SGLT-2 Inhibitors and the Risk of Hospitalization for Community-Acquired Pneumonia: A Population-based Cohort Study

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Short title: SGLT-2 inhibitors and Community-Acquired Pneumonia

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KEY POINTS

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) have been associated with increased risks of genitourinary tract infections and may be associated with an increased risk of community-acquired pneumonia through a similar mechanism.

Current use of SGLT-2i was associated with a decreased risk of hospitalization for community-acquired pneumonia (HCAP) when compared to use of dipeptidyl-peptidase 4 inhibitors, but not when compared to use of glucagon-like peptide-1 receptor agonists.

This study provides reassuring evidence regarding the use of SGLT-2i and the risk of HCAP among patients with type 2 diabetes.

ABSTRACT

Purpose: Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) have been associated with an increased risk of genitourinary tract infections. Through similar biological mechanisms, they may also increase the risk of community-acquired pneumonia. Our objective was to compare the rate of hospitalization for community-acquired pneumonia (HCAP) with SGLT-2i compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) among patients with type 2 diabetes.

Methods: We used the United Kingdom's Clinical Practice Research Datalink Gold, linked to hospitalization data, to construct a cohort of patients with type 2 diabetes. Using a time-dependent Cox proportional hazards model, we estimated the adjusted hazard ratio (HR) for HCAP with current use of SGLT-2i versus DPP-4i.

Results: Among 29,896 patients, 705 HCAPs occurred over a mean follow-up of 1.7 years (standard deviation: 1.2). Incidence rates for SGLT-2i and DPP-4i users were 6.2 (95% confidence interval [CI]: 3.7, 10.2) and 17.8 (95% CI: 15.3, 20.7) per 1000 person-years, respectively. Current use of SGLT-2i was associated with a decreased risk of HCAP compared to current use of DPP-4i (adjusted HR: 0.48, 95% CI: 0.28, 0.82). However, a comparison of SGLT-2i versus glucagon-like peptide-1 receptor agonists (GLP-1 RA) found no difference in risk of HCAP (adjusted HR: 0.94, 95% CI: 0.44, 1.89).

Conclusions: SGLT-2i are associated with a decreased rate of HCAP compared to DPP-4i, but not when compared to GLP-1 RA, among patients with type 2 diabetes.

1. INTRODUCTION

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are a novel class of glucose-lowering drugs used for the treatment of type 2 diabetes[1]. In addition to their glucose lowering effects, SGLT-2i also improve cardiovascular outcomes[2-4], which has made them increasingly prescribed in recent years[5]. However, the United States Food and Drug Administration has issued a safety warning for an increased risk of genital and urinary tract infections[6], possibly due to increased bacterial proliferation resulting from glycosuria.

Some SGLT-2i also have affinities for SGLT-1 receptors found in the lungs and intestines[7]. Inhibition of SGLT-1 receptors in rat alveolar cells leads to increased airway surface liquid glucose concentration, which translates directly to increased proliferation of pathogenic bacteria[8], which may lead to lung infections such as community-acquired pneumonia (CAP). This mechanism may be analogous to the increased risk of genital and urinary tract infections in patients taking SGLT-2i; increased glucose levels in the mucous and respiratory tract have been shown to increase bacterial proliferation[9-11]. With their varying affinities for SGLT-1[12], different SGLT-2i may have different safety profiles with respect to pneumonia. SGLT-2i have been shown to increase the risk of other infections[13], but uncertainty remains for the risk of CAP. Results from randomized controlled trials (RCTs) do not show an increased risk of CAP with SGLT-2i[2], but to our knowledge, the association between SGLT-2i and the risk of CAP has not been examined previously with real-world data. The objective of our study was to compare the rate of hospitalization for CAP (HCAP) between patients with type 2 diabetes using SGLT-2i and those using dipeptidyl-peptidase 4 inhibitors (DPP-4i).

2. METHODS

Data source

This study was conducted using data from the Clinical Practice Research Datalink (CPRD) Gold[14], which contains the primary care records of >15 million patients in the United Kingdom (UK). It contains information on prescriptions, diagnoses, laboratory data, and lifestyle characteristics not typically found in administrative databases such as body mass index (BMI) and smoking status[15]. CPRD Gold data were linked to data from the Hospital Episodes Statistics (HES)[16], which contains the full hospitalization records of patients. Linkage is available for 76% of English practices (58% of all CPRD Gold practices). In the CPRD Gold, diagnoses are recorded using Read codes, and prescriptions are recorded using product codes and classified according to the British National Formulary. Diagnoses in HES are recorded using the International Classification for Disease 10th edition (ICD-10). Data from the CPRD Gold has been shown to be of high quality, and linkage between databases has been validated[17].

The Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital have approved the protocol of this study (protocol number: 18-232ARA), which was made available to journal reviewers.

Study population

Base cohort

We assembled a base cohort of all patients receiving a first-ever prescription for a non-insulin antidiabetic medication, including SGLT-2i, DPP-4i, metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 receptor agonists (GLP-1 RA), alpha-glucosidase inhibitors, meglitinides, guar gum (or combinations of these drugs) between April 1, 1998 and July 31, 2017. Base cohort entry was defined by the date of this first prescription. We subsequently

excluded patients meeting any of the following criteria at base cohort entry: 1) age ≤18 years; 2) a database history of <365 days; 3) a previous prescription for insulin; 4) a previous diagnosis of polycystic ovary syndrome (another indication for metformin); or 5) a diagnosis of gestational diabetes in the prior year.

Study cohort

From the base cohort, we identified patients who initiated a new antidiabetic drug class between 2013 (the year SGLT-2i were approved in the UK) and 2017. These patients included those who initiated antidiabetic drugs and those switching to or adding on an antidiabetic drug for which they had no previous recorded prescriptions. We defined study cohort entry with the date of this new prescription. From the study cohort, we excluded patients with a diagnosis of pneumonia in the 30 days prior to study cohort entry and those with a diagnosis of cancer or human immunodeficiency virus at any time prior to study cohort entry. We also excluded patients who were hospitalized in the 30 days prior to study cohort entry to ensure that events were community-acquired as opposed to nosocomial pneumonia. In addition, we excluded patients with a prescription for anti-tuberculosis medications in the year prior to study cohort entry. Patients were followed until occurrence of the outcome (defined below), censoring due to nosocomial pneumonia (defined as a pneumonia hospitalization within 30 days of a previous hospitalization for another diagnosis, a diagnosis of pneumonia not within the first 2 days of a hospitalization or followed by a transfer to another unit of care), end of registration with the CPRD, or end of the study period (July 31st, 2017), whichever occurred first.

Exposure

We defined exposure using a time-dependent approach. Each person-day of follow-up was classified into one of five mutually-exclusive exposure categories: 1) current use of SGLT-2i (with or without the use of non-DPP-4i antidiabetic drugs); 2) current use of DPP-4i (with or without the use of non-SGLT-2i antidiabetic drugs; the reference category); 3) current use of insulin with or without the use of antidiabetic drugs other than SGLT-2i and DPP-4i; 4) current use of antidiabetic medications other than SGLT-2i, DPP-4i, and insulin; and 5) no current use of antidiabetic drugs. Current use was defined by a prescription that overlapped with the day of follow-up being classified, assuming that prescriptions had a duration of 30 days and allowing for a 30-day grace period to account for non-adherence and the biological half-life of these drugs. We used DPP-4i as the reference category for two principal reasons. First, as with SGLT2i, it is a class of drugs that is used for the second- to third-line treatment of type 2 diabetes. It thus provided a clinically relevant comparison and reduced the possibility of time-lag bias[18]. Second, although previous studies have suggested that DPP-4i are associated with an increased risk of infections [19,20], previous studies of CAP showed no increased risk with the use of DPP-4i [21-25].

Outcome

The primary endpoint of our study was HCAP, defined by an ICD-10 code in HES for pneumonia (ICD-10: J10.x – J18.x, J22.x, J85.0, J85.1, J86.x, B01.2, B05.2, B25.0, in any position) in the first 2 days of hospitalization without a transfer to another unit of care and the absence of hospitalization in the previous 30 days. This approach prevented misclassification of nosocomial pneumonia as CAP. ICD-10 codes for pneumonia have been validated[26].

Covariates

Patient characteristics were measured at study cohort entry and included age, sex, year and season of cohort entry (high risk of pneumonia from October 1st to March 31st, low risk from April 1st to September 30th). We also identified the following comorbidities in the CPRD and HES in the year prior to cohort entry: alcohol-related disorders, asthma, bronchitis, bronchiectasis, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and arterial hypertension. Prescription drug use, assessed in the year before study cohort entry, was also measured and included use of immunosuppressive agents, inhaled bronchodilators, inhaled corticosteroids, statins, systemic antibiotics, systemic corticosteroids, and vaccinations for pneumonia and influenza. We also adjusted for a diagnosis of pneumonia in the year prior to cohort entry, the last measures of systolic and diastolic blood pressure and hemoglobin A1c (HbA1c) available in the year prior to study cohort entry, and lifestyle variables (smoking, BMI recorded in the 5 years prior to study cohort entry). To adjust for overall health status, we assessed the number of drug classes, number of physician visits, and number of hospitalizations in the year before cohort entry. Measure of diabetes severity included duration of treated diabetes, as well as macrovascular (myocardial infarction, stroke) and microvascular (neuropathy, retinopathy, nephropathy) complications of diabetes measured at any time prior to cohort entry.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of SGLT-2i users and DPP-4i users at cohort entry. We calculated crude incidence rates of HCAP and 95% confidence intervals (CIs) based on the Poisson distribution.

We used time-dependent Cox proportional hazards models with follow-up time as the underlying time axis to obtain hazard ratios (HRs) and 95% CIs for HCAP with the use of SGLT-

2i versus use of DPP-4i. For each patient, follow-up began on the date of study cohort entry. Our models were adjusted for covariates measured at study cohort entry. Age and duration of treated diabetes were modeled using restricted cubic splines with 5 knots[27]. We used multiple imputation for missing covariate data[28].

We conducted 3 secondary analyses. First, we repeated our primary analyses with SGLT-2i subclassified by molecule (canagliflozin, dapagliflozin, and empagliflozin). Second, we sub-classified duration of current use (0-1, 1-2, and 2+ years) using a time-dependent approach to assess a possible duration-response relationship. Finally, we included interaction terms in our Cox proportional hazards models and stratified analyses to assess potential effect modification by history of respiratory disease at cohort entry (asthma, COPD, previous pneumonia) and by age (70+ vs ≤70 years).

To test the robustness of our findings, we conducted 8 sensitivity analyses. These included 1) varying the grace period to 0 and 60 days, 2) excluding patients with a history of insulin use at cohort entry, 3) adjusting our models for previous use of antidiabetic drugs at cohort entry, 4) a high-dimensional propensity-score (HDPS)[29] matched analysis with an as-treated exposure definition, 5) adjustment for disease risk score, 6) censoring patients with a diagnosis of pneumonia within 90 days of a hospitalization, 7) using GLP-1 RA as the active comparator instead of DPP-4i, and 8) restricting our outcome definition to hospitalizations of patients that were admitted through the emergency department. Additional details on sensitivity analyses are provided in Appendix 1 of the Supplementary Material.

3. RESULTS

A total of 29,896 patients met the study inclusion criteria (Figure 1). Mean overall follow-up was 1.7 (standard deviation: 1.2) years. A total of 705 patients were hospitalized for CAP, for an overall incidence rate of HCAP of 13.7 (95% CI: 12.7, 14.7) per 1,000 person-years.

Compared with DPP-4i users, SGLT-2i users were younger, more likely to be obese, more likely to use inhaled bronchodilators, inhaled corticosteroids, and systemic antibiotics (Table 1). Patients using SGLT-2i were less likely to have had a stroke or myocardial infarction prior to cohort entry compared to patients using DPP-4i. Markers of general health such as mean numbers of hospitalizations, drug classes, and physician visits in the previous year were similar between groups.

The crude incidence rate of HCAP was 6.2 per 1000 person years (95% CI: 3.7, 10.2) for patients using SGLT-2i and 17.8 (95% CI: 15.3, 20.7) in patients using DPP-4i (Table 2). After adjusting for potential confounders, the use of SGLT-2i was associated with a decreased risk of HCAP compared with use of DPP-4i (HR: 0.48, 95% CI: 0.28, 0.82). There was no evidence that the risk of HCAP differed by molecule (dapagliflozin, HR: 0.60, 95% CI: 0.34, 1.06; canagliflozin, 0.37, 95% CI: 0.09, 1.49), although 95% CIs were wide; no HCAPs occurred among patients currently using empagliflozin. We did not find evidence of a duration-response relationship between SGLT-2i and HCAP as compared to DPP-4i (Supplemental Table S1) or that the association varied with age ($\leq$ 70 years, HR: 0.51, 95% CI: 0.28, 0.93; > 70 years, HR: 0.40, 0.10, 1.65; Supplemental Table S3). Similarly, the association did not vary by history of respiratory disease at study cohort entry (Supplemental Table 4). The inclusion of interaction terms for age (Supplemental Table S2) and for history of respiratory disease (Supplemental Table S5) also did not modify our results.

Sensitivity analyses

The results of our sensitivity analyses are summarised in Figure 2 and presented in detail in Supplemental Tables S6-S11. Results consistent with those of our primary analysis were obtained across most sensitivity analyses. However, current use of SGLT-2i was not associated with the risk of HCAP compared with the current use of GLP-1 RA (HR: 0.94, 95% CI: 0.44, 1.89).

4. DISCUSSION

The objective of our study was to evaluate the risk of HCAP with the use of SGLT-2i as compared to DPP-4i. Contrary to our hypothesis, we found a decreased risk of HCAP among patients with type 2 diabetes using SGLT-2i as compared to DPP-4i (HR: 0.48, 95% CI: 0.28, 0.82). There was no evidence that the association varied by SGLT-2 molecule, duration of current use, age, or history of respiratory diseases. In contrast, we found that SGLT-2i were not associated with the risk of HCAP compared to GLP-1 RA (HR: 0.91, 95% CI: 0.44, 1.89).

To our knowledge, this is the first population-based study to investigate the association between SGLT-2i and HCAP. Although we hypothesized an increased risk of HCAP with SGLT-2i, a protective association was observed when comparing SGLT-2i to DPP-4i but not when SGLT2i were compared to GLP-1 RA. This may be explained in several ways. First, it is possible that SGLT-2i are protective with respect to HCAP. In the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) Trial, patients randomized to dapagliflozin had fewer occurrences of bronchitis (dapagliflozin: n=13, 0.2%; placebo: n=32, 0.4%) than those randomized to placebo[2]. In addition, a clinical trial is currently evaluating the therapeutic effect of dapagliflozin on COVID-19 disease progression[30]. The observed null association for HCAP when SGLT2 inhibitors were compared with GLP-1 RA adds some support of this hypothesis. Indeed, several studies have reported protective associations between the use of GLP-1 RA and respiratory function[31-33] and risk of infections[34]. Second, it is also possible that the observed protective association is the result of an increased risk of pneumonia with DPP-4i. However, although there may be a biological mechanism linking DPP-4i to an increased risk of infections[35-37], most previous studies of the pneumonia risk of DPP-4i did not identify an increased risk,[21-25,38] suggesting that this is an unlikely explanation for the observed

association. Third, the observed association may be the result of residual confounding. As physicians typically avoid prescribing SGLT-2i to patients with dementia or with limited autonomy because of the monitoring and management that they require (e.g., to avoid dehydration and infections)[39], it is possible that patients with type 2 diabetes using SGLT-2i are inherently healthier than those using DPP-4i. This possibility is supported by the limited overlap between the distributions of the HDPS of users of SGLT-2i and users of DPP-4i in our sensitivity analysis (Figure S1). Similarly, due to their injectable nature, GLP-1 RA may also be channeled towards healthier patients who are able and comfortable performing daily injections[40]. Thus, despite our use of an active comparator and rigorous statistical adjustment, we are unable to rule out potential residual confounding due to frailty and other patient characteristics.

Given the increased risk of genitourinary tract infections with SGLT-2i and the potential analogous biological mechanism in the lungs[9-11], the results of the present study provide some reassurance to physicians and patients with respect to the pneumonia risk of SGLT-2i. Although canagliflozin may have more affinity to SGLT-1 receptors in the lung than dapagliflozin or empagliflozin[12], we found no difference in association by molecule, although our molecule-specific estimates are accompanied by wide 95% CIs. Patients with type 2 diabetes are at an elevated risk of pneumonia[41] and have worse outcomes than patients without type 2 diabetes, underscoring the importance of prudence in this population.

This study has several strengths. First, our time-dependent exposure definition allowed us to account for treatment switches and to avoid immortal-time bias[42]. Second, data from the CPRD allowed us to control for many covariates that are not available in most administrative databases, such as BMI, HbA1c, and smoking status. Third, linkage of CPRD data with HES data helped us ensure that we were capturing clinically relevant events with severe disease and allowed us to

reduce misclassification between CAP and other respiratory events[43]. Fourth, due to the population-based nature of the CPRD and HES, our results are highly generalizable to patients with type 2 diabetes that are seen in routine clinical care.

Our study has potential limitations. As mentioned previously, confounding by contraindication due to frailty (and other poorly characterized markers in databases such as the CPRD) may have affected our results, where SGLT-2i may have been channeled towards younger and healthier patients without dementia[39]. Time-varying confounding due to changes in concomitant drug use and changes in health status during follow-up is also possible. However, with a mean duration of follow-up of 1.7 years, it is unlikely to result in important bias. We restricted our outcome definition to hospitalized events, as an outpatient diagnosis of CAP is more prone to misclassification. However, cases of HCAP are clinically relevant as they represent patients with severe disease. Although outcome misclassification is possible, HES data have been validated, and our sensitivity analysis restricting to events admitted from the emergency department confirmed our primary findings[44]. Additionally, as the CPRD records prescriptions and not dispensings, exposure misclassification is possible, although it is likely non-differential and would bias our results towards the null. As well, we assumed a prescription duration of 30 days, but this may also induce some exposure misclassification if the duration of exposure differs from our assumptions. Furthermore, the small number of exposed events, particularly in some secondary analyses, and the relatively modest duration of follow-up, may limit the conclusions that can be drawn from some secondary analyses. The small number of exposed events also prevented us from examining if treatment effects differed between new users of antidiabetic drugs who switched to or added a new antidiabetic drug.

5. CONCLUSIONS

The present study found that SGLT-2i were associated with a decreased risk of HCAP compared to DPP-4i, but not compared to GLP-1 RA, among patients with type 2 diabetes. Although these results suggest that SGLT-2i have beneficial effects with respect to HCAP when compared with the use of DPP-4i, residual confounding is possible, and there remains a need to replicate these results. Nonetheless, this study provides reassuring evidence concerning the risk of HCAP with the use of SGLT-2i and provides further information for the assessment of risks and benefits of these drugs.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to declare.

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AUTHOR CONTRIBUTIONS

Dr. Filion conceived the study idea and supervised the study. Ms. Brunetti drafted the manuscript. Ms. Brunetti and Ms. Reynier performed statistical analyses. All authors contributed to the study design, were involved in the interpretation of the data, and reviewed the manuscript for intellectual content. Dr. Filion is the guarantor of this study.

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437 **Table 1**: Baseline characteristics of users of SGLT-2 inhibitors and DPP-4 inhibitors***.**

Characteristics	Current use of SGLT-2 inhibitors 1,011	Current use of DPP-4 inhibitors 5,552	Total† 29,896
Age (years)	58.1 (9.5)	63.0 (11.9)	59.7 (13.3)
Male sex	370 (36.6)	2,089 (37.6)	12,330 (41.2)
Diabetes duration (years)	8.0 (3.8)	6.5 (3.7)	2.3 (3.7)
Calendar year at cohort entry			
2013	87 (8.6)	2,244 (40.4)	10,086 (33.7)
2014	256 (25.3)	1,402 (25.3)	7,554 (25.3)
2015	321 (31.8)	1,038 (18.7)	6,259 (20.9)
2016	251 (24.8)	644 (11.6)	4,227 (14.1)
2017	96 (9.5)	224 (4.0)	1,770 (5.9)
High-risk season (October 1 to March 31) ‡	461 (45.6)	2,907 (52.4)	15,358 (51.4)
Comorbidities§			
Alcohol-related disorders	34 (3.4)	172 (3.1)	773 (2.6)
Any pneumonia	8 (0.8)	61 (1.1)	283 (1.0)
Asthma	119 (11.8)	536 (9.7)	3,085 (10.3)
Bronchitis	45 (4.5)	244 (4.4)	1,254 (4.2)
Bronchiectasis	S‖	8 (0.1)	34 (0.1)
Cardiovascular disease	57 (5.6)	420 (7.6)	1,819 (6.1)
Cerebrovascular disease	16 (1.6)	148 (2.7)	612 (2.1)
Chronic obstructive pulmonary disorder	54 (5.3)	297 (5.4)	1,580 (5.3)
Arterial hypertension	247 (24.4)	1,270 (22.9)	6,522 (21.8)
BMI			
<18.5 kg/m^2	S	10 (0.2)	72 (0.2)
18.5 – 24.9 kg/m^2	28 (2.8)	469 (8.5)	2,521 (8.4)
25.0 – 29.9 kg/m^2	180 (17.8)	1,605 (28.9)	8,086 (27.1)
≥30.0 kg/m^2	799 (79.0)	3,428 (61.7)	17,522 (58.6)
Missing	S	40 (0.7)	1,695 (5.7)
Demographic/lifestyle			
Number of physician visits	8.2 (7.4)	7.3 (6.7)	6.4 (6.6)
Number of hospitalizations			
0	925 (91.5)	5,044 (90.9)	27,340 (91.5)
1	66 (6.5)	387 (7.0)	1,973 (6.6)
>1	20 (2.0)	121 (2.2)	583 (2.0)
Number of drug classes	13.0 (6.7)	12.1 (6.1)	9.7 (6.3)
Smoker	641 (63.4)	3,488 (62.8)	17,771 (59.4)
Missing	12 (1.2)	60 (1.1)	979 (3.3)
Blood pressure			
Systolic	134.8 (13.9)	134.3 (14.1)	135.2 (15.1)
Missing	24 (2.4)	126 (2.3)	2,345 (7.8)
Diastolic	78.1 (8.3)	77.4 (8.6)	79.1 (9.3)
Missing	28 (2.8)	145 (2.6)	2,432 (8.1)

Characteristics	Current use of SGLT-2 inhibitors 1,011	Current use of DPP-4 inhibitors 5,552	Total† 29,896
Glycated hemoglobin (HbA1c)	9.4 (1.7)	8.9 (1.5)	8.7 (1.9)
Missing	36 (3.6)	134 (2.4)	2,862 (9.6)
Medications			
Immunosuppressive agents	23 (2.3)	65 (1.2)	416 (1.4)
Inhaled bronchodilators	191 (18.9)	886 (16.0)	5,169 (17.3)
Inhaled corticosteroids	145 (14.3)	648 (11.7)	3,789 (12.7)
Statins	812 (80.3)	4,544 (81.8)	18,552 (62.1)
Systemic antibiotics	445 (44.0)	2,260 (40.7)	12,106 (40.5)
Systemic corticosteroids	85 (8.4)	412 (7.4)	2,617 (8.8)
Pneumonia vaccine	11 (1.1)	55 (1.0)	377 (1.3)
Influenza vaccine	176 (17.4)	864 (15.6)	3,568 (11.9)
Complications of diabetes			
Myocardial infarction	51 (5.0)	453 (8.2)	2,001 (6.7)
Stroke	31 (3.1)	345 (6.2)	1,397 (4.7)
Neuropathy	19 (1.9)	79 (1.4)	151 (0.5)
Retinopathy	306 (30.3)	1,644 (29.6)	4,040 (13.5)
Nephropathy	S	43 (0.8)	106 (0.4)

Abbreviations: SGLT-2 = sodium-glucose co-transporter 2, DPP-4= dipeptidyl peptidase-4, BMI= body mass index

*Data are presented as n (%) or mean ± standard deviation

†Includes patients who entered the study cohort with a new prescription of SGLT-2 inhibitors, DPP-4 inhibitors or any other antidiabetic medication.

‡Season of study cohort entry

§Comorbidities were assessed at any time prior to study cohort entry. Prescription drug use, previous diagnosis of pneumonia, hemoglobin A1c (HbA1c), number of hospitalizations, number of physician visits and number of drug classes were assessed in the year prior to cohort entry. Smoking and body mass index were assessed in the 5 years prior to cohort entry.

‖As per confidentiality policies of the Clinical Practice Research Datalink, numbers <5 are suppressed. Suppressed values are denoted with an S.

Table 2. Association between the use of SGLT-2 inhibitors compared to the use of DPP-4 inhibitors and the risk of hospitalization for community-acquired pneumonia among patients with type 2 diabetes.

Exposure †	Events	Person-Years	Incidence Rate (95% CI) ‡	Crude HR (95% CI)	Adjusted HR (95% CI) §
Current use of DPP-4 inhibitors	168	9430	17.8 (15.3, 20.7)	1.0 (Ref)	1.0 (Ref)
Current use of SGLT-2 inhibitors	15	2432	6.2 (3.7, 10.2)	0.34 (0.20, 0.58)	0.48 (0.28, 0.82)
Current use of Dapagliflozin	S ¶	S	7.3 (4.2, 12.5)	0.40 (0.23, 0.71)	0.60 (0.34, 1.06)
Current use of Canagliflozin	S	S	5.8 (1.5, 23.2)	0.32 (0.08, 1.29)	0.37 (0.09, 1.49)
Current use of Empagliflozin	0	299	0 (0.0, 0.0)	---	---

Abbreviations: SGLT-2: sodium-glucose co-transporter 2, DPP-4: dipeptidyl peptidase 4, CI: confidence interval, HR: hazard ratio, Ref: reference category

† Data for other exposure categories (current treatment with insulin, current treatment with other antidiabetic drugs, and no current antidiabetic treatment [i.e. patients who discontinued treatment]) are not shown in the table but were considered in the Cox proportional hazards model for the accurate estimation of the treatment effects.

‡ Incidence rates are expressed as events per 1,000 person-years.

§ The model was adjusted for the following covariates: age (restricted cubic splines), sex, race, duration of treated diabetes (restricted cubic splines), year of cohort entry (categorical), season of the cohort entry, smoking and body mass index (BMI) in the five years before cohort entry, comorbidities (alcohol-related disorders, asthma, bronchitis, bronchiectasis, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, arterial hypertension, and any pneumonia in the year before cohort entry), prescription drug use (immunosuppressive agents, inhaled bronchodilators, inhaled corticosteroids, statins, systemic antibiotics, systemic corticosteroids), vaccination for respiratory conditions (pneumonia, influenza), macrovascular (myocardial infarction, stroke) and microvascular (neuropathy, retinopathy, nephropathy) complications of diabetes, systolic and diastolic blood pressure, hemoglobin A1c (HbA1c; last measure recorded in the previous year), number of drug classes, number of physician visits, and number of hospitalizations in the year before cohort entry. BMI, smoking, race, blood pressure, HbAc1 variables were imputed by multiple imputation.

¶ As per confidentiality policies of the Clinical Practice Research Datalink, numbers <5 are suppressed. Suppressed values are denoted with an S.

FIGURE LEGENDS

Figure 1. Flow chart describing construction of study cohort. Abbreviations: HES: Hospital Episodes Statistics, HIV: Human Immunodeficiency Virus.

Figure 2. Forest plot of sensitivity analyses of the association between use of SGLT-2 inhibitors versus DPP-4 inhibitors and the risk of hospitalization for community-acquired pneumonia. Abbreviations: CI: confidence interval, DEPT: department, DRS: disease risk score, GLP-1: glucagon-like peptide-1, HDPS: high dimensional propensity score, HR: hazard ratio, OAD: oral antidiabetic drug.

Figure 1

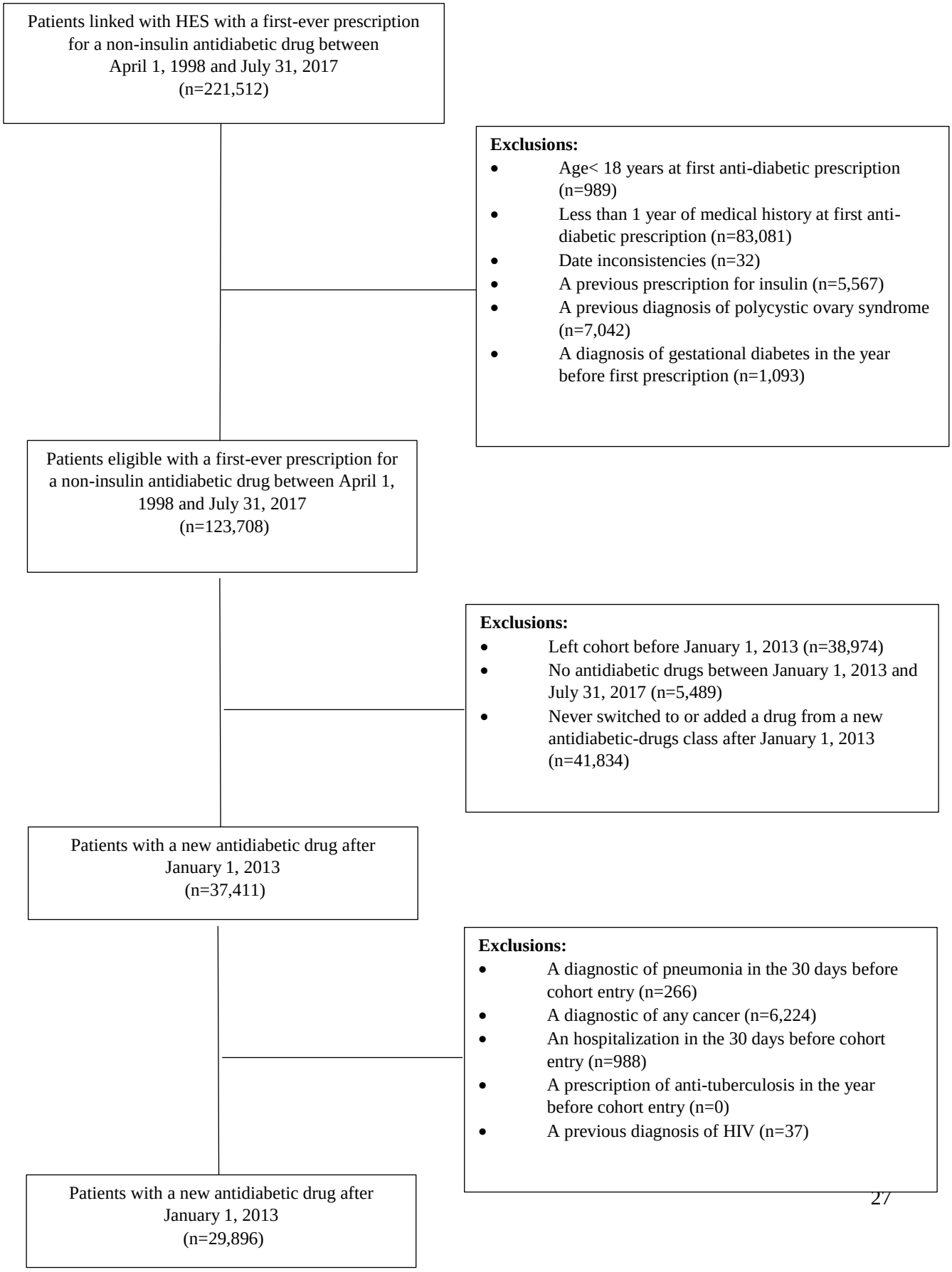
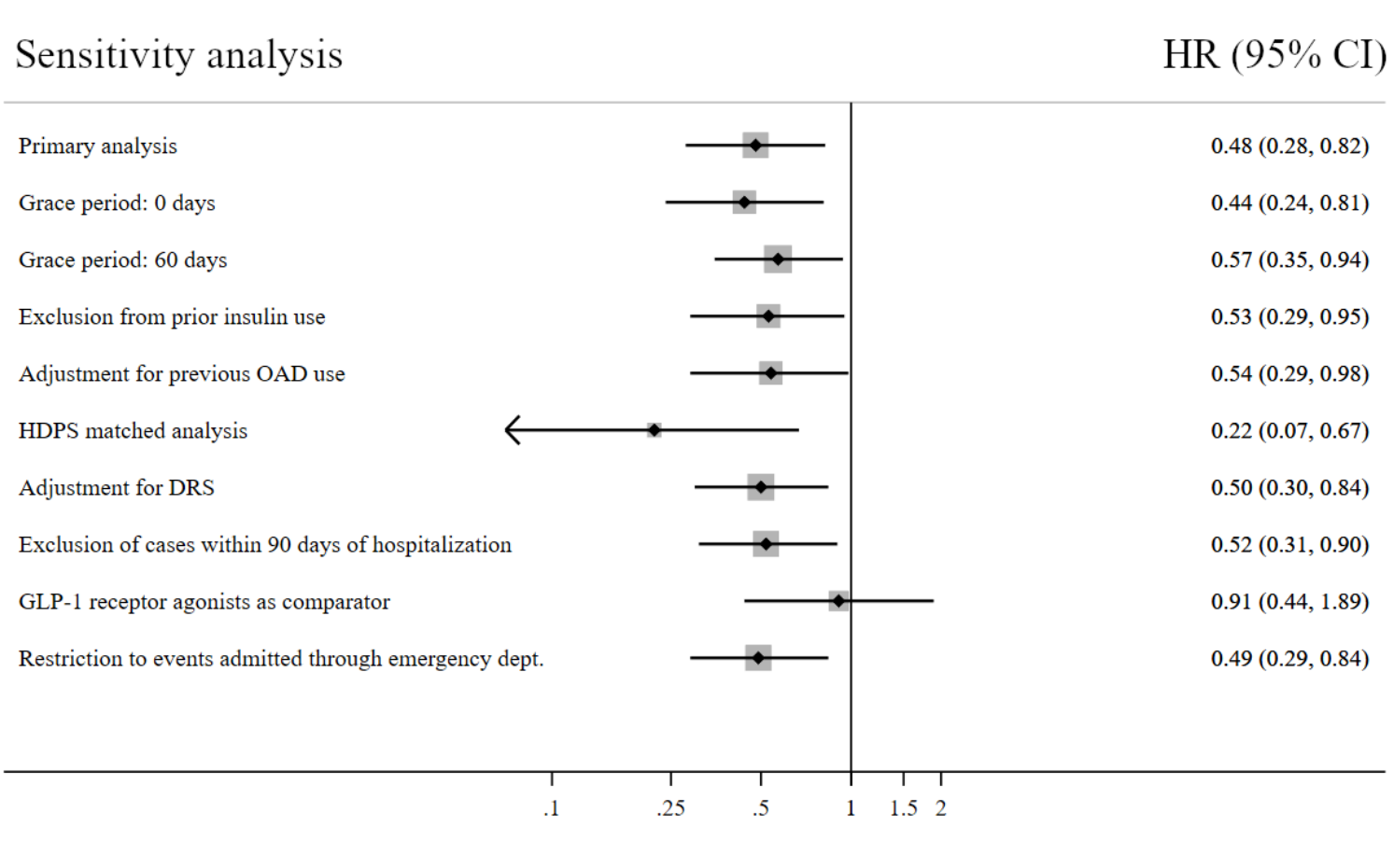

Patients linked with HES with a first-ever prescription for a non-insulin antidiabetic drug between April 1, 1998 and July 31, 2017 (n=221,512)
Exclusions:
Age< 18 years at first anti-diabetic prescription (n=989)
Less than 1 year of medical history at first anti-diabetic prescription (n=83,081)
Date inconsistencies (n=32)
A previous prescription for insulin (n=5,567)
A previous diagnosis of polycystic ovary syndrome (n=7,042)
A diagnosis of gestational diabetes in the year before first prescription (n=1,093)
Patients eligible with a first-ever prescription for a non-insulin antidiabetic drug between April 1, 1998 and July 31, 2017 (n=123,708)
Exclusions:
Left cohort before January 1, 2013 (n=38,974)
No antidiabetic drugs between January 1, 2013 and July 31, 2017 (n=5,489)
Never switched to or added a drug from a new antidiabetic-drugs class after January 1, 2013 (n=41,834)
Patients with a new antidiabetic drug after January 1, 2013 (n=37,411)
Exclusions:
A diagnostic of pneumonia in the 30 days before cohort entry (n=266)
A diagnostic of any cancer (n=6,224)
An hospitalization in the 30 days before cohort entry (n=988)
A prescription of anti-tuberculosis in the year before cohort entry (n=0)
A previous diagnosis of HIV (n=37)
Patients with a new antidiabetic drug after January 1, 2013 (n=29,896)

Figure 2


Sensitivity analysis
HR (95% CI)
Primary analysis
0.48 (0.28, 0.82)
Grace period: 0 days
0.44 (0.24, 0.81)
Grace period: 60 days
0.57 (0.35, 0.94)
Exclusion from prior insulin use
0.53 (0.29, 0.95)
Adjustment for previous OAD use
0.54 (0.29, 0.98)
HDPS matched analysis
0.22 (0.07, 0.67)
Adjustment for DRS
0.50 (0.30, 0.84)
Exclusion of cases within 90 days of hospitalization
0.52 (0.31, 0.90)
GLP-1 receptor agonists as comparator
0.91 (0.44, 1.89)
Restriction to events admitted through emergency dept.
0.49 (0.29, 0.84)
.1
.25
.5
1
1.5
2