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RESEARCH LETTER

WILEY

Association between antidiabetic drug use and the risk of COVID-19 hospitalization in the INSIGHT Clinical Research Network in New York City

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1 | BACKGROUND

Patients with type 2 diabetes (T2D), especially those with poor glycaemic control, have an increased risk for coronavirus disease 2019 (COVID-19) and severe outcomes such as hospitalization and death.[1-5] In addition, some antidiabetic drugs have been postulated to influence the course of severe acute respiratory syndrome coronavirus 2 infection, although studies examining the association between antidiabetic drugs and the risk of COVID-19 have shown inconsistent results and were often prone to confounding by indication.[6-11] The question of whether to discontinue a certain antidiabetic drug and initiate a different drug to lower the risk for COVID-19 infection in the outpatient setting remains uncertain. In this retrospective study, we examined the association between prescriptions for different classes of second-line antidiabetic drugs in the year prior to the beginning of the COVID-19 pandemic and the subsequent risk of COVID-19 hospitalization in a large cohort of patients with T2D in New York City.

2 | METHODS

We conducted a retrospective cohort study using data from the INSIGHT Clinical Research Network (CRN), comprised of electronic health record (EHR) data from a large, diverse patient population who received care at five academic medical centres in New York City.[12] The study was approved by the Weill Cornell Medicine and Memorial Sloan Kettering Cancer Center Institutional Review Boards. Informed consent was waived. Adult patients in the INSIGHT CRN with evidence of T2D and at least one HbA1c and serum creatinine measurement in the year prior to the index date of 15 March 2020 were included. The index date was chosen as the date upon which exponential increases in COVID-19 cases in New York City were observed.[13] Patients were required to have at least one prescription for metformin and at least one prescription for a non-insulin antidiabetic drug in the baseline (preindex) year. Patients on metformin monotherapy and those on insulin were excluded.

Exposure to four classes of antidiabetic drugs, sulphonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and/or glucagon-like peptide-1 (GLP-1) agonists, were defined based on having at least one prescription in the baseline year (Table S1). Patients with no exposure to the drug class of interest were treated as the reference group in each comparison. For example, patients with a sulphonylurea prescription were compared with those without a sulphonylurea prescription in the baseline year. All patients were followed until 15 June 2020 for the primary outcome of COVID-19 hospitalization, defined by a discharge diagnosis code for COVID-19 and/or a positive COVID-19 test result either during or 2 weeks prior to the hospitalization (Table S2). In-hospital death during a COVID-19 hospitalization was

examined as a secondary outcome. We also described characteristics of COVID-19 hospitalizations that could be indicative of disease severity and pathogenesis, including co-morbid diabetic ketoacidosis (DKA), acute kidney injury (AKI), and hypoglycaemia (Table S2). Directed acyclic graphs were used to select potential confounders a priori. Covariate information was collected from the baseline year and included demographics, vital signs, laboratory measurements, selected co-morbidities using the Elixhauser algorithm, electronic prescriptions, and health utilization metrics (Table S1).

For the primary analysis, we compared time to COVID-19 hospitalization in the four drug exposure groups in four separate Cox proportional hazards models that used propensity score weighting with matching weights[14,15] and additional adjustment for all covariates (Table S3; Figures S1 and S2). Two sensitivity analyses were performed. First, we limited the study sample to patients with high predicted EHR data continuity scores, a measure of the predicted proportion of all healthcare encounters captured in the EHR data (Table S4). Second, we restricted the study's primary drug exposure period to 6 months prior to the index date to further reduce the possibility of exposure misclassification. We also performed subgroup analyses in specific groups of sex, race/ethnicity, age (≤65 and >65 years), and quintiles of social deprivation index.

TABLE 1 Risk of COVID-19 hospitalization and in-hospital death by antidiabetic drug prescriptions in the year prior to 15 March 2020

Outcome	Sulphonylurea N = 13 068	DPP-4 inhibitor N = 14 674	SGLT2 inhibitor N = 8248	GLP-1 agonist N = 7476
Primary analysis				
First COVID-19 hospitalization, n	121	130	53	62
Person-days of follow-up	1 192 947	1 340 715	755 018	683 419
Unadjusted rate/1000 person-days	0.10	0.10	0.07	0.09
Unadjusted HR (95% CI)	1.33 (1.04, 1.71)	1.25 (0.97, 1.61)	0.76 (0.56, 1.02)	1.06 (0.80, 1.41)
Weighted HR[a] (95% CI)	1.35 (1.02, 1.78)	1.34 (1.00, 1.79)	1.11 (0.80, 1.55)	1.68 (1.19, 2.38)
Adjusted HR[b] (95% CI)	1.44 (1.09, 1.91)	1.33 (1.00, 1.78)	1.09 (0.78, 1.53)	1.64 (1.15, 2.33)
In-hospital death from COVID-19, n	29	32	11	17
Person-days of follow-up	1 199 661	1 347 699	758 098	686 693
Unadjusted rate/1000 person-days	0.02	0.02	0.01	0.02
Unadjusted HR (95% CI)	1.45 (0.86, 2.46)	1.46 (0.86, 2.48)	0.67 (0.34, 1.29)	1.36 (0.77, 2.40)
Weighted HR[a,b] (95% CI)	1.49 (0.85, 2.64)	1.76 (0.97, 2.48)	1.18 (0.58, 2.43)	3.45 (1.59, 7.48)
Sensitivity analysis: excluding patients with low predicted EHR continuity	N = 1776	N = 2286	N = 1282	N = 1473
First COVID-19 hospitalization, n	37	44	16	26
Person-days of follow-up	160 568	207 135	116 894	133 729
Unadjusted rate/1000 person-days	0.23	0.21	0.14	0.19
Unadjusted HR (95% CI)	1.41 (0.91, 2.18)	1.28 (0.83, 1.98)	0.66 (0.38, 1.14)	1.05 (0.66, 1.67)
Weighted HR[a,b] (95% CI)	1.55 (0.97, 2.48)	1.27 (0.77, 2.09)	0.96 (0.52, 1.76)	1.65 (0.94, 2.92)
Sensitivity analysis: prescription required in 6 mo prior to index date	N = 9420	N = 10 608	N = 6225	N = 5727
First COVID-19 hospitalization, n	87	105	38	49
Person-days of follow-up	860 180	968 437	569 866	523 446
Unadjusted rate/1000 person-days	0.10	0.11	0.07	0.09
Unadjusted HR (95% CI)	1.19 (0.90, 1.56)	1.38 (1.05, 1.81)	0.67 (0.47, 0.95)	1.03 (0.75, 1.43)
Weighted HR[a,c] (95% CI)	1.22 (0.89, 1.67)	1.53 (1.11, 2.12)	0.97 (0.66, 1.42)	1.92 (1.30, 2.83)

Abbreviations: DPP-4, dipeptidyl peptidase-4; EHR, electronic health record; GLP-1, glucagon-like peptide-1; SDI, social deprivation index; SGLT2, sodium-glucose co-transporter-2.

[a]Propensity scores estimated the probability of being in the drug exposure category; matching weights used in the outcome model.

[b]For all secondary outcomes and sensitivity and subgroup analyses, we used Cox proportional hazards models weighted with propensity score matching weights and without additional covariate adjustment, because of the possibility of low event numbers.

[c]Adjusted for the following covariates: age, sex, race, Hispanic ethnicity, SDI quintile, body mass index, systolic blood pressure, diastolic blood pressure, creatinine, baseline Elixhauser co-morbidities (uncomplicated hypertension, obesity, renal failure, chronic pulmonary disease, complicated hypertension, cardiac arrhythmia, hypothyroidism, fluid and electrolyte disorders, congestive heart failure, depression), baseline medications (insulin, metformin, sulphonylurea, DPP-4, SGLT2, GLP-1, thiazolidinedione, antihypertensives, aspirin, statins, immunosuppressants, antidepressants, antipsychotics), baseline inpatient encounters, baseline outpatient encounters, baseline ED encounters, and baseline outpatient medications.

3 | RESULTS

We identified 30 747 patients who met all study inclusion criteria (Figure S3); 13 068 patients on sulphonylureas, 14 674 on DPP-4 inhibitors, 8248 on SGLT2 inhibitors, and 7476 on GLP-1 agonists in the baseline year. Propensity score weighting using matching weights improved the balance of covariate distributions across the drug exposure comparison groups, with standardized mean differences of less than 0.10 for all covariates (Table S5).[16]

The unadjusted rates of COVID-19 hospitalization (94.1% of all events identified through ICD-10 discharge diagnosis codes) were 0.10, 0.10, 0.07, and 0.09 per 1000 person-days for patients with baseline prescriptions for sulphonylureas, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists, respectively (Table 1). Compared with patients with no exposure to the drug class in the baseline year, the observed rates of hospitalization were greater for sulphonylureas (adjusted hazard ratio [HR] 1.44, 95% confidence interval [CI] 1.09, 1.91), DPP-4 inhibitors (adjusted HR 1.33, 95% CI 1.00, 1.78), and GLP-1 agonists (adjusted HR 1.64, 95% CI 1.15, 2.33) (Table 1) in our study population. The rate of hospitalization was not significantly different for patients on SGLT2 inhibitors compared with those with no exposure to SGLT2 inhibitors (adjusted HR 1.09, 95% CI 0.78, 1.53). The observed rate of in-hospital death during a COVID-19 hospitalization was higher only among patients with a GLP-1 agonist prescription (weighted HR 3.45, 95% CI 1.59, 7.48) in the study population. As expected, this outcome was rare in all exposure groups, and the effect estimates for all drug comparisons had wide confidence intervals. AKI diagnoses were present in 152 (62.3%), DKA diagnoses in 16 (6.6%), and hypoglycaemia diagnoses in 35 (14.3%) of COVID-19 hospitalizations (Table 2).

The sensitivity analysis excluding patients with low predicted EHR continuity was overall consistent with the primary analysis, but absolute rates of COVID-19 hospitalization were approximately twice as high in the subgroup with high EHR continuity, ranging from 0.14 to 0.23 events per 1000 person-days (Table 1). Results of the sensitivity analysis requiring primary antidiabetic drug exposures in the 6 months prior to the index date were consistent overall with the primary analysis (Table 1), as were the results of the subgroup analyses (Table S6). An additional sensitivity analysis examined pairwise comparisons of the four drug classes of interest, in which all patients were using one or the other of the two drugs being compared, and no other antidiabetic drugs, except for metformin. In this analysis none of the study drugs were clearly associated with a lower rate of hospitalization (Table S7).

4 | CONCLUSIONS

Among T2D patients prescribed metformin and at least one other non-insulin antidiabetic drug, the use of sulphonylureas, DPP-4 inhibitors, or GLP-1 agonists was each associated with a greater risk of COVID-19 hospitalization compared with non-use of those drugs. Results were consistent across multiple sensitivity and subgroup analyses. Because death attributable to COVID-19 in the hospital was rare, we had limited power to examine this outcome.

Our study had several limitations, including possible exposure and covariate misclassification, missed outcome events, and small sample size for certain exposure groups (Table S8). While residual confounding may be a possible explanation for our main findings, further studies are needed to better understand why these drugs may be associated with worse outcomes in diabetes patients who are on second-line agents. None of the second-line antidiabetic drugs we examined were associated with a lower risk of severe COVID-19 outcomes, which supports deprioritizing the study of these drugs as anti-COVID-19 drugs.

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TABLE 2 Presence of diagnosis codes[a] or laboratory values consistent with acute kidney injury, diabetic ketoacidosis, and hypoglycaemia in COVID-19 hospitalizations and non-COVID-19–related hospitalizations by antidiabetic drug prescription in baseline year

Secondary outcome	Total N = 30 747	Sulphonylurea N = 13 068	DPP-4 inhibitor N = 14 674	SGLT2 inhibitor N = 8248	GLP-1 agonist N = 7476
COVID-19 hospitalizations, n (%)	244	121	130	53	62
AKI (diagnosis)	152 (62.3%)	71 (58.7%)	87 (66.9%)	23 (43.4%)	37 (59.7%)
AKI (lab)[b]	136 (55.7%)	66 (54.5%)	72 (55.4%)	27 (50.9%)	36 (58.1%)
Diabetic ketoacidosis	16 (6.6%)	11 (9.1%)	9 (6.9%)	5 (9.4%)	4 (6.5%)
Hypoglycaemia (diagnosis)	35 (14.3%)	22 (18.2%)	16 (12.3%)	4 (7.5%)	7 (11.3%)
Hypoglycaemia (lab)[c]	18 (7.4%)	9 (7.4%)	9 (6.9%)	5 (9.4%)	2 (3.2%)

Abbreviations: AKI, acute kidney injury; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2.

[a]Diagnoses were identified using ICD-10-CM discharge diagnosis codes from a COVID-19 hospitalization (eTable 2).

[b]The laboratory-based AKI definition identified patients whose highest creatinine measurement during the hospitalization was >0.5 mg/dl greater than their baseline, >2 times greater than their baseline creatinine level, or >4 mg/dl. This definition includes patients with end-stage renal disease, and they would be classified as having AKI.

[c]The laboratory-based hypoglycaemia definition identified patients with at least one blood glucose measurement <50 mg/dl during hospitalization.

CONFLICT OF INTEREST

No conflicts to declare for any author.

AUTHOR CONTRIBUTIONS

JYM is responsible for study design, data analysis, and manuscript composition. WS and NW were responsible for data analysis. SB, FW, YZ, ABR, and AIM were responsible for study design and manunscript composition. JHF is responsible for study design, data analysis, and manuscript composition and is the guarantor of the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14704.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from INSIGHT CRN. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of INSIGHT CRN.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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