Association between SGLT2 Inhibitors vs DPP-4 Inhibitors and Risk of Pneumonia Among Patients with Type 2 Diabetes

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Short title: SGLT2 inhibitors and pneumonia

Keywords: diabetes, SGLT2 inhibitor, DPP4 inhibitor, pneumonia, retrospective cohort study

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Funding support: N/A

Disclosure: The authors have no conflicts of interest to declare.

Abstract

Context: Patients with diabetes are at a higher risk of pneumonia and pneumonia mortality. Sodium-glucose co-transporter 2 inhibitors (SGLT2is), the latest class of glucose-lowering agents, were shown to reduce the risk of pneumonia in clinical trials. However, the real-world effectiveness of SGLT2is on the risk of pneumonia is largely unknown.

Objective: To investigate the associations between SGLT2is use and the risk of pneumonia and pneumonia mortality compared to dipeptidyl peptidase-4 inhibitors (DPP4is) using an electronic medical database in Hong Kong.

Design: A retrospective cohort study. The "prevalent new-user" design was adopted to account for the previous exposure to the study drugs being compared. Propensity score (PS) matching (1:4) was used to balance the baseline characteristics of the two groups.

Setting and participants: Electronic health data of type 2 diabetes patients using SGLT2is and DPP4is between 2015 and 2018 was collected from the Clinical Data Analysis and Reporting System (CDARS).

Main Outcome Measures: Pneumonia incidence and mortality.

Results: The PS-matched cohort consisted of 6,664 users of SGLT2is and 26,656 users of DPP4is, with a mean follow-up of 3.8 years. Poisson regression showed that SGLT2is use was associated with lower risk of pneumonia compared to DPP4is with an absolute rate difference of 4.05 per 1000 person-years (95% CI: 2.61-5.51). The corresponding IRR was 0.71 (95% CI: 0.62-0.81). Similar reduction in risk of pneumonia death was observed (HR: 0.57; 95% CI: 0.42-0.77).

Conclusion: Compared to DPP4is, SGLT2is use was associated with a reduced risk of pneumonia and pneumonia mortality in a real-world setting.

Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT2is) belong to the latest class of glucose-lowering agents for type 2 diabetes (T2D). They lower blood glucose by promoting renal glucose excretion (1). SGLT2is have been studied extensively in recent years for their pleiotropic properties in addition to glucose-lowering. Large-scale clinical trials and cohort studies both reported reduced risks of cardiovascular and renal events with SGLT2is uses among diabetic patients (2-5).

Patients with diabetes are at a higher risk of pneumonia (6) and pneumonia mortality (7). Population-based studies reported associations between metformin use and reduced risks of pneumonia hospitalization (8, 9). However, similar effects were not reported for other classes of glucose-lowering drugs, including sulfonylurea (10), thiazolidinediones (10), and dipeptidyl peptidase-4 inhibitors (DPP4is) (11), while the association of SGLT2is with pneumonia remains largely unclear. A recent meta-analysis of 8 placebo-controlled clinical trials reported a reduced risk of pneumonia among participants treated with SGLT2is (12). However, clinical trials often include highly selected patients and, hence, compromise the generalizability to the real-world population. Therefore, clinical trials tend to provide evidence on drug efficacy instead of drug effectiveness. Studies using real-world populations often provide a higher degree of generalizability than clinical trials, and the evidence generated from such population-based studies is considered complementary to clinical trials.

The present study aimed to investigate the associations between SGLT2is use and the risk of pneumonia and pneumonia mortality using a territory-wide representative electronic medical database in Hong Kong.

Materials and Methods

Data Source

The Clinical Data Analysis and Reporting System (CDARS) is an electronic medical database managed by the Hospital Authority (HA) of Hong Kong. The HA is a statutory body providing territory-wide public healthcare services. It manages all 42 public hospitals and 120 public outpatient clinics (general and specialist) in Hong Kong. It was estimated that more than 90% of the known diabetes patients are under the HA's care (13). According to the 2016 Hong Kong census, about 92% of the population was Han Chinese (14). Therefore, the CDARS includes a highly ethnically homogeneous population. The CDARS stores records from outpatient, emergency, and inpatient visits, including diagnosis, dispensing, clinical procedure and operation, laboratory test and measurement, and death registry records. The ethical approval of this study has been granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref: UW 19-154).

Study Cohort

The study cohort consisted of all diabetes patients with prescription records of SGLT2is or DPP4is between 2015 (the year SGLT2is was first prescribed by the HA) and 2018. Patients who started SGLT2is, including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, were classified as "exposed". Patients who started DPP4is, including sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, and omarigliptin, but had not been prescribed with SGLT2is before, were classified as "control". DPP4is were chosen as a comparator because both SGLT2is and DPP4is were commonly used as second- or third-line anti-diabetic agents in Hong Kong, thus avoiding confounding by indication. In addition, a recent meta-analysis of clinical trials showed no association between DPP4is and the risk of pneumonia (11). Exclusion

criteria were: 1) patients with the use of SGLT2is before index date for the DPP4i control group; 2) patients with DPP4i and SGLT2i initiated on the same date; 3) patients of type 1 diabetes (T1D); 4) patients with prescription records of index drugs for only 1 day; 5) patients who received dialysis or renal transplant within 1 year before index date; and 6) patients with no laboratory measurements of HbA1c or eGFR within 1 year before index date (Figure 1). T1D was defined according to a previous validation study (15): 1) the number of T1D diagnosis records to the number of T2D diagnosis records ratio ≥4 (15); 2) prescribed with insulin and no other glucose-lowering agents within the first year of diabetes diagnosis (15); or 3) age at diagnosis <30. The cohort was followed until the occurrence of study outcomes (pneumonia incidence or pneumonia death), the end of study (December 31, 2020), or death, whichever came first.

"Prevalent New-User" Design

Since DPP4is were an older class of glucose-lowering agents and have been widely used before SGLT2is became available in Hong Kong, many patients who started SGLT2is were ongoing or previous DPP4is users. To account for the prior exposure to an active comparator, the present study adopted the "prevalent new-user" design (16). In brief, the design matched study participants on the length of previous exposure to the comparator being studied (i.e. DPP4is in the present study) in a time-dependent manner (Supplemental Figure 1) (17). In the present study, index dates for the SGLT2i group were defined as the date SGLT2is first-ever prescribed, and index dates for the DPP4i group were defined as each prescription start date of DPP4is. Therefore, each patient in the DPP4i group would have multiple index dates according to the number of DPP4i prescription start dates the patient had. Each patient in the SGLT2i group was matched with the patients in the DPP4i group according to the duration of previous

exposure to DPP4is (±30 days) and the calendar period (±60 days) at respective index dates. For the DPP4i control group, lengths of previous exposure to DPP4is and baseline covariates were assessed at each prescription start date of DPP4is. Each patient in the DPP4i group was matched with multiple patients in the SGLT2i group in a time-dependent manner, using individual prescription start dates as index dates. For patients initiating SGLT2is without previous use of DPP4is, they were matched with patients first initiating DPP4is (i.e., 0 day of previous exposure to DPP4is). This "prevalent new-user" design allowed a valid comparison between patients who switched to SGLT2is from DPP4is and patients who stayed on DPP4is.

Outcome

Outcomes of interest were: 1) the first pneumonia incidence following index day defined by ICD-9 480.x to 487.0 coded in the CDARS diagnosis database (18), and 2) pneumonia mortality defined by ICD-10 J12 to J18 coded in the CDARS death registry (18). Pneumonia outcomes included both community-acquired and hospital-acquired pneumonia. Validation of the ICD-9 codes used in defining pneumonia incidence was performed by manual inspection of the radiological records and the clinical notes written by the attending physicians. 100 patients coded with ICD-9 480.x to 487.0 between 2019 and 2020 were randomly selected. 97% of the selected patients had either evidence from chest X-ray or at least one of the following clinical signs and symptoms: fever (>38°C) with no other recognized cause, shivers, leucopenia (leukocyte count >10 000 cells/μL or <4000 cells/μL), cough, dyspnea, tachypnea, and pleuritic chest pain, resulting in a positive predictive value of 97%. For more stringent criteria for pneumonia diagnosis, 87% of the selected patients had evidence from chest X-ray plus at least one of the above clinical signs and symptoms, resulting in a positive predictive value of 87%.

Propensity Score Matching

The propensity score (PS) matching (19) was adopted to balance the patients' characteristics between the exposed and control groups. A sum of 67 covariates, including history of pneumonia, were chosen to reflect the overall health status of the study participants (Supplemental Table 1) (17). To account for the difference between patients who initiated SGLT2is/DPP4is as their first anti-diabetic medication and those who did not, the medication history of individual classes of anti-diabetic drug use and the total number of different anti-diabetic drug classes used were also included in the PS model. PS was calculated using conditional logistic regression stratified by the matched pairs resulted from the "prevalent new-user" design (Supplemental Figure 1) (17). To reduce the risk of residual confounding (20), patients in the SGLT2i exposed group with PS <5th percentile and patients in the DPP4i control group with PS >95th percentile were trimmed. The SGLT2i group was matched 1:4 with the DPP4i group in chronological order of SGLT2i index dates. The PS matching was done within each matched pair using sequential greedy matching (21) with a caliper of 0.2 standard deviations (SD) without replacement. Patients once selected as DPP4i control in one matched pair were no longer available to be matched in subsequent matched pairs. The balance of covariates in the PS matched cohort was assessed by standardized mean difference (SMD). Covariates with SMD >0.1 were considered unbalanced and they were adjusted in the subsequent regression analyses (18).

Additional covariates for regression analyses

To account for the co-medication with other glucose-lowering agents, the concurrent use of metformin, sulfonylureas, meglitinides, glucagon-like peptide-1 agonists, acarbose,

thiazolidinediones, and insulin at baseline, and the total number of different concurrent glucose-lowering agents at baseline were included as patient characteristics. For multiple prescription records, any two records with no more than 30 days apart were considered an ongoing prescription. Concurrent use was defined as any ongoing prescription which started any time before and ended no earlier than 30 days after index date. A 30-day window was used to account for variations in doctor's appointments.

Statistical analyses

Patient characteristics were presented as mean (SD) for continuous variables and as frequency (%) for categorical variables. Covariates with SMD>0.1 after PS matching were adjusted in all regression analyses. Incidence rates and incidence rate ratios (IRR) were estimated using Poisson regression. Absolute rate difference (ARD) was defined as (1- IRR) * incidence rate of the control group, where the IRR was estimated by the regression coefficient, and the incidence rate of the control group was estimated by the regression intercept. The bootstrap percentile interval was used to estimate the 95% confidence intervals (CIs) for incidence rates and ARDs. For pneumonia mortality, hazard ratio (HR) was estimated using competing risk regression with non-pneumonia deaths counted as competing events. The analyses were done with an intention-to-treat principle, which patients who discontinued the use of index drugs were not censored. Interactions with gender were tested using interaction terms. A statistically significant level was defined as a two-sided p-value ≤ 0.05.

Sensitivity analyses

Three sensitivity analyses were conducted to assess the robustness of the results. First, the cohort was censored upon discontinuation of index drug, in addition to event occurrence, study

end, and death. Discontinuation was defined as more than 90 days without a new prescription after the end date of the last prescription. Second, all patients with pneumonia diagnosis 1 year before index dates were excluded. Third, a narrower ICD-9 definition for bacterial pneumonia (481, 482, 483, 485, and 486) (22) was used.

All statistical analyses were performed using R version 4.1.0.

Results

Between 2015 and 2018, there was a total of 9,895 patients first started SGLT2is and 93,481 patients first started or continued with DPP4is in the CDARS database. Each patient in the SGLT2i group was matched with patients in the DPP4i group according to the duration of previous exposure to DPP4is (±30 days) and the calendar period (±60 days) at respective index dates. After screening for exclusion criteria, a matched cohort of 8,811 SGLT2i patients and 85,931 paired DPP4i patients (equivalent to 806,466 paired DPP4i prescription dates) remained available for PS matching (Figure 1). The final 1:4 PS-matched cohort consisted of 6,664 patients in the SGLT2i group and 26,656 patients in the DPP4i group. All covariates showed an SMD of below 0.1 after PS matching, except for the concurrent use of sulfonylureas, thiazolidinediones, and insulin (Supplemental Table 2) (17). Among the SGLT2i group, 1.1% were canagliflozin, 70.2% were dapagliflozin, 28.7% were empagliflozin, and none were ertugliflozin.

Association between SGLT2is and pneumonia risk

The cohort was followed for a median of 3.8 (interquartile range (IQR): 1.5) years for the SGLT2i group and 3.7 (IQR: 1.6) years for the DPP4i group. Further adjustment for the concurrent use of sulfonylureas, thiazolidinediones, and insulin was made in the regression analyses. The use of SGLT2is was associated with a significantly reduced risk of pneumonia compared to the use of DPP4is (ARD: 4.05 per 1000 person-years, 95% CI: 2.61-5.51; IRR: 0.71, 95% CI: 0.62-0.81; p<0.001; Table 1). Additional analysis using Cox proportional hazards regression resulted in a similar estimate (data not shown). There was no significant interaction with gender (p=0.840). The association remained significant when patients were censored at discontinuation of index drug (IRR: 0.59, 95% CI: 0.49-0.72, p<0.001), when patients with pneumonia history were excluded from the cohort (IRR: 0.74, 95% CI: 0.65-0.85, p<0.001), and when a narrower ICD-9 definition for bacterial pneumonia was used (IRR: 0.72, 95% CI: 0.63-0.81; p<0.001) (Table 2).

Association between SGLT2is and pneumonia death

The cohort was followed for a median of 3.8 (IQR: 1.5) years for both the SGLT2i group and the DPP4i group. Competing risk regression, adjusted for the concurrent use of sulfonylureas, thiazolidinediones, and insulin, showed that the use of SGLT2is was associated with a significantly reduced risk of pneumonia death compared to the use of DPP4is (HR: 0.57, 95% CI: 0.42-0.77, p<0.001; Table 3). There was no significant interaction with gender (p=0.540).

Discussions

The present study was a territory-wide retrospective cohort study investigating the associations of the use of SGLT2is with pneumonia risk and mortality using electronic health records in Hong Kong. The PS-matched cohort showed that SGLT2is use was associated with a

significantly reduced risk of pneumonia and pneumonia mortality compared to DPP4is use. The association remained significant in sensitivity analyses which censored patients at discontinuation of index drug, excluded patients with pneumonia history, and used a narrower ICD-9 definition for bacterial pneumonia.

The results of the present study agreed with a recent study by Brunetti *et al*. (23) reporting that the use of SGLT2is was associated with a reduced risk of pneumonia. Compared to that study, the strength of the present study was the use of the "prevalent new-user design" to account for previous exposure to DPP4is before initiation of SGLT2is, which was very common due to DPP4is being an older class of glucose-lowering drugs. This design provided better control of the switch from DPP4is to SGLT2is by matching the cohort on the length of previous exposure to DPP4is, hence reducing bias. The association between SGLT2is use and pneumonia risk observed in the present study (IRR: 0.71, 95% CI: 0.62-0.81) was more modest and closer to that reported in a recent meta-analysis of clinical trials (12) (risk ratio: 0.85; 95% CI: 0.76–0.95), suggesting that the stronger association reported in the previous study (23) (HR: 0.48; 95% CI: 0.28-0.82) could be over-estimated. In addition, the present study showed that SGLT2is use was associated with a reduced risk of pneumonia mortality.

Potential mechanisms

Although the study by Brunetti *et al*. (23) hypothesized that SGLT2is would increase the airway glucose concentration via inhibition of SGLT1 receptors in the lungs and subsequently lead to an increased risk of pneumonia, their study results showed otherwise. Patients with hyperglycemia were shown to have elevated glucose concentrations in the nasal cavity and the lower airway (24). This increase in airway glucose concentration was shown to promote

bacterial proliferation in sputum samples of patients with COPD (25, 26). The speculation was that increased airway glucose concentration could be a factor mediating the higher risk of respiratory infection observed in diabetic patients. Therefore, by improving glucose homeostasis, glucose-lowering agents could potentially reduce the risk of respiratory infection. An animal study showed that diabetic mice treated with dapagliflozin had reduced airway glucose concentration and reduced bacterial count after being infected with *P. aeruginosa* (27). However, SGLT1 glucose transporters, not SGLT2 glucose transporters, are primarily expressed in epithelial cells. The detailed mechanism on how SGLT2is could reduce airway glucose concentration requires further study.

Strengths and limitations

The present study had several strengths. First, the CDARS clinical database is a comprehensive health database with detailed records of diagnosis, dispensing, clinical procedures, laboratory tests, and death registries. It has a high territory-wide coverage of more than 90% of the known diabetes patients in Hong Kong. The CDARS provided an appropriate representation of the population. Second, by matching the length of previous exposure to DPP4is in a "prevalent new-user" design, this study allowed a fair comparison between the use of SGLT2is and DPP4is. Using DPP4is as a comparator also avoided time-lagging bias (28) and allowed a clinically relevant comparison since both SGLT2is and DPP4is are used as second- or third-line anti-diabetic treatment. There was also no significant association between DPP4is and pneumonia risk as reported in a recent meta-analysis of clinical trials (11). Third, a PS calculated from 67 covariates, which covered a wide range of clinically relevant conditions, would greatly reduce potential confounding.

Nevertheless, there were limitations. First, the CDARS database does not contain lifestyle data. However, it should be able to capture any clinically relevant effects via clinical diagnoses and conditions. Second, patients' compliance to prescriptions could not be ascertained through the CDARS. Potential bias could arise when there was differential compliance between the two groups. Third, there was a potential by-indication bias. The need to add or switch to SGLT2is from DPP4is could be due to poor glycemic control and/or the presence of comorbidities. They were often associated with worse clinical outcomes. Such bias would result in an increased risk of pneumonia and pneumonia mortality among SGLT2i users. However, this would not affect the overall conclusion of the present study since the bias, if existed, would only under-estimate the beneficial effects of SGLT2is, rather than over-estimate them. Forth, the algorithm used to exclude T1D patients might not be able to distinguish all T1D patients from T2D patients. However, the bias should be negligible since T1D contributes only to a relatively small proportion of the diabetes population, and the exclusion criteria of diagnosis age<30 should be able to screen out the majority of T1D patients.

Clinical implications

SGLT2is have gained a lot of attention in recent years for their beneficial effects on CVD and renal outcomes in addition to the glucose-lowering effect. Multiple clinical trials and population-based studies on this topic have been published. Conversely, SGLT2is' effects on infections were less studied. Diabetes managements usually put primary focus on microvascular and macrovascular outcomes. It has been shown that diabetes patients are at a higher risk of pneumonia hospitalizations. They also have a longer stay (29), and a higher risk of pneumonia mortality (7). The present study showed that the use of SGLT2is was associated with a reduced risk of both pneumonia incidence and mortality among T2D patients. With a

deeper understanding of the role of SGLT2is in respiratory infections, a better prognosis of diabetic patients could be achieved.

In conclusion, the use of SGLT2is was associated with a reduced risk of pneumonia and pneumonia mortality in T2D patients.

Acknowledgments

We express our gratitude to Mr. Ricky Wong for his work and effort in data collection.

Data Availability

Restrictions apply to the availability of all data generated or analyzed during this study to preserve patient confidentiality and because they were used under license by the Hospital Authority (HA) of Hong Kong.

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414 Table 1. Association between SGLT2 inhibitors and risk of pneumonia.

Group	No. of subjects	No. of events	Total person-year	Median follow-up in year (IQR)	Incidence rate per 1000 person-years[a] (95% CI)	Absolute rate difference per 1000 person-years[a] (95% CI)	Incidence rate ratio (95% CI)	P
DPP4i	26656	1464	95022	3.7 (1.6)	13.94 (12.49-15.54)	4.05 (2.61-5.51)	1	---
SGLT2i	6664	277	24162	3.8 (1.5)	9.89 (8.45-11.52)		0.71 (0.62-0.81)	<0.001

415 [a] Estimated by (1- incidence rate ratio) * incidence rate of the control group.

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417 Table 2. Sensitivity analyses for the association between SGLT2 inhibitors and risk of

418 pneumonia.

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Group	No. of subjects	No. of events	Total person-year	Median follow-up in year (IQR)	Incidence rate per 1000 person-years[a] (95% CI)	Absolute rate difference per 1000 person-years[a] (95% CI)	Incidence rate ratio (95% CI)	P
Patients censored at discontinuation of index drugs								
DPP4i	26656	1039	73394	2.8 (2.3)	14.03 (12.28-15.96)	5.72 (3.86-7.67)	1	---
SGLT2i	6664	114	12964	1.4 (2.4)	8.31 (6.62-10.25)		0.59 (0.49-0.72)	<0.001
Patients with pneumonia history within 1 year before index date excluded								
DPP4i	26384	1396	94090	3.7 (1.6)	20.43 (17.98-23.11)	5.25 (3.05-7.43)	1	---
SGLT2i	6596	264	23949	3.8 (1.5)	15.18 (12.80-17.90)		0.74 (0.65-0.85)	<0.001
Bacterial pneumonia (ICD-9 481, 482, 483, 485, and 486)								
DPP4i	26656	1445	95057	3.7 (1.6)	13.81 (12.37-15.41)	3.92 (2.49-5.40)	1	---
SGLT2i	6664	276	24165	3.8 (1.5)	9.89 (8.46-11.53)		0.72 (0.63-0.81)	<0.001

420 [a] Estimated by (1- incidence rate ratio) * incidence rate of the control group.

421

Table 3. Competing risk regression for the association between SGLT2 inhibitors and pneumonia mortality.

Group	No. of subjects	No. of pneumonia death	No. of non-pneumonia death	Total person-year	Median follow-up in year (IQR)	Hazard ratio (95% CI)	P
DPP4i	26656	320	1235	96986	3.8 (1.5)	1	---
SGLT2i	6664	48	240	24547	3.8 (1.5)	0.57 (0.42-0.77)	<0.001

426 Figure legends:

427 Figure 1. Flow diagram.