities, that is, malignancy, hypertension, cerebrovascular disease, coronary artery disease, and congestive heart failure (CHF) are listed in the eTable 1 (http://links.lww.com/CCM/H330). Concomitant cardiovascular medications, including aspirin, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs); laboratory results were also obtained. Baseline laboratory results were defined as results closest to the index date.

Statistical Analysis

All analyses were performed with prespecified outcome and statistical methods. Based on data in published literature and biological plausibility, we constructed a logistic regression model that predicted the likelihood of receiving SGLT2 inhibitors or DPP-4 inhibitors. These included age, sex, baseline HbA1c, duration of diabetes, eGFR, previous ICU admission, underlying malignancy, hypertension, cerebrovascular disease, coronary artery disease, CHF, use of metformin, insulins, sulfonylureas, GLP-1 agonists, thiazolidinedione, ACEIs or ARBs, beta-blockers, statins and ezetimibe, calendar year of index medication initiation, risk for amputation, risk for fractures, and risk for genitourinary infections. Risk for amputation was defined using history of peripheral vascular disease or lower limb amputation. Risk for fractures was defined using history of osteoporosis or fractures, and risk for genitourinary infections was defined using history of urinary tract infections or positive urine cultures. The final study cohort consisted of two comparison groups—"SGLT2 inhibitors" and "DPP-4 inhibitors"—generated by 1:2 propensity score matching using a caliper of 0.2 times SD of the logit of propensity score.

Unadjusted analyses were made using chi-square tests for categorical variables and Student *t* test or Wilcoxon rank-sum tests for continuous variables. Cox proportional hazards regression was performed to evaluate the relationship between use of SGLT2 inhibitors or DPP-4 inhibitors and clinical outcomes in a time-to-first-event analysis.

Sensitivity Analyses

First, we performed sensitivity analysis by including all complete cases before propensity score matching. A multivariable Cox proportional hazards model adjusting for the same variables in the propensity score model was used to examine the association between study groups and the co-primary outcomes. Next, we repeated the analysis in all complete cases before propensity score matching using inverse probability treatment weighting to adjust for the same set of confounders. An on-treatment analysis was performed to account for possible differences in treatment duration.

Since the complete case method was adopted to address missing data in the primary statistical analysis, we tested the robustness of our results by repeating the multivariable Cox regression analysis with the entire cohort using the technique of multiple imputations by chained equations to account for missing data. We calculated E-values to quantify the association that a

confounder would need to have with clinical outcomes to nullify the primary analyses (16). Finally, to better ensure that the observed association between medication groups and clinical outcomes was not due to some underlying cause unrelated to the mechanistic hypothesis, falsification testing was performed with two clinical outcomes, trauma and acute cholecystitis. These outcomes were selected based on unlikely causal relationships with the medication groups, and detailed ICD-9-CM codes are listed in eTable 1 (http://links.lww.com/CCM/H330).

Exploratory Analysis

Subgroup analyses were performed according to the following seven dichotomized subgroups: age greater than 65 years, sex, HbA1c greater than 8%, eGFR less than 60 mL/min/1.73 m^2, previous heart failure, number of oral hypoglycemic agents greater than or equal to 2, and index medication initiation during or after 2018.

All analyses were performed using Stata MP software, Version 16.1 (StataCorp, College Station, TX). A two-tailed *p* value of less than 0.05 was considered statistically significant.

RESULTS

Patients and Characteristics

Between January 2015 and December 2019, a total of 73,111 patients were considered for inclusion: 4,053 (5.5%) were excluded after application of exclusion criteria. Of the remaining 69,058 patients, a total of 6,674 (9.7%) were excluded from complete case analysis due to missing values in any of the variables used in the propensity score matching model. After 1:2 propensity score matching, a total of 10,308 SGLT2 inhibitors users and 17,664 DPP-4 inhibitors users were included in the final analysis, representing 44.8% of the complete case cohort (**eFig. 1**, http://links.lww.com/CCM/H330). The mean age of the cohort was 59 ± 11 years, and 17,416 (62.3%) were male. Baseline characteristics and medications prescribed of the propensity score matched cohort and the complete case cohort are shown in **Table 1** and **eTable 2** (http://links.lww.com/CCM/H330), respectively. All variables in Table 1 were included in the propensity score model, and apart from certain oral anti-diabetic agents were well-balanced between groups with standardized difference less than 0.1. The median follow-up period was 2.9 years (2.3–4.0 yr).

ICU Admission

Table 2 describes the primary and secondary outcomes in SGLT2 inhibitors users and DPP-4 inhibitors users. Critical illness requiring ICU admission occurred in 286 patients (2.8%) in the SGLT2 inhibitor group and 645 patients (3.7%) in the DPP-4 inhibitor group. The risk of ICU admission was lower in SGLT2 inhibitors users compared with DPP-4 inhibitors users (hazard ratio [HR], 0.79; 95% CI, 0.69–0.91; $p = 0.001$), translating to an absolute between-group difference of 0.9 percentage points (95% CI, 0.5–1.3) and a number needed to treat of 114. The severity of illness upon ICU admission was lower in SGLT2 inhibitors users compared with DPP-4 inhibitors users (median APACHE IV-predicted risk of death 0.08 [0.03–0.25] vs 0.14 [0.05–0.36]; $p < 0.001$). The ICU length of stay was similar between the two groups. The risk of emergency ICU admission was lower in SGLT2 inhibitors users (208 [2.0%] vs 496 [2.8%]; HR, 0.75; 95% CI, 0.64–0.89; $p = 0.001$), as was the risk of nonoperative ICU admission (151 [1.5%] vs 415 [2.4%]; HR, 0.66; 95% CI, 0.54–0.79; $p < 0.001$). Kaplan-Meier survival curves showed that the use of SGLT2 inhibitors was associated with lower risks of critical illness requiring any ICU admission, emergent ICU admission, and nonoperative ICU admission (**Fig. 1**). Admissions for sepsis were fewer in SGLT2 inhibitors users compared with DPP-4 inhibitors users (45 [0.4%] vs 134 [0.8%]; HR, 0.61; 95% CI, 0.43–0.85; $p = 0.004$). Data for other causes of ICU admission are presented in **eTable 3** (http://links.lww.com/CCM/H330).

All-Cause Mortality

The co-primary outcome of all-cause mortality occurred in 315 patients (3.1%) in the SGLT2 inhibitor group and 1,327 patients (7.5%) in the DPP-4 inhibitor group. The risk of death was lower in SGLT2 inhibitors users compared with DPP-4 inhibitors users (HR, 0.44; 95% CI, 0.38–0.49; $p < 0.001$), translating to an absolute between-group difference of 4.5 percentage points (95% CI, 3.9–5.0) and a number needed to treat of 22 (Table 2). The risk of mortality due to infectious causes was

TABLE 1.
Baseline Characteristics of Subjects After Propensity Score Matching

Characteristics	Sodium-Glucose Cotransporter 2 Inhibitors, *n* = 10,308	Dipeptidyl Peptidase-4 Inhibitors, *n* = 17,664	Standardized Difference
Age, yr	58.9 ± 10.8	59.8 ± 11.2	0.088
Sex, female	3,726 (36.1%)	6,830 (38.7%)	0.052
Baseline hemoglobin A1c, %	8.6 ± 1.6	8.6 ± 1.6	0.013
Duration of diabetes, yr	7.4 ± 5.7	7.5 ± 5.7	0.004
Estimated glomerular filtration rate, mL/min/1.73 m2	80.8 ± 20.1	80.0 ± 23.9	−0.036
Previous ICU admission	591 (5.7%)	961 (5.4%)	−0.013
Malignancy	492 (4.8%)	885 (5.0%)	0.011
Hypertension	7,937 (77.0%)	13,278 (75.2%)	−0.043
Cerebrovascular disease	795 (7.7%)	1,444 (8.2%)	0.017
Coronary artery disease	2,812 (27.3%)	4,129 (23.4%)	−0.090
Congestive heart failure	684 (6.6%)	1,123 (6.4%)	−0.011
Metformin	9,429 (91.5%)	15,817 (89.5%)	−0.066
Insulins	4,149 (40.3%)	6,700 (37.9%)	−0.048
Sulfonylureas	5,002 (48.5%)	9,487 (53.7%)	0.104
Glucagon-like peptide-1 agonists	253 (2.5%)	27 (0.2%)	−0.204
Thiazolidinedione	1,562 (15.2%)	1,912 (10.8%)	−0.129
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers	7,213 (70.0%)	11,909 (67.4%)	−0.055
Beta-blockers	4,246 (41.2%)	6,750 (38.2%)	−0.061
Lipid-lowering medications[a]	8,155 (79.1%)	13,656 (77.3%)	−0.044
Index year ≥ 2018	6,888 (66.8%)	11,213 (63.5%)	−0.070
Risk for amputation[b]	828 (8.0%)	1,427 (8.1%)	0.002
Risk for fractures[c]	578 (5.6%)	1,020 (5.8%)	0.007
Risk for genitourinary infections[d]	1,745 (16.9%)	3,156 (17.9%)	0.025

[a]Lipid-lowering medications included atorvastatin, fluvastatin, rosuvastatin, simvastatin, and ezetimibe.
[b]Risk for amputation was defined using history of peripheral vascular disease or lower limb amputation.
[c]Risk for fractures was defined using history of osteoporosis or fractures.
[d]Risk for genitourinary infections was defined using history of urinary tract infections or positive urine cultures.
All results were presented with frequency (percentage) or mean ± SD.

lower in SGLT2 inhibitors users compared with DPP-4 inhibitors users (59 [0.6%] vs 414 [2.3%]; HR, 0.26; 95% CI, 0.20–0.34; $p < 0.001$). The risk of cardiovascular death was lower in SGLT2 inhibitors users (105 [1.0%] vs 332 [1.9%]; HR, 0.58; 95% CI, 0.46–0.72; $p < 0.001$), as was the risk of renal-related mortality (3 [0.03%] vs 25 [0.14%]; HR, 0.22; 95% CI, 0.07–0.73; $p = 0.014$). Kaplan-Meier survival curves demonstrated that the use of SGLT2 inhibitors was associated with lower risks of all-cause mortality, mortality due to infectious, cardiovascular, and renal causes, compared with use of DPP-4 inhibitors (**Fig. 2**).

Sensitivity Analyses

After adjustment by multivariable Cox regression, the risk of ICU admission was lower in SGLT2 inhibitors users compared with DPP-4 inhibitors users (HR, 0.85; 95% CI, 0.74–0.97; $p = 0.016$) in the

TABLE 2.
Primary and Secondary Outcomes

Outcomes	Event Rates per 100 Patient-Year[a]		Hazard Ratio (95% CI)	*p*
	SGLT2 Inhibitors	DPP-4 Inhibitors		
Primary outcomes				
ICU admission	0.94 (0.84–1.05)	1.18 (1.09–1.27)	0.79 (0.69–0.91)	*0.001*
All-cause mortality	1.02 (0.91–1.14)	2.38 (2.26–2.51)	0.44 (0.38–0.49)	*< 0.001*
Secondary outcomes				
Emergent ICU admission	0.68 (0.60–0.78)	0.91 (0.83–0.99)	0.75 (0.64–0.89)	*0.001*
Nonoperative ICU admission	0.50 (0.42–0.58)	0.76 (0.69–0.84)	0.66 (0.54–0.79)	*< 0.001*
Mortality due to:				
Infections	0.19 (0.15–0.25)	0.74 (0.67–0.82)	0.26 (0.20–0.34)	*< 0.001*
Cardiovascular	0.34 (0.28–0.41)	0.60 (0.53–0.66)	0.58 (0.46–0.72)	*< 0.001*
Renal	0.01 (0.003–0.03)	0.04 (0.03–0.07)	0.22 (0.07–0.73)	*0.014*
On-treatment analysis				
ICU admission	0.83 (0.72–0.95)	1.07 (0.97–1.17)	0.77 (0.65–0.91)	*0.003*
All-cause mortality	0.49 (0.40–0.58)	1.11 (1.01–1.22)	0.44 (0.36–0.54)	*< 0.001*
Falsification outcomes				
Trauma	0.38 (0.32–0.46)	0.43 (0.38–0.49)	0.87 (0.70–1.09)	0.23
Cholecystitis	0.25 (0.20–0.31)	0.28 (0.24–0.33)	0.88 (0.67–1.16)	0.37
ICU specific outcomes[b]	SGLT2 inhibitors, *n* = 10,308	DPP-4 inhibitors, *n* = 17,664		
ICU length of stay, d	3 (2–5)	3 (2–6)		0.64
Acute Physiology and Chronic Health Evaluation IV predicted risk of death[c]	0.08 (0.03–0.25)	0.14 (0.05–0.36)		*< 0.001*

DPP-4 = dipeptidyl peptidase-4, SGLT2 = sodium-glucose cotransporter 2.

[a]Results are presented as rate per 100 patient year (95% CI).

[b]Results are presented as median (interquartile range).

[c]Among 931 people required ICU admission, two patients (0.2%) had missing Acute Physiology and Chronic Health Evaluation IV predicted values, therefore, *n* = 929.

complete case cohort (*n* = 62,384), as was the risk of all-cause mortality (HR, 0.53; 95% CI, 0.47–0.60; $p < 0.001$), which were consistent with the primary analysis. These associations remained significant after adjustment by inverse probability treatment weighting as determined by the propensity score (ICU admission: HR, 0.76; 95% CI, 0.71–0.81; $p < 0.001$ and all-cause mortality: HR, 0.43; 95% CI, 0.41–0.45; $p < 0.001$). The median duration of treatment were similar in the two medication groups (SGLT2 inhibitors: 953 d [403–1,367 d] and DPP-4 inhibitors: 967 d [400–1,351 d]; $p = 0.70$), and results in the on-treatment analysis were similar to the intention-to-treat analysis.

A total of two variables, baseline HbA1c and eGFR, in the propensity score model had missing data. Multiple imputation was conducted, and the imputed cohort included all 6,674 patients (9.7%) who were excluded due to missing values in any of the variables used in the propensity score model. The association between SGLT2 inhibitors and ICU admission in the imputed dataset remained significant (adjusted HR, 0.79; 95% CI, 0.69 to 0.90; $p < 0.001$), as was the association with all-cause mortality (adjusted HR, 0.52; 95% CI, 0.46–0.58; $p < 0.001$). The E-value for the HR for new ICU admission is 1.63, while the E-value for the HR for all-cause mortality is 2.94, suggesting that for an unmeasured confounder to render the primary results statistically insignificant, it would need to

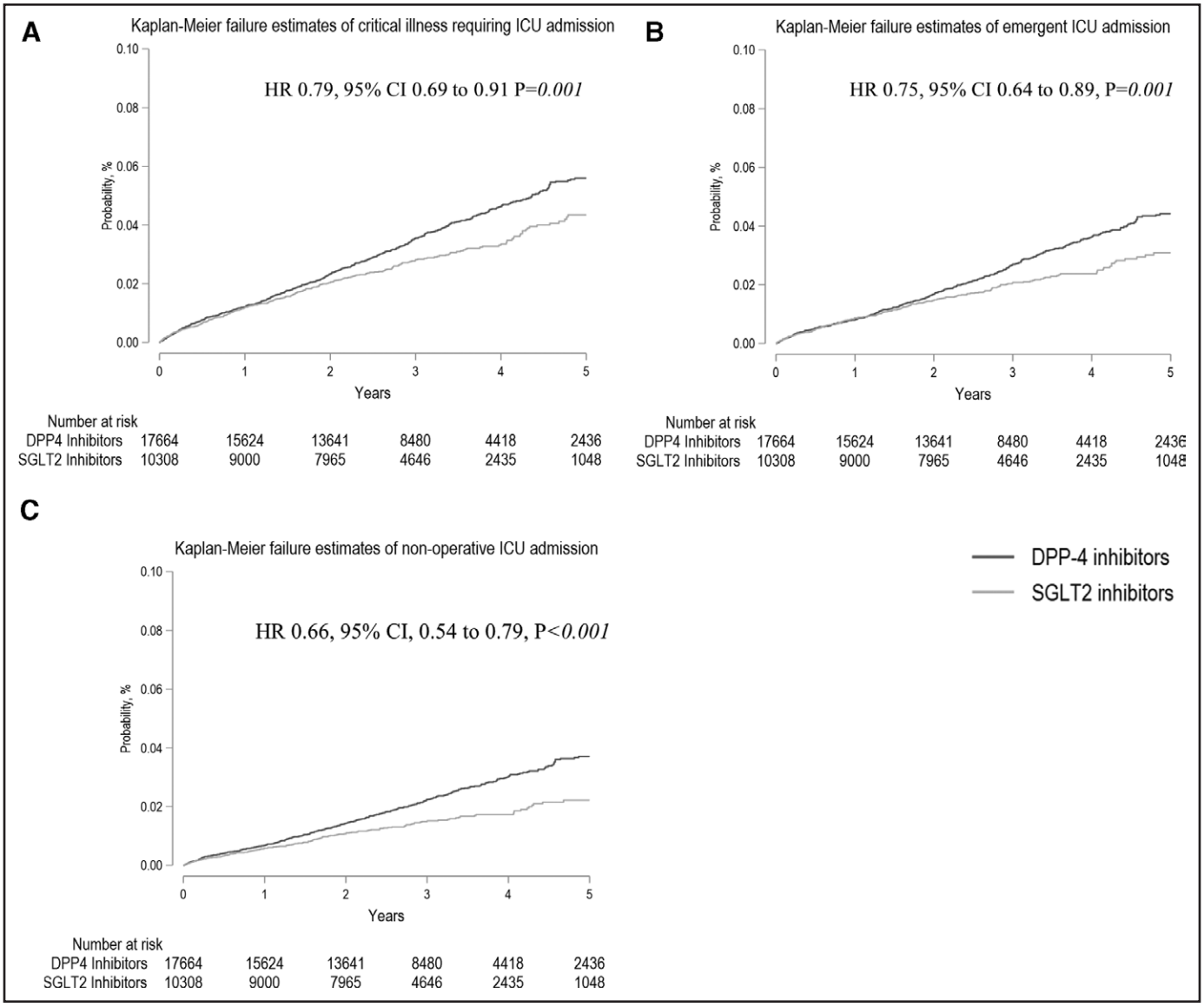

Figure 1. Estimated probabilities of ICU admission stratified by sodium-glucose cotransporter 2 (SGLT2) inhibitor group and dipeptidyl peptidase-4 (DPP-4) inhibitor group. Use of SGLT2 inhibitors was associated with lower risks of critical illness requiring any ICU admission (hazard ratio [HR], 0.79; 95% CI, 0.69–0.91; $p = 0.001$) (**A**), emergent ICU admission (HR, 0.75; 95% CI, 0.64–0.89; $p = 0.001$) (**B**), and nonoperative ICU admission (HR, 0.66; 95% CI, 0.54–0.79; $p < 0.001$) (**C**) compared with use of DPP-4 inhibitors.

be very strongly associated with ICU admission and all-cause mortality (> 60% difference in prevalence between SGLT2 inhibitors users and DPP-4 inhibitors users, and a HR > 1.6 or < 0.6 on ICU admission). Finally, falsification testing showed that the clinical outcomes of trauma and acute cholecystitis were not significantly associated with medication group. Detailed results of sensitivity analyses are presented in Table 2.

Subgroup Analyses

The effect of SGLT2 inhibitors on the outcomes of ICU admission and all-cause mortality was modified by eGFR (p for interaction < 0.001 and 0.004, respectively), with patients with eGFR less than 60 mL/min/1.73 m^2 deriving more clinical benefit than those with eGFR greater than or equal to 60 mL/min/1.73 m^2. The benefit of SGLT2 inhibitors on ICU admission was greater in patients on less than two oral hypoglycemic agents (p for interaction = 0.042) and the benefit of SGLT2 inhibitors on all-cause mortality was greater in patients who were initiated on index medication before 2018 (p for interaction = 0.025). The associations between SGLT2 inhibitors and outcomes were not modified by age, sex, HbA1c level, or previous CHF (p for interaction > 0.05 for

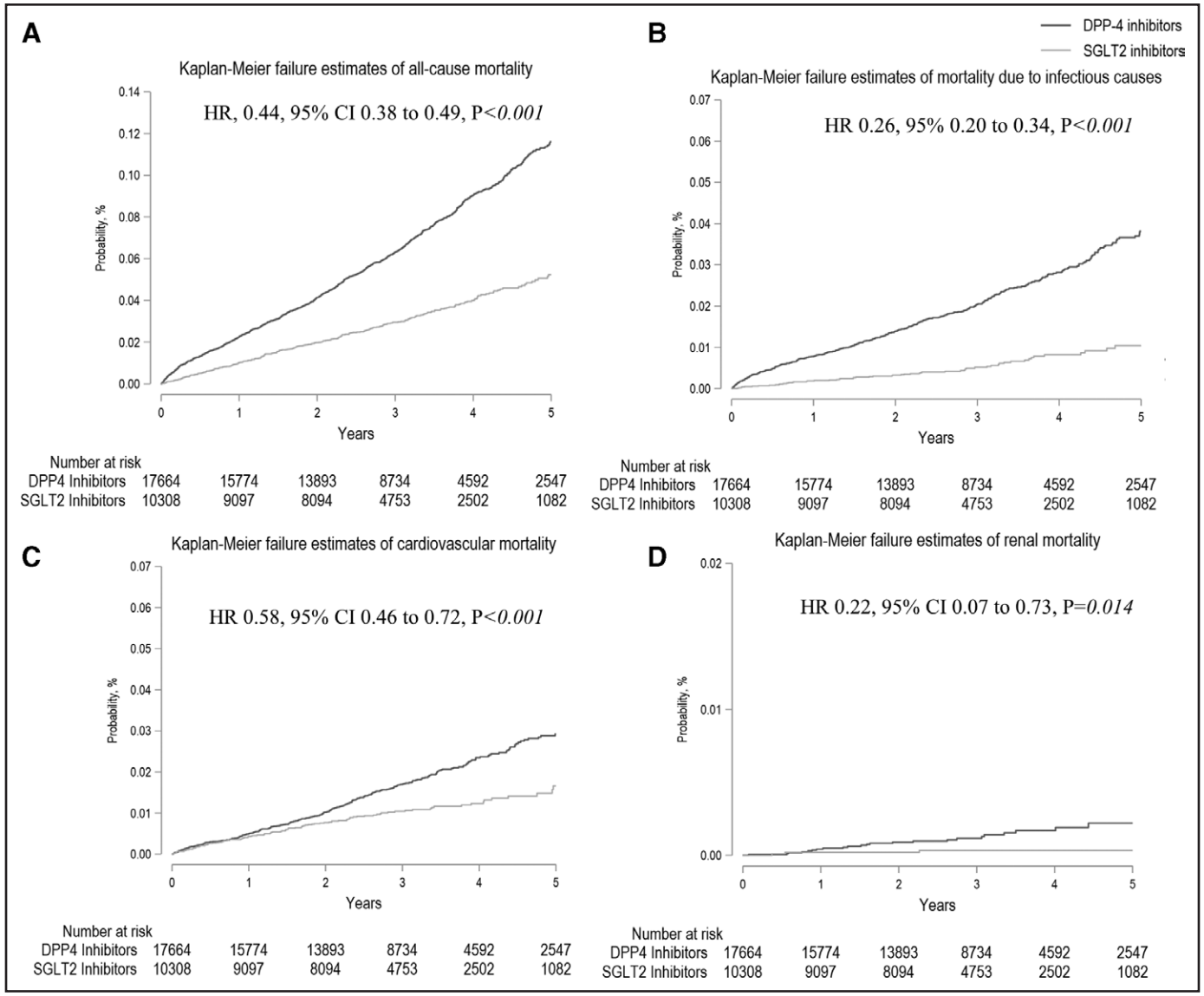

Figure 2. Estimated probabilities of all-cause mortality stratified by sodium-glucose cotransporter 2 (SGLT2) inhibitor group and dipeptidyl peptidase-4 (DPP-4) inhibitor group. Use of SGLT2 inhibitors was associated with lower risks of all-cause mortality (hazard ratio [HR], 0.44; 95% CI, 0.38–0.49; $p < 0.001$) (**A**), mortality due to infectious causes (HR, 0.26; 95% CI, 0.20–0.34; $p < 0.001$) (**B**), cardiovascular mortality (HR, 0.58; 95% CI, 0.46–0.72; $p < 0.001$) (**C**), and renal mortality (HR, 0.22; 95% CI, 0.07–0.73; $p = 0.014$) (**D**) compared with use of DPP-4 inhibitors.

all) (**eTable 4**, http://links.lww.com/CCM/H330; and **Fig. 3**).

Safety Outcomes

Safety outcomes are reported in **Table 3**. The risks of lower limb amputation, new requirement for dialysis, acute pulmonary edema, and urinary tract infection were significantly lower in SGLT2 inhibitors users compared with DPP-4 inhibitors users ($p < 0.05$ for all). The risk of DKA was similar between the SGLT2 inhibitor users and DPP-4 inhibitor users (160 [1.6%] vs 297 [1.7%]; $p = 0.41$).

DISCUSSION

In this cohort of 69,058 adult patients with type 2 diabetes, initiation of SGLT2 inhibitors compared with DPP-4 inhibitors were associated with lower risks of critical illness, decreased disease severity, and lower all-cause mortality over a median follow-up of 2.9 years. We identified that infections- and sepsis-related admissions to ICU and mortality were concurrently mitigated by the use of SGLT2 inhibitors. The beneficial effects of SGLT2 inhibitors were seen across various subgroups of age and underlying comorbid conditions,

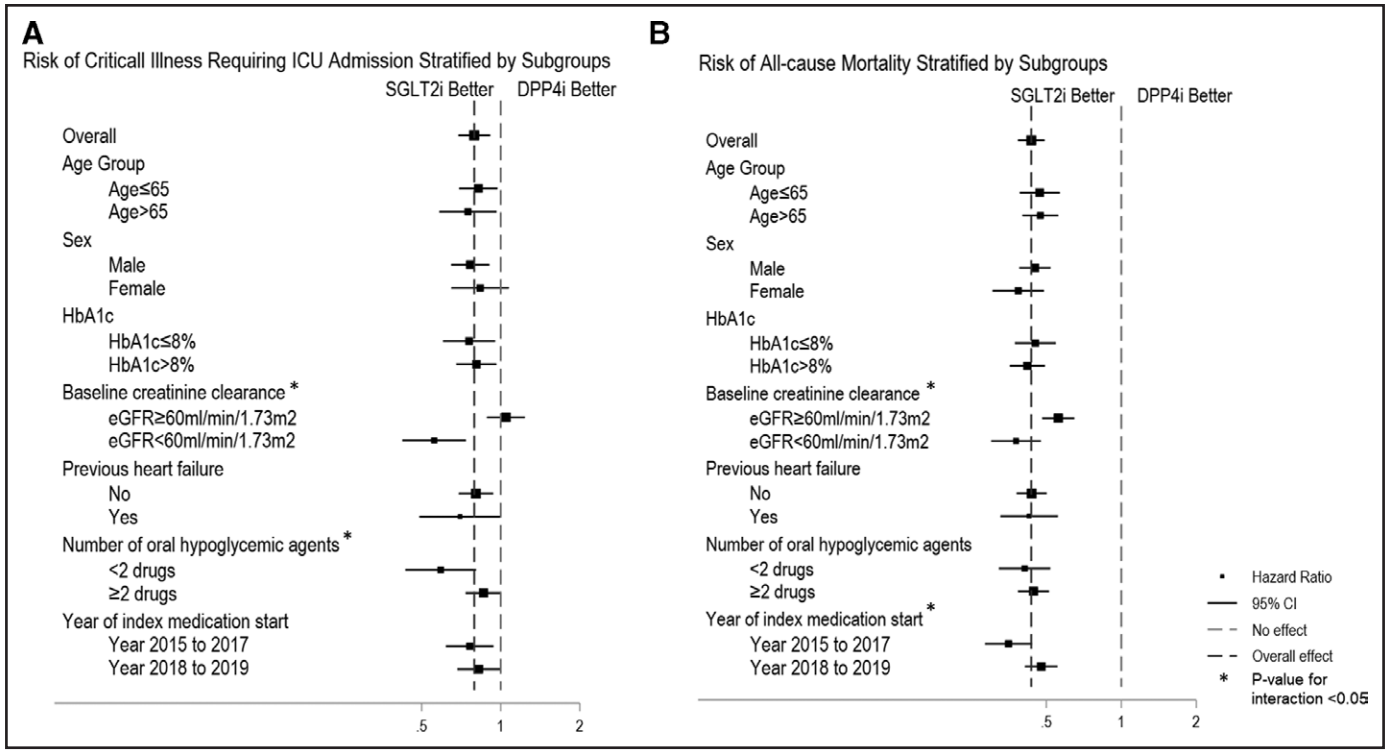

Figure 3. Forest plots for subgroups analyses. The effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on the outcomes of ICU admission and all-cause mortality was modified by estimated glomerular filtration rate (eGFR) (p for interaction < 0.001 and 0.004, respectively). Patients who were on less than two oral hypoglycemic agents and patients who were initiated on index medication before 2018 also derived greater clinical benefit. There was no effect modification in other predefined subgroups for the two co-primary outcomes—critical illness requiring any ICU admission (**A**) and all-cause mortality (**B**). DDP4i = dipeptidyl peptidase-4 inhibitor, HbA1c = hemoglobin A1c.

and the protection appeared to be more pronounced in patients with chronic renal impairment.

SGLT2 inhibitors have been shown to effectively reduce MACE and renal events among patients with type 2 diabetes (7–10). Since hospitalizations secondary to decompensated heart failure and decline in renal function are clearly reduced with the use of SGLT2 inhibitors, it would be reasonable to extrapolate a reduction in burden of critical illnesses and admissions to ICU. However, SGLT2 inhibitors have been associated with a two- to 10-fold risk of DKA (8, 17), along with other safety concerns including a doubling in risk of severe urinary tract infection (18), hospital admission for infections (19), volume depletion (8, 20), hypotension (21), or even amputation (9). Taken together, the net effect of SGLT2 inhibitors on critical illness and the utilization of ICU resources remains to be clarified. To our knowledge, this topic has never been evaluated in any randomized trials or observational studies.

In the current study including a large representative cohort of patients with type 2 diabetes, we observed that the risk of critical illness requiring admission to ICU was reduced by approximately 20% with the use of SGLT2 inhibitors. The biological mechanisms underlying the protective effects of SGLT2 inhibitors against critical illnesses are multidimensional, among which benefits in cardiac and renal function are two of the most important. SGLT2 inhibitors can improve cell life programming (22), arterial stiffness (23), cardiac structure and function (24, 25), and reduce cardiorenal effects and albuminuria (26, 27); hence, the strong cardiorenal efficacy observed in clinical trials (28). In our cohort, the absolute differences in mortality due to cardiovascular and renal causes were 0.9% and 0.1%, respectively.

More specific to acute and critical illnesses, SGLT2 inhibitors have been associated with protective effects against pneumonia, sepsis, and infection-related mortality (13). This may be related to the anti-inflammatory properties of SGLT2 inhibitors, mediated through down-regulation of cytokine production by macrophages and inflammasomes (29). Alternative mechanisms such as counteracting lipopolysaccharide (LPS)-induced vascular hyperpermeability and

TABLE 3.
Safety Outcomes

Safety Outcomes	Sodium-Glucose Cotransporter 2 Inhibitors, *n* = 10,308, *n* (%)	Dipeptidyl Peptidase-4 Inhibitors, *n* = 17,664, *n* (%)	*p*
Diabetic ketoacidosis[a]	160 (1.6)	297 (1.7)	0.41
Lower limb amputation	26 (0.3)	89 (0.5)	*0.002*
New requirement for dialysis[b]	44 (0.4)	289 (1.6)	*< 0.001*
Acute pulmonary edema	61 (0.6)	152 (0.9)	*0.013*
Urinary tract infection	214 (2.1)	840 (4.8)	*< 0.001*

[a]Diabetic ketoacidosis was defined as using *International Classification of Diseases*, 9th Revision, Clinical Modification code or an elevated beta-hydroxybutyrate level.
[b]New requirement for dialysis refers to patients who were started and maintained on dialysis with no record of receiving dialysis prior to the index date.

improving intestinal barrier function have also been demonstrated in animal models (30, 31). The beneficial effects of SGLT2 inhibitors were observed across all categories of ICU admission but were most evident in reducing nonoperative ICU admissions, which in our cohort referred to emergency admissions due to nonsurgical causes. When further stratified by disease category, the reduction in ICU admission due to sepsis was the most striking, with a 40% reduction in risk for SGLT2 inhibitors users. The milder severity of illness upon ICU admission may be partially explained by pathophysiological mechanisms such as damping of LPS-induced acute renal injury in animal models (14), possibly undermining the greater benefit derived in patients with renal impairment and eGFR less than 60 mL/min/1.73 m^2. The reduction of sepsis-related complications in chronic users of SGLT2 inhibitors, if confirmed in follow-up prospective trials, could have significant implications for the population with diabetes, to whom up to 6% of infection-related hospitalizations and 12% of infection-related deaths had been attributed (32). It remains to be examined whether users of SGLT2 inhibitors for reasons other than diabetes would derive similar clinical benefits.

The significant reduction in all-cause mortality of SGLT2 inhibitors that has been demonstrated in randomized trials was further validated in our cohort (9, 11), as were reductions in death due to cardiovascular, renal, and infection-related causes, with a number needed to treat of 22. Recent studies have shown that the clinical benefit derived from SGLT2 inhibitors begins to manifest as early as 13 days (33). The potential cost-efficiency of SGLT2 inhibitors in decreasing healthcare utilization and morbidities across broad populations of patients with cardiovascular risk factors, risks for progressive renal injury, and even immunosuppressed or infection-prone individuals could amount to significant cost-benefit ratios across hospital intensive care systems (34).

The current study had some limitations. First, the observational nature of the study conferred risks of unmeasured confounding and bias, but the large cohort size with complete longitudinal electronic healthcare records and incident new user design minimized selection, information, and recall biases (35). We used rigorous propensity score matching, and the findings were consistent in many sensitivity analyses. The utilization of an active comparator of DPP-4 inhibitors allowed evaluation of SGLT2 inhibitors in a typical decision bifurcation during escalation of diabetes care. Second, we only collected prescription data and could not ascertain drug adherence, which could have biased the results toward the null. Third, patients were censored if they crossed over to or added on the other drug class, and the effect of continuing both drug classes is unclear.

CONCLUSIONS

In conclusion, we showed that patients with type 2 diabetes who were on SGLT2 inhibitors were independently associated with reduction in admission to the ICU, milder disease severity, and lower all-cause mortality compared with patients on DPP-4 inhibitors. The use of SGLT2 inhibitors in the critical care setting remains to be clarified in future prospective trials.

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Drs. P. Y. Ng and A. K.-Y. Ng and Ms. Yiu were responsible for the conception and design of the study. Drs. P. Y. Ng, A. K.-Y. Ng, and Ip analyzed the data collected by Drs. Ip and Wu. Drs. P. Y. Ng and A. K.-Y. Ng interpreted the data. Drs. P. Y. Ng, A. K.-Y. Ng, and Ip drafted the article. All authors revised and approved the final article and are accountable for the accuracy and integrity of the work.

This study was supported by Sanming Project of Medicine in Shenzhen, China (No. SZSM201911020) and HKU-SZH Fund for Shenzhen Key Medical Discipline (No. SZXK2020081).

The authors have disclosed that they do not have any potential conflicts of interest.

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