Association Between Glucagon-Like Peptide 1 Receptor Agonist and Sodium–Glucose Cotransporter 2 Inhibitor Use and COVID-19 Outcomes

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OBJECTIVE

To determine the respective associations of premorbid glucagon-like peptide-1 receptor agonist (GLP1-RA) and sodium–glucose cotransporter 2 inhibitor (SGLT2i) use, compared with premorbid dipeptidyl peptidase 4 inhibitor (DPP4i) use, with severity of outcomes in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

RESEARCH DESIGN AND METHODS

We analyzed observational data from SARS-CoV-2–positive adults in the National COVID Cohort Collaborative (N3C), a multicenter, longitudinal U.S. cohort (January 2018–February 2021), with a prescription for GLP1-RA, SGLT2i, or DPP4i within 24 months of positive SARS-CoV-2 PCR test. The primary outcome was 60-day mortality, measured from positive SARS-CoV-2 test date. Secondary outcomes were total mortality during the observation period and emergency room visits, hospitalization, and mechanical ventilation within 14 days. Associations were quantified with odds ratios (ORs) estimated with targeted maximum likelihood estimation using a super learner approach, accounting for baseline characteristics.

RESULTS

The study included 12,446 individuals (53.4% female, 62.5% White, mean ± SD age 58.6 ± 13.1 years). The 60-day mortality was 3.11% (387 of 12,446), with 2.06% (138 of 6,692) for GLP1-RA use, 2.32% (85 of 3,665) for SGLT2i use, and 5.67% (199 of 3,511) for DPP4i use. Both GLP1-RA and SGLT2i use were associated with lower 60-day mortality compared with DPP4i use (OR 0.54 [95% CI 0.37–0.80] and 0.66 [0.50–0.86], respectively). Use of both medications was also associated with decreased total mortality, emergency room visits, and hospitalizations.

CONCLUSIONS

Among SARS-CoV-2–positive adults, premorbid GLP1-RA and SGLT2i use, compared with DPP4i use, was associated with lower odds of mortality and other adverse outcomes, although DPP4i users were older and generally sicker.

Diabetes is one of the comorbidities most strongly associated with severe coronavirus disease 2019 (COVID-19) in the U.S. (1). Data from early in the pandemic suggested approximately two times greater risk of death among individuals with type 2 diabetes compared with the risk for those without (2), as well as a greater risk of requiring hospitalization and intensive care (3,4).

Two classes of antihyperglycemic medications, glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), have been associated with a reduction of cardiorenal events and mortality in large trials of cardiovascular outcomes (5–8), heart failure (9,10), and renal outcomes (11,12) in populations at high risk of cardiorenal events. Benefits associated with these medications appear most pronounced among individuals with type 2 diabetes and comorbid cardiovascular disease, heart failure, chronic kidney disease, and obesity (1,2,4,13,14), conditions that also incur the highest risk for severe COVID-19. Additionally, plausible mechanisms for the protective effects of GLP1-RA and SGLT2i in COVID-19, independent of their glycemic effects, have been speculated (15,16).

Yet, it is not known how the use of new antihyperglycemic medications is associated with severity of COVID-19. Therefore, our objective was to characterize the association of premorbid use of GLP1-RA and SGLT2i with COVID-19 outcomes. The study hypothesis was that use of both classes of medications would be associated with improved outcomes in the setting of COVID-19 infection. Characterizing these associations among individuals with type 2 diabetes may reveal interventional strategies to improve outcomes for a population at high risk for COVID-19–associated mortality. We selected individuals using dipeptidyl peptidase 4 inhibitors (DPP4i) as a comparator group because DPP4i, like the GLP1-RA and SGLT2i, are branded products that can be considered for second-line use after the initiation of metformin (17) and have been used in other real-world analyses to reduce the potential for confounding by clinical indication or socioeconomic status (18).

RESEARCH DESIGN AND METHODS

Study Design and Population

We analyzed data from a cohort study using COVID-19 data from health care systems across the U.S. contributing to the National COVID Cohort Collaborative (N3C) (19). The N3C cohort includes individuals with any encounter after 1 January 2020 and one or a combination of more than one of a set of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) laboratory tests, predefined based on diagnostic codes as defined by the N3C phenotype definition team (20,21).

For individuals included in N3C, the data set includes electronic health record (EHR) data from the same health system beginning 1 January 2018. In contrast to many COVID-19 data resources, the N3C data set encompasses individual-level data contributed by clinical sites across the U.S. The data set continues to grow as new individuals and institutions are added.

The University of North Carolina at Chapel Hill Office of Human Research Ethics determined that the research protocol did not constitute human subjects research (19). The study protocol was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) on 5 October 2020 (no. 37860).

Individuals were included in the study if they were at least 18 years of age in 2020 with a positive SARS-CoV-2 PCR test and at least one ambulatory prescription of an antihyperglycemic medication of interest (GLP1-RA, SGLT2i, or DPP4i [according to the ATC codes listed in Supplementary Table 1]) in the 24 months preceding the SARS-CoV-2 PCR test. Information about drug prescriptions was based on information that captures prescriptions that were written or renewed during ambulatory visits and does not reflect dispensing. We excluded individuals with a history of both DPP4i and SGLT2i/GLP1-RA prescriptions within the previous 24 months of positive SARS-CoV-2 PCR test, i.e., concurrent use of DPP4i and either GLP1-RA or SGLT2i. Subjects on both GLP1-RA and SGLT2i contributed to both exposure arms. A total of 1,422 individuals had concurrent use of GLP-1RA and SGLT2i. We defined comorbidities based on the individual categories of diseases or diagnoses used to generate the updated Charlson Comorbidity Index (22). There were no inclusion criteria pertaining to diabetes diagnosis.

Measures, Definitions, and Outcomes

We defined the index date for each individual as the date of the first positive SARS-CoV-2 PCR test. The primary outcome was mortality within 60 days of any positive SARS-CoV-2 PCR test. Secondary outcomes were mortality during any time after index date (total mortality) and emergency room visits, hospitalization, and mechanical ventilation (i.e., intubation or ventilation) within 14 days of any positive SARS-CoV-2 PCR test. Compared with that for the other outcomes, the observation period for total mortality will vary between individuals, depending on the date of positive PCR test relative to the date of data release. All outcome assessments were consistent with a 2020 consensus statement on common outcome measures for COVID-19 clinical research (23).

Medical history and demographics were identified with use of all available data prior to the index date. Drug exposure were assessed with data from up to 24 months prior to the index date. Continuous variables, such as laboratory measurements and BMI, were also assessed with data from up to 24 months prior to the index date, with use of the most recent measurement.

Statistical Analysis

We conducted analyses in the order specified in the study protocol and as prespecified after the accrual of at least 150 deaths in the GLP1-RA and DPP4i populations pooled. Analyses were conducted on the N3C data with release dated 23 February 2021.

Baseline characteristics were summarized according to medication use with standardized mean differences (SMD) before and after propensity score weighting (PSW). Crude proportions for the primary and secondary outcomes were summarized.

To determine the association of GLP-1 RA and SGLT2i with outcomes, we used targeted maximum likelihood estimation (TMLE), using a super learner approach (24,25), as the primary statistical analysis method. TMLE is a semiparametric double robust method that improves the chance of correct model specification by allowing for flexible estimation using nonparametric machine learning methods for both the outcome and exposure model. The TMLE

uses the propensity scored exposure arms in the outcome model.

A sensitivity analysis examined inverse probability treatment weighted (IPTW) logistic regression using propensity scores. As prespecified in the protocol, stabilized weights were truncated at the 5% and 95% percentile, and covariates with SMD >0.1 after PSW were included in the outcome model. Both methods account for the baseline characteristics indicated in Table 1. In the case where the PSW exposure arms are not well-balanced, the TMLE produces larger SEs than the IPTW method. In addition to crude summaries, primary and secondary outcomes were also summarized after PSW.

For assessment of residual confounding relating to age and estimated glomerular filtration rate (eGFR), the primary and secondary analyses were repeated post hoc on an age-restricted cohort including only individuals aged 45–80 years and an eGFR-restricted cohort including only individuals with eGFR $\geq$45 mL/min/1.73 m^2. Both estimation procedures (i.e., TMLE and IPTW) were tested in the post hoc restricted cohorts.

As specified in the study protocol, missing values in continuous covariates were imputed based on an individual's medication arm, sex, and age with a linear regression model. Categorical covariates were imputed based on the majority category within the individual's medication arm. To evaluate the impact of imputing missing data in covariates, we performed a sensitivity analysis using only sex and age as covariates, which were, by definition, fully observed. Indicator variables for whether the individual has missing covariate information was also included in the TMLE model, which will induce wider confidence intervals if the information is missing not at random.

Significance testing was based on a 5% level. All analyses were done with Palantir Foundry hosted within the N3C Data Enclave, a cloud-based FedRAMP moderate-security enclave (19). Foundry is built on an Apache Spark back end, and analysis for this study was done with Python 3.6 and R 3.5.1. Statistical modeling was done with the tmle, ipw, and survey R packages.

RESULTS

As of 23 February 2021, there were 3,453,825 individuals across 42 contributing sites in the N3C database, including 629,242 with COVID-19. Of these, 12,446 individuals from 35 contributing sites were eligible for inclusion in the analyses (Supplementary Fig. 1). Crude and weighted baseline information is presented in Table 1 with SMD for weighted characteristics. Of the study population, 62.5% was White and 53.4% female, and mean ± SD age was 58.6 ± 13.1 years. The individuals in the DPP4i exposure arm were older and had a lower BMI than the individuals in the GLP1-RA and SGLT2i subgroups (age 64 years vs. 56 and 58 years, respectively, and BMI 33 kg/m^2 vs. 37 and 35 kg/m^2). For DPP4i there were also higher proportions of individuals with chronic kidney disease or end-stage renal disease, myocardial infarction, congestive heart failure, cancer, dementia, or stroke and there was a slightly lower use of insulin. After PSW, the exposure populations were comparable (Table 1). The distribution of the truncated propensity scores used in the model is shown in Supplementary Fig. 2.

The crude 60-day mortality rate in all individuals in the study was 3.11% (387 of 12,446) and differed according to class of premorbid medication use: 2.06% (138 of 6,692) and 2.32% (85 of 3,665) for individuals prescribed GLP1-RA and SGLT2i, respectively, and 5.67% (199 of 3,511) for individuals prescribed DPP4i (Table 2). Total mortality rate over the observation period was 2.29% (153 of 6,692) and 2.48% (91 of 3,665) for individuals prescribed GLP1-RAs and SGLT2i and 6.18% (217 of 3,511) for individuals prescribed DPP4i. The other crude secondary outcomes, including the proportion of emergency room visits, hospitalizations, and mechanical ventilation within 14 days of a positive SARS-CoV-2 test, are shown in Table 2. The primary and secondary outcomes after PSW are shown in Supplementary Table 2. After PSW, the 60-day mortality and total mortality in individuals prescribed GLP1-RA was 2.31% (149 of 6,475) and 2.58% (167 of 6,475), respectively, versus 4.86% (154 of 3,175) and 5.33% (169 of 3,175) in individuals prescribed DPP4i (Supplementary Table 2). The weighted 60-day mortality and total mortality rate was 2.70% (95 of 3,504) and 2.87% (100 of 3,504) for individuals prescribed SGLT2i vs. 4.74% (163 of 3,445) and 5.18% (178 of 3,445) for individuals prescribed DPP4i (Supplementary Table 2).

The results from the TMLE and IPTW analyses are presented as odds ratios (ORs) with 95% CIs in Fig. 1. Crude ORs for the same cohort are shown in Supplementary Table 3. The following results are reported from the TMLE analyses. Compared with DPP4i users, GLP1-RA users had lower odds of 60-day mortality (OR 0.54 [95% CI 0.37, 0.80]). The estimated risk difference in 60-day mortality between GLP1-RA and DPP4i use was −0.020 (95% CI −0.035, −0.0044), or 2.0 fewer deaths per 100 COVID-19 cases.

GLP1-RA use was also associated with lower odds relative to DPP4i use of total mortality (OR 0.56 [95% CI 0.39, 0.82]) and emergency room visits (OR 0.81 [95% CI 0.69, 0.96]), hospitalization (OR 0.73 [95% CI 0.62, 0.87]), and mechanical ventilation (OR 0.73 [95% CI 0.55, 0.97]) within 14 days of COVID-19 diagnosis.

Similar to GLP1-RA use, SGLT2i use showed lower odds of 60-day mortality relative to DPP4i use (OR 0.66 [95% CI 0.50, 0.86]). The estimated risk difference in 60-day mortality between SGLT2i and DPP4i use was −0.016 (95% CI −0.026, −0.0057), or 1.6 fewer deaths per 100 COVID-19 cases. SGLT2i use was associated with lower odds of total mortality (OR 0.63 [95% CI 0.49–0.82]), emergency room visits (OR 0.90 [95% CI 0.81, 0.998]) and hospitalization (OR 0.82 [95% CI 0.73, 0.91]) within 14 days of COVID-19 diagnosis. The odds of mechanical ventilation were not significantly different between SGLT2i and DPP4i use. Effect estimates generated from the IPTW analyses were consistent with TMLE estimates (Fig. 1).

The post hoc restricted cohort analyses (age 45–80 years and eGFR $\geq$45 mL/min/1.73 m^2)) yielded consistent effect estimates, with wider CIs reflecting smaller populations (Supplementary Table 4). Results from the sensitivity analysis in the full population, with adjustment only for age and sex, were also consistent with the main analysis (Supplementary Table 3).

CONCLUSIONS

Emerging evidence from the COVID-19 pandemic suggests that individuals with type 2 diabetes comprise a significant portion of the affected population and are at higher risk for severe outcomes including hospitalization and death (1,2). Due to the lack of a

Table 1—Demographics and clinical characteristics before and after PSW, according to premorbid medication use

	Crude characteristics				Weighted characteristics					
	All (N = 12,446)	GLP 1-RA users (N = 6,692)	SGLT2i users (N = 3,665)	DPP4i users (N = 3,511)	GLP 1-RA users (N = 6,475)	DPP4i users (N = 3,175)	SMD	SGLT2i users (N = 3,504)	DPP4i users (N = 3,445)	SMD
Age, years (N = 12,446)†	58.6 ± 13.1	55.7 ± 12.6	57.9 ± 11.7	64.1 ± 12.9	57.91 ± 12.64	59.88 ± 13.46	0.15	60.00 ± 11.66	61.00 ± 13.36	0.08
Sex, female (N = 12,446)†	6,641 (53.36)	3,953 (59.07)	1,642 (44.80)	1,759 (50.10)	3,640 (56.22)	1,696 (53.42)	0.06	1,629 (46.50)	1,635 (47.46)	0.02
Race, White (N = 11,146)†	7,781 (62.52)	4,286 (64.05)	2,422 (66.08)	2,014 (57.36)	4,705 (72.67)	2,273 (71.60)	0.02	2,564 (73.16)	2,483 (72.08)	0.02
Ethnicity, Hispanic or Latino (N = 11,347)†	1,472 (11.83)	778 (11.63)	433 (11.81)	427 (12.16)	765 (11.81)	377 (11.87)	<0.01	412 (11.77)	411 (11.94)	0.01
Current smoker†	680 (5.46)	361 (5.39)	215 (5.87)	185 (5.27)	347 (5.36)	170 (5.37)	<0.01	196 (5.61)	188 (5.46)	0.01
BMI, kg/m^2 (N = 7,044)†	35.4 ± 8.2	37.2 ± 8.1	35.2 ± 7.8	32.7 ± 8.0	35.96 ± 6.23	34.87 ± 6.98	0.16	34.30 ± 5.83	33.83 ± 6.67	0.08
Body weight , kg (N = 6,883)	101.7 ± 26.6	106.7 ± 26.3	102.9 ± 26.0	92.8 ± 25.9	103.80 ± 20.27	98.61 ± 22.18	0.24	99.86 ± 19.61	96.86 ± 21.43	0.15
Glycated hemoglobin, % (N = 9,928)†	8.0 ± 1.9	8.0 ± 2.0	8.2 ± 1.8	7.8 ± 1.9	7.98 ± 1.77	7.97 ± 1.71	<0.01	8.11 ± 1.59	8.04 ± 1.76	0.04
Glycated hemoglobin, mmol/mol	63.9 ± 20.8	63.9 ± 21.9	66.1 ± 19.7	61.7 ± 20.8	63.7 ± 19.3	63.6 ± 18.7	<0.01	65.1 ± 17.4	64.4 ± 19.2	0.04
Heart rate, bpm (N = 5,305)†	85.0 ± 15.7	86.4 ± 15.2	85.1 ± 15.5	83.3 ± 16.4	85.55 ± 10.30	84.72 ± 11.35	0.08	84.49 ± 10.59	84.19 ± 11.08	0.03
Systolic blood pressure, mmHg (N = 7,330)†	131.7 ± 19.1	131.2 ± 18.5	130.3 ± 17.9	133.5 ± 20.9	131.76 ± 14.62	132.21 ± 15.20	0.04	131.31 ± 14.53	132.01 ± 15.18	0.05
Diastolic blood pressure, mmHg (N = 7,328)†	75.8 ± 11.9	76.9 ± 11.6	76.2 ± 11.3	73.5 ± 12.2	75.99 ± 9.31	75.20 ± 9.56	0.08	75.27 ± 9.06	74.84 ± 9.47	0.05
eGFR, mL/min/1.73 m^2 (N = 10,098)†	77.5 ± 29.3	81.0 ± 28.3	81.8 ± 25.3	68.5 ± 31.7	78.41 ± 26.91	75.23 ± 29.99	0.11	78.22 ± 24.18	75.79 ± 29.05	0.9
Creatinine, mg/dL (N = 11,225)	1.2 ± 1.2	1.1 ± 1.0	1.0 ± 0.7	1.5 ± 1.6	1.16 ± 1.08	1.36 ± 1.45	0.15	1.08 ± 0.73	1.30 ± 1.30	0.21
ALT, units/L (N = 9,116)	31.0 ± 37.8	31.3 ± 41.7	32.2 ± 34.1	29.4 ± 28.2	30.99 ± 38.62	30.82 ± 24.72	0.01	31.48 ± 34.07	31.01 ± 25.07	0.02
AST, units/L (N = 9,593)	31.6 ± 68.9	30.8 ± 83.4	29.9 ± 26.8	33.6 ± 55.5	30.95 ± 71.73	32.93 ± 41.61	0.03	30.16 ± 25.59	33.00 ± 42.71	0.08
Medication										
Metformin†	7,667 (61.60)	4,020 (60.07)	2,556 (69.74)	2,128 (60.61)	3,941 (60.87)	1,957 (61.64)	0.02	2,359 (67.33)	2,253 (65.39)	0.04
Sulfonylurea†	3,381 (27.17)	1,487 (22.22)	1,096 (29.90)	1,217 (34.66)	1,689 (26.08)	945 (29.77)	0.08	1,137 (32.45)	1,146 (33.27)	0.02
Insulin†	6,587 (52.92)	3,713 (55.48)	1,928 (52.61)	1,848 (52.63)	3,540 (54.67)	1,733 (54.60)	<0.01	1,806 (51.53)	1,780 (51.68)	<0.01
Statin†	7,476 (60.07)	3,824 (57.14)	2,331 (63.60)	2,274 (64.77)	3,846 (59.40)	1,954 (61.56)	0.03	2,230 (63.64)	2,193 (63.66)	<0.01
ACEi/ARB†	7,321 (58.82)	3,797 (56.74)	2,302 (62.81)	2,150 (61.24)	3,759 (58.06)	1,891 (59.56)	0.03	2,182 (62.29)	2,130 (61.83)	0.01
Remdesivir	965 (7.75)	460 (6.87)	273 (7.45)	343 (9.77)	486 (7.51)	284 (8.93)	0.05	281 (8.02)	313 (9.09)	0.04
Medical history										
Myocardial infarction†*	1,141 (9.17)	502 (7.50)	363 (9.90)	393 (11.19)	548 (8.47)	300 (9.44)	0.03	354 (10.11)	355 (10.30)	0.01
Congestive heart failure†*	2,106 (16.92)	909 (13.58)	623 (17.00)	781 (22.24)	1,014 (15.65)	556 (17.51)	0.05	642 (18.32)	661 (19.17)	0.02
Cancer or metastatic cancer†*	1,228 (9.87)	566 (8.46)	308 (8.40)	457 (13.02)	633 (9.77)	348 (10.96)	0.04	358 (10.21)	377 (10.95)	0.02
Dementia or stroke†*	1,674 (13.45)	693 (10.36)	406 (11.08)	707 (20.14)	828 (12.79)	479 (15.08)	0.07	486 (13.87)	541 (15.71)	0.05
Chronic kidney disease or end-stage renal disease†	2,716 (21.82)	1,236 (18.47)	597 (16.29)	1,109 (31.59)	1,422 (21.96)	812 (25.57)	0.08	741 (21.14)	832 (24.14)	0.07
Peripheral vascular disease*	4,306 (34.60)	2,306 (34.46)	1,115 (30.42)	1,340 (38.17)	2,374 (36.66)	1,110 (34.96)	0.04	1,161 (33.14)	1,189 (34.51)	0.03
Mild liver disease*	1,620 (13.02)	913 (13.64)	493 (13.45)	411 (11.71)	866 (13.37)	397 (12.50)	0.03	463 (13.22)	408 (11.84)	0.04

Continued on p. 1568

Table 1—Continued

	Crude characteristics				Weighted characteristics				
	All (N = 12,446)	GLP 1-RA users (N = 6,692)	SGLT2i users (N = 3,665)	DPP4i users (N = 3,511)	GLP 1-RA users (N = 6,475)	DPP4i users (N = 3,175)	SMD	SGLT2i users (N = 3,504)	DPP4i users (N = 3,445)	SMD
Severe liver disease*	250 (2.01)	107 (1.60)	57 (1.56)	99 (2.82)	116 (1.79)	88 (2.76)	0.07	58 (1.65)	84 (2.45)	0.06
Pulmonary disease*	3,197 (25.69)	1,761 (26.32)	870 (23.74)	923 (26.29)	1,698 (26.22)	837 (26.38)	0.00	844 (24.08)	883 (25.63)	0.04
Coronary artery disease	2,497 (20.06)	1,139 (17.02)	792 (21.61)	841 (23.95)	1,269 (19.60)	625 (19.69)	0.00	816 (23.29)	723 (20.98)	0.06
Heart failure	1,986 (15.96)	850 (12.70)	583 (15.91)	743 (21.16)	950 (14.67)	532 (16.74)	0.06	604 (17.23)	624 (18.10)	0.02
Hypertension	9,456 (75.98)	5,012 (74.90)	2,832 (77.27)	2,764 (78.72)	4,972 (76.80)	2,426 (76.41)	0.01	2,757 (78.68)	2,636 (76.51)	0.05
Liver disease	766 (6.15)	394 (5.89)	231 (6.30)	224 (6.38)	392 (6.05)	207 (6.53)	0.02	222 (6.35)	206 (5.99)	0.02

For categorical parameters, data are n (%). For continuous parameters, data are means ± SDs. For weighted characteristics, data are shown after imputation of missing values. ACEi, ACE inhibitors; ARB, angiotensin receptor blockers. *Charlson Comorbidity Index category. †Characteristics included in model.

large cohort for evaluation, whether and how premorbid antihyperglycemic medication use may impact COVID-19–related outcomes have remained unclear. We examined these associations using N3C, a real-world U.S. database supporting the conduct of reproducible, transparent science investigating hypotheses in connection with COVID-19. Among adults with COVID-19, both GLP1-RA and SGLT2i use were associated with lower 60-day mortality compared with DPP4i use, as well as decreased total mortality, emergency room visits, and hospitalizations. GLP1-RA use was also associated with decreased odds of mechanical ventilation. Effect estimates were consistent across different statistical estimation strategies. In this analysis, DPP4i were selected as an active comparator because they are branded agents that have been well studied with minimal other clinical effects of concern, are among the five second-line therapies with prevalent use (17), and were recently suggested as an optimal comparator as a relatively newer agent among second-line therapies (18).

To date, investigations of potential COVID-19 risk factors have provided insights into individual characteristics that may increase the risk for poorer COVID-19–associated outcomes, such as age, race/ethnicity, socioeconomic status, obesity, and patterns of comorbidities (1,4,13,26). Meanwhile, the results from observational data on the impact of diabetes-related medications in the setting of COVID-19 have yielded mixed findings. For example, DPP4 inhibition garnered early interest as a target for the reduction of coronavirus infection severity via several potential mechanisms including decreased viral entry and immunomodulation (27). In the European Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study no associations were found between DPP4i and COVID-19 outcomes among individuals with diabetes in multivariate analyses (28). In an analysis of inpatient data from Wuhan, China, no association was found of glucose-lowering medications including metformin, insulin, secretagogues, or DPP4i with in-hospital mortality (29). Smaller observational COVID-19 studies from Europe and Asia suggested either benefits or no difference in mortality and other adverse outcomes with DPP4i therapy (28,30–32). For example, a series of studies from northern Italy suggested that premorbid use of DPP4i (30) and inpatient treatment with DPP4i in the setting of severe COVID-19 infection (31) were associated with reduced mortality, with similar trends reported from South Korea (33). Together, the potentially discrepant findings from observational studies underscore the need for confirmation via nonexperimental studies with a new user design as well as trial designs (34).

GLP1-RA have established anti-inflammatory effects, and preclinical studies indicate that GLP1-RA reduce cytokine production and lung inflammation (27). SGLT2i also may exert anti-inflammatory effects via increased fat utilization, shifts in energy metabolism, increases in hematocrit, selective reduction of interstitial volume with minimal changes in blood volume, and maintenance of cytosolic pH (16,35). In addition, both SGLT2i and GLP1-RA are associated with reduced risk of cardiovascular events and chronic kidney disease progression in patients at high risk (14), a population associated with higher mortality in individuals with COVID-19 (2). A recent population-based cohort study in Denmark compared the association of GLP1-RA and DPP4-i use and COVID-19 outcomes with that of SGLT2i use and COVID-19 outcomes and found that the use of incretin-based therapies was not associated with improved clinical outcomes (36), although statistical power was limited by a small sample size.

The research findings should be interpreted with the limitations of the study in mind. The main limitation of the study involves comparisons by prevalent drug prescribing rather than by drug initiation. This limits the causal interpretation of our findings as well as the validity of confounding control, e.g., by HbA_{1c}, since these measures are already affected by prior treatment (37).

We observed large differences in characteristics, including age and comorbidities, across treatment cohorts, with DPP4i users being older and generally sicker than the other two groups. Analytic methods to account for measured differences in these individual patient characteristics led to considerable attenuation of the ORs for both GLP1-RA and SLGT2i. Residual confounding due to, for example, severity of comorbidities or unmeasured confounding could still bias our results, with the true OR being even closer to the null. The post hoc analyses in age-restricted cohorts, in which the difference in mean age between the

Table 2—Crude primary and secondary outcomes according to premorbid medication use

	All (N = 12,446)	GLP1-RA users (N = 6,692)	SGLT2i users (N = 3,665)	DPP4i users (N = 3,511)
60-day mortality, E (%)	387 (3.11)	138 (2.06)	85 (2.32)	199 (5.67)
Total mortality, E (%)*	423 (3.40)	153 (2.29)	91 (2.48)	217 (6.18)
Emergency room visit, E (%)†	3,878 (31.16)	1,930 (28.84)	1,074 (29.30)	1,285 (36.60)
Hospitalization, E (%)†	3,163 (25.41)	1,465 (21.89)	851 (23.22)	1,172 (33.38)
Mechanical ventilation (intubation or ventilation), E (%)†	827 (6.64)	387 (5.78)	226 (6.17)	300 (8.54)

E, number of outcome events (first event only); *N*, total number of individuals; %, proportion of individuals with the outcome. *During the observation period. †Within 14 days after a positive SARS-CoV-2 test.

DPP4i group versus the GLP1-RA or SGLT2i group was <1 year after PSW (age 60.6 vs. 61.6 years for GLP1-RA vs. DPP4i, respectively, and 61.4 vs. 62.0 years for SGLT2i vs. DPP4i), suggest that associations with mortality were robust, particularly for GLP1-RA users compared with DPP4i users (Table 3). Finally, the results may be impacted by population differences reflecting the fact that DPP4i may be used in patients with chronic kidney disease and that the combination of major comorbidities was more frequent among DPP4i users than among the GLP-1RA or SGLT2i users. In the post hoc analyses in an eGFR-restricted cohort, with the aim of capturing a population with moderate-to-good renal function, point estimates were consistent with the main analyses, although the smaller cohorts were not adequately powered for statistical significance.

The results of this observational analysis may also be biased by factors that are difficult to measure and include in the analysis. In particular, GLP1-RA are more expensive than either of the other medications; unfortunately, data on socioeconomic status were not available for use in the current study, which represents a significant limitation of the data set. Other potential unmeasured confounders include differences in prescribing patterns across different care settings (i.e., primary care versus academic medical centers), variable delays in seeking treatment, heterogenous COVID-19 treatment protocols or therapies across different care settings and in different regions of the U.S., and differential clinical trajectories such as hyperglycemia or glycemic variability during infection, which may in turn influence outcomes (38).

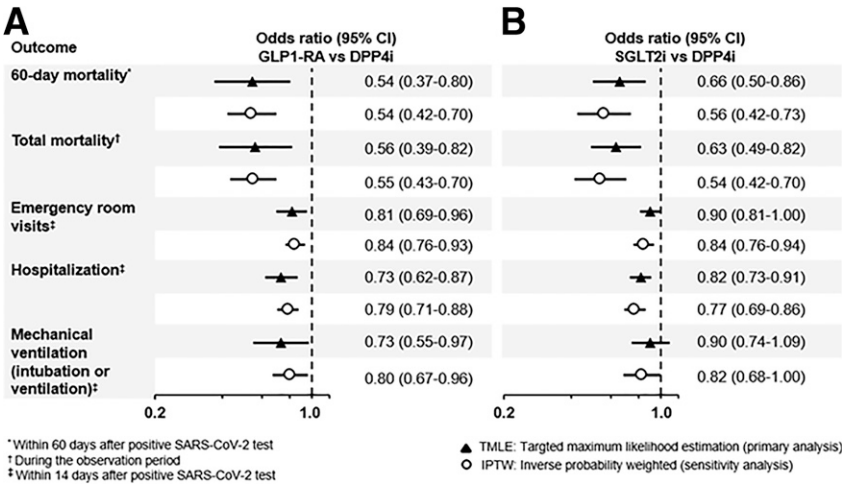

Figure 1—Forest plot depicting ORs for primary and secondary outcomes for patients with a COVID-19 diagnosis and prescription of a GLP1-RA, SGLT2i, or DPP4i, with TMLE (6) and IPTW (C). *A*: ORs for GLP1-RA vs. DPP4i. *B*: ORs for SGLT2i vs. DPP4i. *Within 60 days after positive SARS-CoV-2 test. †During the observation period. ‡Within 14 days after positive SARS-CoV-2 test.

There are several other limitations to the study. The COVID-19 diagnosis code does not represent a standardized time point in the clinical course, due to heterogeneity in timing of testing and assignment of COVID-19 diagnosis, which may contribute to heterogeneity in COVID-19 disease progression at the index date among individuals in the study. Individuals may be lost to follow-up; yet, underreporting of outcomes is expected to be independent of antihyperglycemic medication drug use with limited bias. The study population was defined by prescription of antihyperglycemic medication rather than diabetes ICD-10 code. Since EHR data, including diagnoses, prescriptions, and procedures, are only available when the individual is seen by a provider who contributes to the EHR system, any services conducted by providers external to the contributing EHR systems were not captured. This may limit data on outpatient diabetes regimens for new patient encounters. Although hospitalization rates were generally consistent with previously reported data (39), it is possible that some of the hospitalization events were not COVID-19 related; this limitation is partially addressed by the inclusion of other outcomes that are highly specific to COVID-19 such as mechanical ventilation. Per protocol, we did not consider comparisons with other antihyperglycemic medications, such as metformin monotherapy, and the study was not designed to assess interactions between different medications, such as how metformin may have enhanced associations of GLP1-RA or SGLT2i with improved outcomes. Finally, EHR data provide evidence of whether a drug was

Table 3—ORs in age-restricted cohort for 60-day mortality and secondary outcomes

	Model	GLP1-RA vs. DPP4i use	SGLT2i vs. DPP4i use
60-day mortality	Crude	0.44 (0.34–0.56)	0.45 (0.34–0.59)
	TMLE	0.59 (0.36–0.97)	0.69 (0.52–0.92)
	IPTW	0.52 (0.40–0.68)	0.60 (0.44–0.80)
Total mortality‡	Crude	0.44 (0.35–0.55)	0.44 (0.33–0.57)
	TMLE	0.60 (0.38–0.96)	0.67 (0.51–0.88)
	IPTW	0.53 (0.41–0.69)	0.58 (0.43–0.77)
Emergency room visit§	Crude	0.79 (0.72–0.87)	0.78 (0.70–0.87)
	TMLE	0.88 (0.74–1.04)	0.95 (0.85–1.07)
	IPTW	0.89 (0.80–1.00)	0.90 (0.80–1.00)
Hospitalization§	Crude	0.66 (0.60–0.73)	0.66 (0.59–0.74)
	TMLE	0.80 (0.67–0.95)	0.87 (0.77–0.98)
	IPTW	0.83 (0.74–0.93)	0.81 (0.72–0.91)
Mechanical ventilation (intubation or ventilation)§	Crude	0.75 (0.63–0.89)	0.79 (0.65–0.95)
	TMLE	0.77 (0.55–1.09)	0.95 (0.77–1.17)
	IPTW	0.79 (0.65–0.95)	0.87 (0.71–1.07)

Data are OR (95% CI). The age-restricted cohort included only individuals age 45–80 years (5,341 GLP1-RA users, 3,130 SGLT2i users, and 2,867 DPP4i users). TMLE: primary analysis. IPTW: sensitivity analysis. ‡During the observation period. §Within 14 days after a positive SARS-CoV-2 test.

prescribed—not whether the drug was reliably taken over time. The issue of unknown medication adherence may be particularly important in the setting of a pandemic, during which time economic or other disruptions may augment the challenges of daily adherence. ORs as a measure of association have limitations in the setting of IPTW. The N3C database is an evolving resource; the sample size is currently doubling every 4–6 weeks, and there are efforts to incorporate claims data and social determinants of heath. In the future, we hope to be able to address these limitations and potential residual confounding further. However, the overall effect sizes reported herein are large and robust to various analytic strategies and subgroup analyses, suggesting a potentially clinically relevant result.

There are several strengths of the study. The study population is geographically dispersed in the U.S. and demographically diverse, reflecting the impact of the pandemic on the nation. Currently, no diabetes-specific interventions are known to reduce the risk of a severe outcome of COVID-19, beyond the recommendations for the general population (3). This preliminary evidence for an association of antihyperglycemic medication use with COVID-19–related mortality and morbidity may be explored in the context of other infectious diseases or patient populations in the future. These data add to existing evidence for individual factors associated with risk for unfavorable outcomes.

A randomized global phase 3 trial of SGLT2i in the setting of diabetes and COVID-19 is currently ongoing and is expected to generate definitive data (Dapagliflozin in Respiratory Failure in Patients With COVID-19 [DARE-19], clinical trial reg. no. NCT04350593, ClinicalTrials.gov). A small prospective open-label blinded-evaluation study of semaglutide in COVID-19 is being conducted in Canada (Semaglutide to Reduce Myocardial Injury in PATIents With COVID-19 [SEMPATICO], NCT04615871). Given evidence from retrospective analyses, several randomized trials are planned or have been initiated to investigate the role for DPP4i, as well (NCT04542213, NCT04371978, NCT04341935, and NCT04365517).

In conclusion, this study provides evidence for antihyperglycemic medication class–based differences in COVID-19 outcomes, where premorbid GLP1-RA or SGLT2i prescribing is associated with lower mortality and other adverse clinical outcomes in the setting of a COVID-19 diagnosis as compared with DPP4i prescribing.

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