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Original article

Risk of sepsis and pneumonia in patients initiated on SGLT2 inhibitors and DPP-4 inhibitors

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ABSTRACT

Aim: The organ protective effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors may be beneficial against infectious complications. This real-world study aims to compare the risk of pneumonia and sepsis between SGLT2 inhibitors and dipeptidyl peptidase 4 (DPP-4) inhibitors in patients with type 2 diabetes.
Methods: Using a territory-wide clinical registry in Hong Kong (Clinical Data Analysis and Reporting System [CDARS]), we included patients initiated on SGLT2 inhibitors or DPP-4 inhibitors between January 01, 2015 and December 31, 2019 through 1:2 propensity score matching. The primary outcomes were incident events of pneumonia, sepsis and the related mortality. Cox proportional hazards analysis was used to compare the risk of incident pneumonia and sepsis for SGLT2 inhibitors versus DPP-4 inhibitors.
Results: After propensity score matching, 10,706 new users of SGLT2 inhibitors and 18,281 new users of DPP-4 inhibitors were included. The mean age of all eligible subjects were 60 years (SD 11.07) and 61.1% were male. There were 309 pneumonia events [incidence rate per 1000 person-years (IR) = 11.38] among SGLT2 inhibitors users and 961 events (IR = 20.45) among DPP-4 inhibitors users, with lower risk of pneumonia among SGLT2 inhibitors users (adjusted HR 0.63 [95%CI 0.55–0.72], $p<0.001$). Similarly, SGLT2 inhibitors users had lower incidence of sepsis [164 (IR=6.00) vs. 610 (IR=12.88) events] as well as associated risk of incident sepsis (HR 0.52 [95% CI 0.44–0.62], $p<0.001$), compared to DPP-4 inhibitors users. Outcome analyses showed that SGLT2 inhibitors were associated with lower risk of pneumonia-related death (HR 0.41 [95%CI 0.29–0.58], $p<0.001$), sepsis-related death (HR 0.39 [95%CI 0.18–0.84], $p<0.05$), and infection-related death (HR 0.43 [95%CI 0.32–0.57], $p<0.001$), compared to DPP-4 inhibitors users. Results were consistent when stratified by age, sex, pre-existing cardiovascular disease, and type of SGLT2 inhibitors.
Conclusion: We provide real-world evidence that irrespective of age, sex, prior-existing cardiovascular disease, or type of SGLT2 inhibitors used, patients with type 2 diabetes initiated on SGLT2 inhibitors have lower incidence of pneumonia and sepsis as well as mortality risk associated with pneumonia, sepsis, and infectious diseases, compared with those initiated on DPP-4 inhibitors.

Introduction

Type 2 diabetes is a global epidemic affecting approximately 451 million individuals worldwide [1]. Although cardiovascular disease remains as the largest single contributor to mortality among individuals with diabetes, deaths related to non-vascular and non-cancer complications, including infections, have increased substantially in the last decade [2,3]. Patients with diabetes are at increased risk of pneumonia, sepsis, and related death, compared with those without diabetes [4–6]. Paradoxically, recent large-scale studies have shown that oral hypoglycemic agents, including metformin and thiazolidinediones, are associated with a higher risk of pneumonia [7,8]. Critical evaluation of other hypoglycemic agents in relation to infections is crucial.

Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors are two classes of hypoglycemic

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agents that are increasingly prescribed in routine clinical practice due to their superior HbA1c control ability and favorable safety profiles. In recent years, numerous trials have rigorously documented a clear cardiorenal benefit with SGLT2 inhibitors [9]. Intriguingly, both DPP-4 and SGLT2 inhibitors are suggested to exert pleiotropic and anti-inflammatory effects – which, in theory, is beneficial in patients with pneumonia and sepsis as well [9]. Yet, the pharmaceutical efficacy of DPP-4 and SGLT2 inhibitors in reducing sepsis and pneumonia, remains unclear. The Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) trial, which assessed the safety and efficacy of dapagliflozin among patients hospitalized a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, showed that dapagliflozin was well-tolerated, regardless of diabetes status but did not prevent organ failure or 30-day mortality, compared to placebo [10]. In contrast, a retrospective analysis demonstrated significantly lower risk of mechanical ventilation requirement in SARS-CoV-2 patients treated with SGLT2 inhibitors [11]. Similar controversial results are reported from studies reporting on DPP-4 inhibitors and pneumonia-related complications [12–15]. A recent real-world study from Hong Kong showed that SGLT2 inhibitors were associated with reduced risk of and mortality due to pneumonia, compared to DPP4 inhibitors [16]. However, the influence of age, sex and the underlying clinical status of the subject on the association between SGLT2 inhibitors and pneumonia is unknown. Whether SLGT2 inhibitors also exerts benefit under extreme infection response, such as sepsis, also remains to be investigated. Therefore, among patients with type 2 diabetes, we comprehensively evaluated (1) the incidence of sepsis, pneumonia, and mortality risk associated with sepsis, pneumonia, and infectious diseases between new users of DPP-4 inhibitors vs. SGLT2 inhibitors, (2) whether these effects differ by age, sex, underlying comorbidities, type of SGLT2 inhibitor used, baseline renal function and glycemic control.

Methods

Data source

This retrospective study utilized data from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic health care system developed by the Hong Kong Hospital Authority. The Hospital Authority is a statutory body managing all public healthcare services that provide over 80% of inpatient services to the population of 7.5 million in Hong Kong. Patients' clinical data including, but not limited to, demographics, diagnoses, procedures, drug prescriptions, laboratory investigations, hospitalization details, outpatient visits, and death were prospectively collected by CDARS. Several high-quality population-based studies were performed based on data retrieved from CDARS [17–19]. The *International Classification of Diseases, Ninth Revision (ICD-9)* was used to code diagnosis in CDARS, with a high degree of coding accuracy as reported previously [17,18]. To protect patient's confidentiality, patient data (name and Hong Kong identification number) was anonymized by assigning a unique reference key in CDARS. The study was approved by the Institutional Review Board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority (ref.: UW 21–270).

Study population and exposure definition

We identified all patients with diabetes aged 18 years old or above initiated on a SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin) or a DPP-4 inhibitor (alogliptin, linagliptin, linagliptin-meformin, saxagliptin, sitagliptin, sitagliptin-metformin, vildagliptin, or vildagliptin-metformin) between January 01, 2015 and December 31, 2019. Index date was defined as the first date of SGLT2 inhibitors and DPP-4 inhibitors usage. New users were defined as not receiving SGLT2 inhibitors or DPP-4 inhibitors in the year prior to the index date. Patients with type 1 diabetes, gestational diabetes, HIV infection, death on the index date, no HbA1c or eGFR in the year prior to the index date or who received both SGLT2 inhibitors and DPP-4 inhibitors on the index date were excluded.

Study covariates

We traced patient records to collect demographics (age and sex), calendar year at cohort entry, diabetes duration, diabetic microvascular complications, risk factors for sepsis or pneumonia (malignancy, previous lower respiratory tract infection, urogenital infection, urinary tract infection, gastrointestinal infection, intra-abdominal infection, biliary tract infection, skin or soft tissue infection, miscellaneous infection, and previous sepsis), other comorbidities (cerebrovascular disease, ischemic heart disease, chronic heart failure, atrial fibrillation, hypertension, hyperlipidemia, chronic renal failure, peripheral artery disease, and liver disease), and lifestyle factors (alcoholism, smoking, and obesity). The ICD-9 codes used to identify these conditions are shown in Table S1. Hypertension was defined as the use of anti-hypertensive medications and/or ICD-9 codes of hypertension. Similarly, hyperlipidemia was defined as the use of lipid-lowering medications and/or ICD-9 codes of hyperlipidemia. Obesity was defined as body mass index $\geq$ 25 kg/m^2 and/or ICD-9 codes of obesity. We also documented medication history (anti-diabetic medications [insulin, metformin, sulfonylureas, GLP-1, and thiazolidinediones] and other medications [angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, statins, and aspirin]), and HbA1c and creatinine level in the year prior to the index date. The eGFR was calculated based on the chronic kidney disease epidemiology collaboration (CKD-EPI) equation. All HbA1c measurements following treatment initiation were also collected and time-weighted mean HbA1c was computed by using the sum of the average of two consecutive measurements multiplied time interval between these measurements divided by the sum of the time interval: Time-weighted mean HbA1c = (((HbA1c1 +HbA1c2)/2)*(time2 -time1) +((HbA1c2 +HbA1c3)/2)*(time3 -time2) +…)/ ((time2 -time1) +(time3 -time2) +…). [20]

Follow-up and study endpoints

Patients were followed up from the day after index date until the occurrence of outcome, death or last date of data collection (January 31, 2021), whichever came first. The two primary endpoints of the study were the occurrence of pneumonia (ICD-9 codes: 481–486) and sepsis (ICD-9 codes: 038, 003.1, 036.2 and 785.59(2)) following treatment initiation. Secondary outcomes included pneumonia-related death, sepsis-related death, infection-related death, urinary tract infections (UTI) (ICD-9 codes: 590, 595, 597, 599.0), urogenital infection (ICD-9 codes: 601, 604, 607.1, 607.81, 615, 616.0, 616.1, 616.4, 616.5, 616.8, 616.9) and diabetic ketoacidosis (DKA) (ICD-9 codes: 250.1), assessed separately. To correct for residual bias from unmeasured confounding, analysis was repeated using deep vein thrombosis/pulmonary embolism as a negative control outcome.

Statistical analysis

A propensity score was developed for each episode of treatment initiation to ensure that covariate balance was achieved between new users of SGLT2 inhibitors and DPP-4 inhibitors. Variables, may potentially be associated with treatment allocation or were prognostically significant, that were mentioned above including age, sex, calendar year at cohort entry, diabetes duration, diabetic microvascular complications, risk factors for sepsis or pneumonia, other comorbidities, lifestyle factors, anti-diabetic medications, other medications, HbA1c, and eGFR at baseline were included into a multivariable

logistic regression model to estimate the probability of receiving treatment. New users of SGLT2 inhibitors were propensity-matched to new users of DPP-4 inhibitors with 1:2 ratio, by using nearest-neighbor matching with a caliper width of 0.2 [21,22]. The differences in the prevalence of covariates were considered insignificant if the standardized mean difference (SMD) was ≤0.10. Continuous data are summarized as mean ± standard deviation for normally distributed variables or median with IQR for non-normally distributed variables. Categorical data are expressed as proportions. The risks of primary outcomes among SGLT2 inhibitors users compared to DPP-4 inhibitors users were compared using Cox proportional hazards model to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Variables such as age, sex, calendar year at cohort entry, diabetes duration, and diabetic microvascular complications used in calculating propensity score were included in multivariable Cox model to minimize the effects of confounders, referred as "doubly robust estimation" [23].

Subgroup analyses

Subgroup analyses were performed as stratified by age, sex, baseline drug use (metformin, insulin, and statin), comorbidities (hypertension and cardiovascular disease), type of SGLT2 inhibitors (dapagliflozin, and empagliflozin), baseline eGFR, and glycemic control (time-weighted mean HbA1c). As aspirin also exerts anti-inflammatory effects and has recently been shown to reduce the risk of pneumonia [24], we further performed a subgroup analysis according to aspirin use at baseline. Interaction between SGLT2 inhibitors/DPP-4 inhibitors and different stratified groups was estimated using multivariable Cox regression. Within all subgroups, propensity score was re-calculated and patients were re-matched based on the newly estimated propensity score with a 1:2 ratio as described in the primary analysis.

Sensitivity analyses

First, we used Fine-Gray model to adjust for competing risk, in which death was deemed as a competing event [25]. Second, we used inverse probability of treatment weighting (IPTW) to create a weighted sample by assigning patients with weights, instead of using propensity score matching to balance baseline covariates [26,27]. Third, we excluded the extreme 5% values of propensity score distribution in each group while matching new users of SGLT2 inhibitors to new users of DPP-4 inhibitors with 1:2 ratio. Fourth, we carried out an as-treated approach which censored patients at medication switch, augmentation and discontinuation (30-day gap). Fifth, we excluded patients with sepsis or pneumonia at baseline from the study cohort; further, we estimated the effect of SGLT2 inhibitors in study cohort which excluded patients with sepsis or pneumonia at baseline, or with an event of sepsis, pneumonia or death within 30 days after index date. Finally, we excluded patients with a known diagnosis of infection; because poor glycemic control is associated with increased risk of infection, we adjusted variables used in calculating propensity score and time-weighted mean HbA1c. To eliminate the effect of COVID-19 on our study results, patients were followed up to 31 December 2019 before the COVID-19 pandemic. All statistical analyses were performed using R (V4.0.4) and a two-side P value less than 0.05 was considered statistically significant.

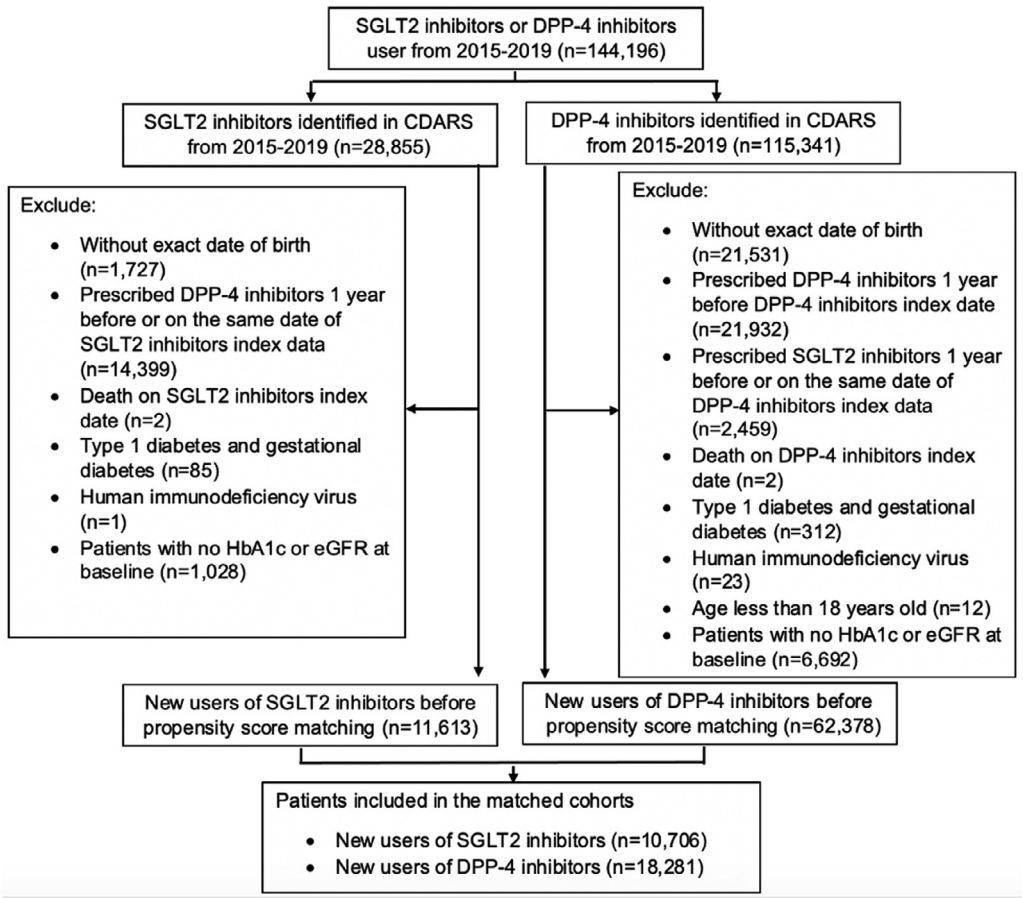

Fig. 1. Flow diagram of SGLT2 inhibitors and DPP-4 inhibitors cohort selection.

Table 1
Distribution of baseline covariates after propensity score matching.

Variables Number of patients	SGLT2 inhibitors *n* = 10,706	DPP-4 inhibitors *n* = 18,281	SMD
Calendar year at cohort entry			
2015	328 (3.06)	561 (3.07)	0.02
2016	1181 (11.03)	2243 (12.27)	0.01
2017	1990 (18.59)	3610 (19.75)	0.02
2018	2702 (25.24)	4577 (25.04)	0.00
2019	4505 (42.08)	7290 (39.88)	0.01
Age (years)	59±11	60±11	0.01
Male	6648 (62.10)	11,074 (60.58)	0.01
Diabetes duration (years)			
<1	971 (9.07)	1820 (9.96)	0.03
1–5	2151 (20.09)	3684 (20.15)	0.00
5–10	2702 (25.24)	4652 (25.45)	0.00
>10	4882 (45.60)	8125 (44.45)	0.02
Diabetic microvascular complications	1680 (15.67)	2749 (15.04)	0.00
Risk factors for sepsis or pneumonia			
Malignancy	680 (6.35)	1205 (6.59)	0.00
Lower respiratory tract infection	580 (5.42)	1004 (5.49)	0.00
Urogenital infection	131 (1.22)	221 (1.21)	0.00
Urinary tract infection	718 (6.71)	1210 (6.62)	0.01
Gastrointestinal infection	474 (4.43)	798 (4.37)	0.00
Intra-abdominal infection	329 (3.07)	531 (2.90)	0.01
Biliary tract infection	207 (1.93)	357 (1.95)	0.00
Skin or soft tissue infection	984 (9.19)	1648 (9.01)	0.00
Miscellaneous infection	1908 (17.82)	3259 (17.83)	0.00
Sepsis	268 (2.50)	467 (2.55)	0.01
Other comorbidities			
Cerebrovascular disease	865 (8.08)	1559 (8.53)	0.01
Ischemic heart disease	2629 (24.56)	3908 (21.38)	0.02
Chronic heart failure	787 (7.35)	1233 (6.74)	0.01
Atrial fibrillation	462 (4.32)	759 (4.15)	0.00
Hypertension	8119 (75.84)	13,677 (74.82)	0.02
Hyperlipidemia	7370 (68.84)	12,340 (67.50)	0.02
Chronic renal failure	108 (1.10)	201 (1.01)	0.00
Peripheral artery disease	165 (1.54)	279 (1.53)	0.00
Liver disease	525 (4.80)	878 (4.90)	0.00
Antidiabetic medications			
Insulin	4425 (41.33)	7095 (38.81)	0.00
Metformin	9737 (90.95)	16,598 (90.79)	0.00
Sulfonylureas	6349 (59.30)	11,581 (63.35)	0.01
GLP-1	121 (1.13)	75 (0.41)	0.03
Thiazolidinediones	1961 (18.32)	2702 (14.78)	0.02
Other medications			
ACEIs	4858 (45.38)	8087 (44.24)	0.01
ARBs	2727 (25.47)	4581 (25.06)	0.00
Beta blockers	4379 (40.90)	7152 (39.12)	0.01
Calcium channel blockers	5665 (52.91)	9628 (52.67)	0.01
Diuretics	1996 (18.64)	3261 (17.84)	0.01
Statins	8258 (77.13)	13,900 (76.04)	0.02
Aspirin	4005 (37.41)	6408 (35.05)	0.01
Lifestyle factors			
Smoking	3710 (34.65)	6045 (33.07)	0.02
Alcoholism	3057 (28.55)	5650 (30.91)	0.03
Obesity	6188 (57.80)	9991 (54.65)	0.02
Laboratory result			
HbA1c (%)	8.30 (7.46–9.40)	8.20 (7.50–9.20)	0.01
eGFR (mg/min/1.73m^2)	86.37 (70.08–97.84)	88.68 (69.41–99.74)	0.02

Variables are presented as n (%), mean±standard deviation, or median (interquartile range).
Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors; SMD, standardized mean difference.

Results

Our study included 11,613 new users of SGLT2 inhibitors and 62,378 new users of DPP-4 inhibitors prior to propensity score matching (Fig. 1). Before matching, compared to new users of DPP-4 inhibitors, new users of SGLT2 inhibitors were younger, more likely to be male, obese, have ischemic heart disease and use insulin, but less often a history of urinary tract infection and chronic renal failure (Table S2). After 1:2 propensity score matching, baseline characteristics were well-balanced (Table 1) between the included 10,706 new users of SGLT2 inhibitors and 18,281 new users of DPP-4 inhibitors. The mean age of the matched cohort was 60 years (SD 11.07) and 61.1% were male. The most commonly prescribed SGLT2 inhibitor and DPP-4 inhibitor were empagliflozin (64.04%) and linagliptin (26.43%), respectively.

Primary analysis

For pneumonia, there were 309 events among new users of SGLT2 inhibitors during a median follow-up of 2.29 years (incidence rate per 1000 person-years (IR) = 11.38), compared with 961 events among DPP-4 inhibitors during a median follow-up of 2.33 years (IR = 20.45). SGLT2 inhibitors users had a 37% lower risk of incident pneumonia (adjusted HR 0.63 [95% CI 0.55–0.72], $p<0.001$) compared to users of DPP-4 inhibitors regardless of the duration of diabetes (Table 2).

For sepsis, SGLT2 inhibitors users had 164 events during a median follow-up of 2.31 years (IR = 6.00), compared to 610 events during a median follow-up of 2.35 years (IR = 12.88) among DPP-4 inhibitors users. SGLT2 inhibitors users had a 48% lower risk of incident sepsis (adjusted HR 0.52 [95% CI 0.44–0.62], $p<0.001$) compared to new users of DPP-4 inhibitors regardless of the duration of diabetes (Table 2).

Table 2
Risk of pneumonia and sepsis in propensity score matched cohort.

	SGLT2 inhibitors (*n* = 10,706)	DPP-4 inhibitors (*n* = 18,281)	P value
Pneumonia			
Events, n (%)	309 (2.89)	961 (5.26)	
Median follow-up (years)	2.29	2.33	
Incidence rate[†]	11.38 (10.15–12.73)	20.45 (19.79–21.79)	
Unadjusted HR	0.55 (0.49–0.63)		**<0.001**
Adjusted HR[‡]	0.63 (0.55–0.72)		**<0.001**
Sepsis			
Events, n (%)	164 (1.53)	610 (3.34)	
Median follow-up (years)	2.31	2.35	
Incidence rate[†]	6.00 (5.12–7.00)	12.88 (11.88–13.94)	
Unadjusted HR	0.46 (0.39–0.55)		**<0.001**
Adjusted HR[‡]	0.52 (0.44–0.62)		**<0.001**

Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers, DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HR, hazard ratio; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.
[‡] Adjusted for calendar year at cohort entry, age, sex, diabetes duration, diabetic microvascular complications, malignancy, previous lower respiratory tract infection, previous urogenital infection, previous urinary tract infection, previous gastrointestinal infection, previous intra-abdominal infection, previous biliary tract infection, previous skin or soft tissue infection, previous miscellaneous infection, sepsis, cerebrovascular disease, ischemic heart disease, chronic heart failure, atrial fibrillation, hypertension, hyperlipidemia, chronic renal failure, peripheral artery disease, liver disease, insulin, metformin, sulfonylureas, GLP-1, thiazolidinediones, ACEIs, ARBs, beta blockers, calcium channel blockers, diuretics, statins, aspirin, smoke, alcoholism, obesity, HbA1c and eGFR.
[†] per 1000 person-years.

For secondary outcome analyses, there were lower number of deaths relating to pneumonia (42 vs. 227), sepsis (8 vs. 40), and infectious diseases (60 vs. 309) among SGLT2 inhibitor users, compared to DPP-4 inhibitor users. 42 events of pneumonia-related death among SGLT2 inhibitors compared with 227 events among DPP-4 inhibitors. Similarly, SGLT2 inhibitors were associated with a lower risk of death related to pneumonia (adjusted HR 0.41 [95%CI 0.29−0.58], $p<0.001$), sepsis (adjusted HR of 0.39 [95%CI 0.18−0.84, $p<0.05$]), and infectious diseases (adjusted HR 0.43 [95%CI 0.32−0.57], $p<0.001$), compared to DPP-4 inhibitors (Table S3). Of note, SGLT2 inhibitors users also had a lower risk of UTI (adjusted HR 0.59 [95% CI 0.51−0.68], $p<0.001$), and similar risk of urogenital infection (adjusted HR 1.18 [95% CI 0.76 −1.83], $p = 0.46$) (Table S4) and DKA (adjusted HR 0.97 [95% CI 0.70 −1.35], $p = 0.86$), compared to DPP-4 inhibitor users (Table S5).

Subgroup analysis

Results of subgroup analysis are shown in Figs. 2 and 3. SGLT2 inhibitors were associated with a lower risk of both pneumonia and sepsis on subgroup analysis stratifying patients by age (≤60 vs >60), sex (female vs male), cardiovascular disease, eGFR (≥60 vs <60 mg/min/1.73m^2), time-weighted mean HbA1c (<7.0% vs ≥7.0%), concomitant use of metformin, insulin, statin, or aspirin and type of SGLT2 inhibitors. Significant interaction term was found between SGLT2/DPP-4 inhibitors and use of glucose-lowering drugs as well as statin medication ($p_{interaction}<0.01$). SGLT2 inhibitors were associated with a 41% lower risk of pneumonia among those with insulin, compared with a 29% lower risk among those without insulin. Similarly, SGLT2 inhibitors conferred lower risk among those without metformin or without statin (**Fig. 2**). Similar result was observed when sepsis was considered as outcome (**Fig. 3**).

Sensitivity analyses

Results of sensitivity analyses (1) adjusting for competing risk, (2) excluding extreme values, (3) IPTW and (4) as-treated analysis were consistent with the primary analysis. When pneumonia was considered as the primary outcome, adjusting for death as a competing risk (adjusted HR 0.65 [95%CI 0.57−0.74]), performing Cox regression after propensity score trimming (adjusted HR 0.64 [95%CI 0.55 −0.74]), and using IPTW to balance baseline covariates (adjusted HR 0.64 [95%CI 0.61−0.68]) did not change the point estimates. The results were consistent even when an as-treated approach was used instead of an intention-to-treat approach (HR 0.50 [95%CI 0.41 −0.61]). Excluding patients with pneumonia at baseline, an event of pneumonia or death within 30 days after the index date, infectious diseases at baseline, adjusted time-weighted mean HbA1c, or further followed patients up to 31 December 2019 likewise demonstrated a lower risk of pneumonia among SGLT2 inhibitors users (Tables S6, S9). Similar results were observed when sepsis was considered as the primary outcome in sensitivity analysis (Table S7, S9).

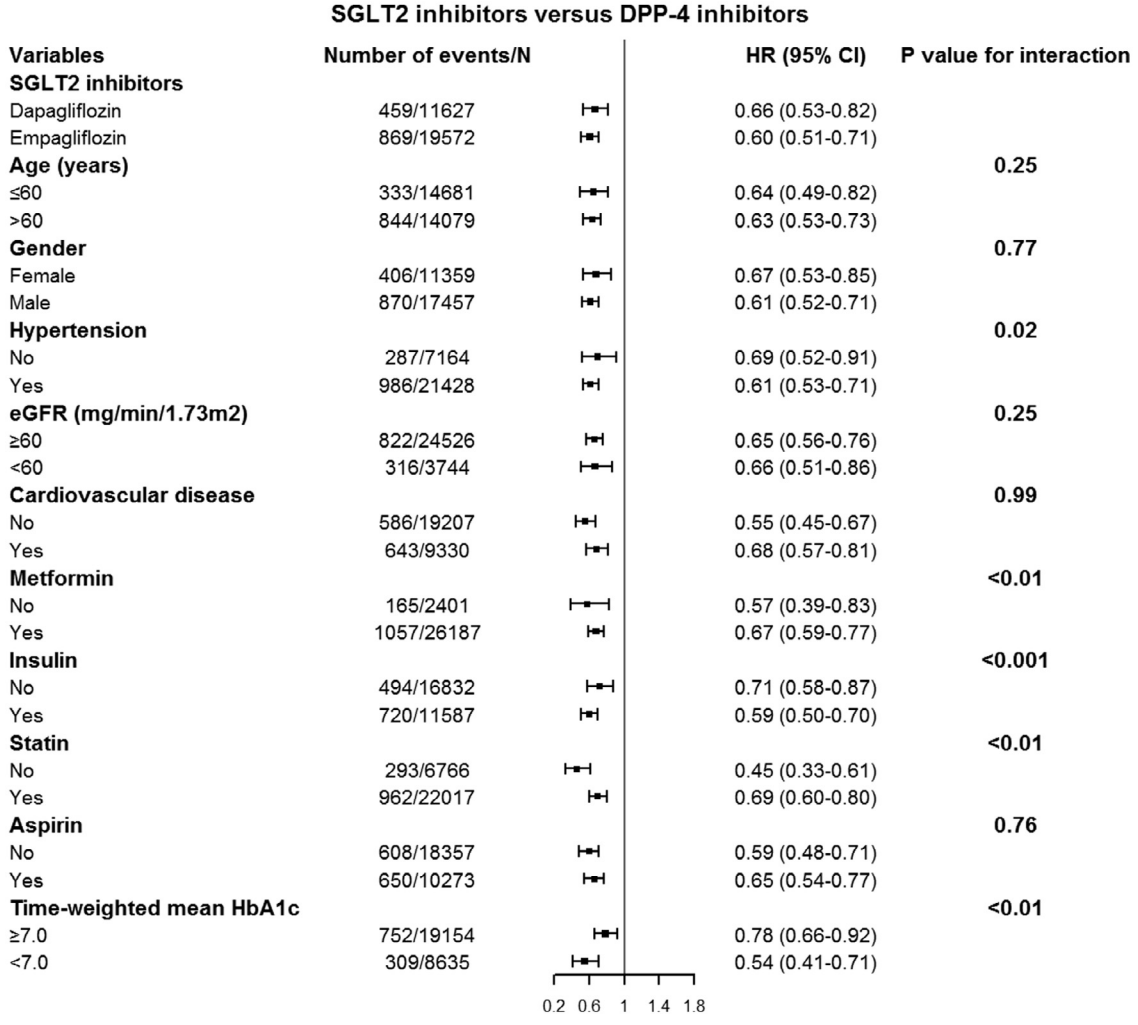

Fig. 2. Stratified analyses for the risk of pneumonia in propensity score matched cohort.

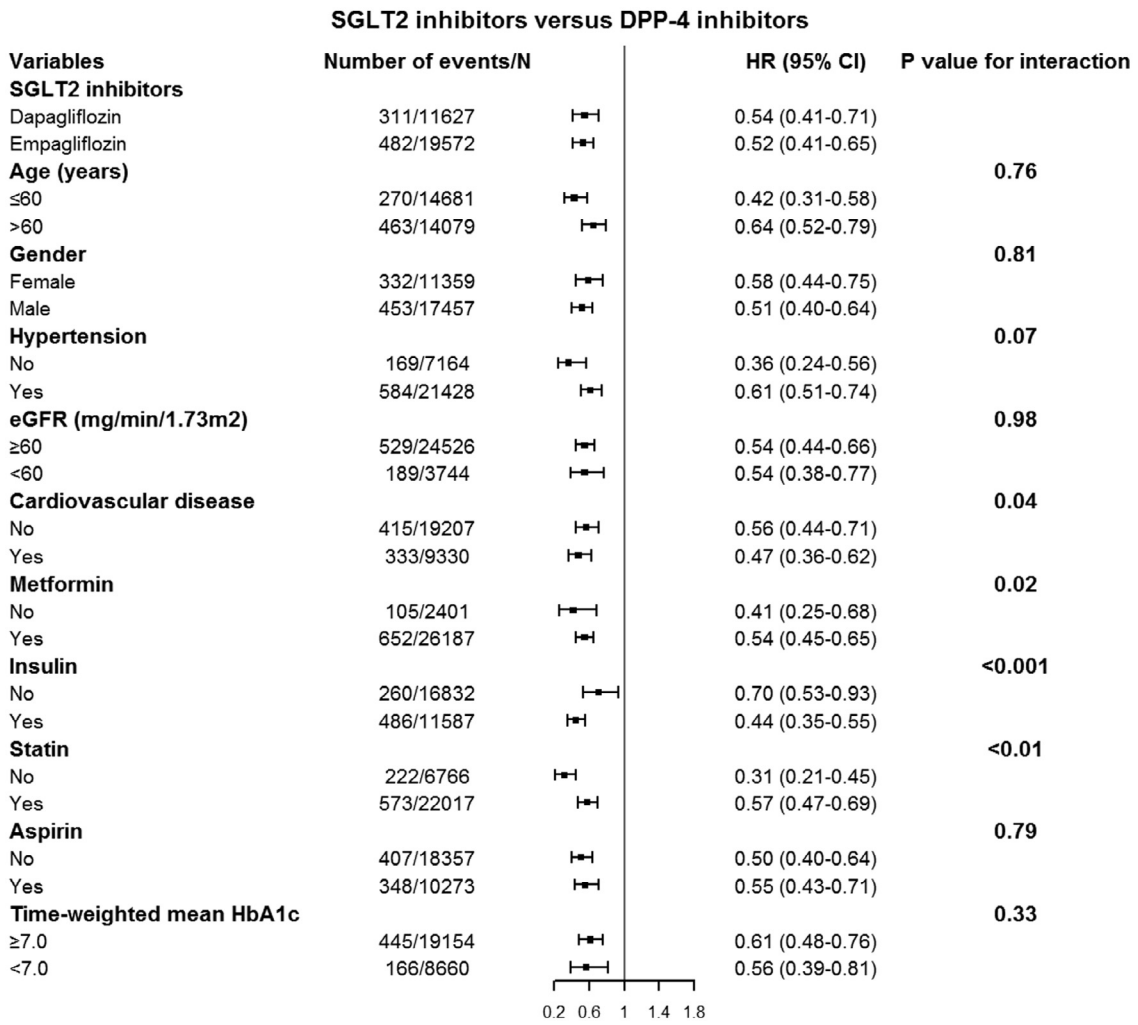

Fig. 3. Stratified analyses for the risk of sepsis in propensity score matched cohort.

We used venous thromboembolism (deep vein thrombosis or pulmonary embolism) as a negative control outcome for further analysis (Table S8). The risk of venous thromboembolism was similar between users of SGLT2 inhibitors and DPP-4 inhibitors with an adjusted HR of 0.91 (95% CI 0.62−1.35, $p = 0.65$) after multivariable adjustment.

Discussion

In this territory-wide cohort study of a well-matched population of over 28,000 patients with type 2 diabetes, our study demonstrated that new users of SGLT2 inhibitors was associated with a significantly lower risk of incident pneumonia/sepsis as well as pneumonia/sepsis/infection related death, compared with new users of DPP-4 inhibitors, irrespective of age, sex, comorbidities, type of SGLT2 inhibitor, baseline kidney function and glycemic control. Our results are in congruence with previous reports that have shown that SGLT2 inhibitors are associated with lower incidence of pneumonia[28] and death related to pneumonia [16]. We have extended these findings by also interrogating sepsis and sepsis-related death as outcomes. Importantly, we also showed that our results, for both pneumonia and sepsis, were also consistent across a range of subgroup analyses (age, sex, comorbidities, type of SGLT2 inhibitor, baseline kidney function and glycemic control), rigorous sensitivity analyses, accounting for competing risk.

Patients with diabetes are susceptible to infectious diseases and face a disproportionally high risk of adverse outcomes when infections occur. In a large cohort of 96,630 subjects with type 2 diabetes and 191,822 matched control without diabetes, type 2 diabetes was associated with a 1.58-fold increased risk of pneumonia and 2.25-fold increased risk of sepsis compared to those without diabetes [5]. In particular, pneumonia is the most common type of infection and the second leading cause of death, a risk that is apparent among elderly patients and anticipated to become more prevalent due to our aging population [3]. Further, diabetic patients with poor glycemic control, as compared with those with optimal glycemic control (HbA1c range 6−7%), were associated with higher risk of sepsis and pneumonia [29]. Thus, strategies that can reduce the risk of pneumonia and sepsis are urgently warranted to optimize outcomes among patients with type 2 diabetes. Alarmingly, the risk of infection is increased – rather than reduced with the use of several classes of hypoglycemic agents, including metformin, sulfonylureas and thiazolidinediones [7,8,30]. While novel agents, including SGLT2 inhibitors and DPP-4 inhibitors, has proved to be effective in glycemic control, their role in infectious complications is unclear [6].

Although SGLT2 inhibitors have been found to exert anti-inflammatory and pleiotropic effects, and thus may have plausible benefits and protection against infection, the association between SGLT2 inhibitors and infection has not been well defined. Previous trials evaluating the cardiorenal protective effect of SGLT2 inhibitors has observed a lower incidence of pneumonia and sepsis, compared with placebo [31,32]. However, these randomized controlled trials were not adequately powered to detect all infection-related adverse

outcomes, particularly when these outcomes were not adjudicated. One population-based cohort study showed that the use of SGLT2 inhibitors (n = 1011) was associated with fewer incident hospitalization for community acquired pneumonia, compared with DPP-4 inhibitors (n = 5552). Nonetheless, the study was limited by a small sample size and did not account for residual confounders (such as renal function) [28]. The DARE-19 trial directly tested whether the SGLT2 inhibitor dapagliflozin may reduce the risk of multi-organ failure and death in patients hospitalized with COVID-19 and who have cardiometabolic risk factors. Although the trial did not reach its primary endpoint, there were numerically fewer adverse clinical events in the dapagliflozin arm, and the trial may have been under-powered given the much lower incidence of the primary endpoint than originally anticipated [10]. Indeed, DARE-19 raised a hypothesis that SGLT2 inhibitors may afford organ protection in other types of acute illness – a hypothesis being tested as part of the TACTIC-E (Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted with COVID-19 – Experimental Drugs and Mechanisms) study [33].

Similarly, studies on DPP-4 inhibitors, another class of frequently prescribed hypoglycemic agent, have shown conflicting results. DPP-4 inhibitors were associated with an increased risk of infections in some studies, especially higher in the risk of upper respiratory tract infection [12] and aspiration pneumonia [13], but, were not associated with increased serious infections in some others [12,15,30]. Notably, there are no sizable head-to-head clinical trials or observational studies comparing the effect of SGLT2 inhibitors with DPP-4 inhibitors on infections to-date, despite both being common second line hypoglycemic agents. Our study, using real-world data from a large Asian population-based cohort, is the first to demonstrate that the initiation of SGLT2 inhibitors was associated with reduced sepsis, and related deaths, compared with DPP-4 inhibitors.

Although the mechanism remains elusive, the pleiotropic properties of SGLT2 inhibitors could possibly explain the lower infection rates. SGLT2 inhibitors reduce adiposity, which potentially attenuates inflammation [34]. Indeed, the levels of inflammatory cytokines, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and matrix metalloproteinase 7, are reported to be lower with SGLT2 inhibitors usage [35–37]. Furthermore, levels of haematocrit and hemoglobin, which may improve oxygen delivery to the tissues, are increased among users of SGLT2 inhibitors – particularly beneficial among patients with sepsis [38,39]. Finally, sepsis and pneumonia are greatly influenced by other organ systems; those with chronic kidney disease [40] and heart failure [41] are independently associated with increased infection risk and infection-related death in patients with diabetes. Therefore, the cardio-renoprotection associated with SGLT2 inhibitors might indirectly reduce the risk of pneumonia and sepsis as well. Further studies are warranted to understand the mechanisms associated with SGLT2 inhibitors and the reduced risk of infections.

Clinical implications

In the current guidelines [42], metformin is recommended as the first-line oral hypoglycemic agent. Yet, metformin was associated with an increased risk of infection [7]. Among patients with suboptimal glycemic control, SGLT2 inhibitors, DPP-4 inhibitors, and thiazolidinediones are recommended, but thiazolidinediones similarly predispose patients to a higher risk of infection and related death [8]. The current study provides novel real-world evidence showing a lower risk of infection with SGLT2 inhibitors, as compared to DPP-4 inhibitors. Although clinical caution of diabetic ketoacidosis has been advised among patients with severe illness, the safety profile of SGLT2 inhibitors has been well-acknowledged. Importantly, the lower risk of incident pneumonia and sepsis by SGLT2 inhibitors was consistent in high-risk subgroups, including those with age above 60, cardiovascular disease, suboptimal diabetes control (time-weighted mean HbA1c $\geq$ 7.0%), and higher risk of infection complications. Using real-world data, the current study suggests that SGLT2 inhibitors are associated with lower infection complications among individuals with diabetes, compared to DPP-4 inhibitors. Further investigations through randomized studies are necessary to confirm these findings.

Strengths and weaknesses

Our study has several limitations. As it is an observational study, the results are prone to residual confounding. Nevertheless, we accounted for a broad range of baseline comorbidities and clinical correlates with potential prognostic implications in our analysis. To further minimize the risk of residual confounding, we have shown that the risk of negative control outcome (i.e. venous thromboembolism) was not associated with the use of SGLT2 inhibitors.

One of the important strengths of this study is that we made use of a territory-wide electronic health care database (CDARS) with thorough records of patients' routine clinical care. Diagnoses, hospitalization, laboratory tests and drug prescriptions of each patient could be retrieved, which allowed the collection of the relevant information required to preclude common biases in conventional observational studies such as selection and recall biases. Second, the use of DPP-4 inhibitors as an active comparator enabled an appropriate comparison between the treatment and control arms at similar stages of glucose management. Third, the robustness of the results demonstrated in the current study is enhanced with propensity score analytics, doubly robust estimation, competing risk regression, and a wide range of rigorous sensitivity analyses. Fourth, only new users of SGLT2 inhibitors/DPP-4 inhibitors were included, minimizing the effect on outcome by baseline drug use.

Conclusion

In this large population-based cohort of diabetes, we demonstrated that users of SGLT2 inhibitors were associated with a substantially lower risk of sepsis, pneumonia, and the sepsis/pneumonia/infection related death, compared with users of DPP-4 inhibitors. These results hold important clinical implications in reducing the attendant complications of diabetes. Mechanistic insights into lower infection complications with SGLT2 inhibitors merit further investigations.

Availability of data and materials

Data are available upon reasonable request by contacting Dr Yiu Kai-Hang.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Mei-Zhen Wu: Formal analysis, Data curation, Writing – review & editing. **Chanchal Chandramouli:** Data curation, Writing – review & editing. **Pui-Fai Wong:** Data curation, Writing – review & editing. **Yap-Hang Chan:** Data curation, Writing – review & editing. **Hang-**

Long Li: Data curation, Writing – review & editing. **Si-Yeung Yu:** Data curation, Writing – review & editing. **Yi-Kei Tse:** Data curation, Writing – review & editing. **Qing-Wen Ren:** Data curation, Writing – review & editing. **Shuk-Yin Yu:** Data curation, Writing – review & editing. **Hung-Fat Tse:** Data curation, Writing – review & editing. **Carolyn S.P. Lam:** Supervision, Data curation, Formal analysis. **Kai-Hang Yiu:** Supervision, Data curation, Formal analysis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2022.101367.

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