Diabetes Ther (2024) 15:1169–1186
https://doi.org/10.1007/s13300-024-01562-1

ORIGINAL RESEARCH

Association of Premorbid GLP-1RA and SGLT-2i Prescription Alone and in Combination with COVID-19 Severity

Klara R. Klein · Trine J. Abrahamsen · Anna R. Kahkoska · G. Caleb Alexander · Christopher G. Chute · Melissa Haendel · Stephanie S. Hong · Hemalkumar Mehta · Richard Moffitt · Til Stürmer · Kajsa Kvist · John B. Buse · on behalf of the N3C Consortium

Received: January 22, 2024 / Accepted: March 4, 2024 / Published online: March 27, 2024

ABSTRACT

Introduction: People with type 2 diabetes are at heightened risk for severe outcomes related to COVID-19 infection, including hospitalization, intensive care unit admission, and mortality. This study was designed to examine the impact of premorbid use of glucagon-like peptide-1 receptor agonist (GLP-1RA) monotherapy, sodium-glucose cotransporter-2 inhibitor (SGLT-2i) monotherapy, and concomitant GLP1-RA/SGLT-2i therapy on the severity of outcomes in individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods: Utilizing observational data from the National COVID Cohort Collaborative through September 2022, we compared outcomes in 78,806 individuals with a prescription of GLP-1RA and SGLT-2i versus a prescription of dipeptidyl peptidase 4 inhibitors (DPP-4i) within 24 months of a positive SARS-CoV-2 PCR test. We also compared concomitant GLP-1RA/SGLT-2i therapy to GLP-1RA and SGLT-2i monotherapy. The primary outcome was 60-day mortality,

Members of the N3C Consortium are listed in Acknowledgment section.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-024-01562-1.

K. R. Klein (✉) · A. R. Kahkoska · J. B. Buse
Division of Endocrinology and Metabolism, Department of Medicine, University of North Carolina School of Medicine, Campus Box #7172, 8072 Burnett Womack, 160 Dental Circle, Chapel Hill, NC 27599, USA
e-mail: klara_klein@med.unc.edu

T. J. Abrahamsen · K. Kvist
Novo Nordisk A/S, Søborg, Denmark

A. R. Kahkoska
Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, USA

G. C. Alexander
Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

G. C. Alexander · H. Mehta
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

G. C. Alexander · S. S. Hong
Division of General Internal Medicine, Johns Hopkins Medicine, Johns Hopkins University, Baltimore, MD, USA

C. G. Chute
Schools of Medicine, Public Health, and Nursing, Johns Hopkins University, Baltimore, MD 21287, USA

M. Haendel
Center for Health AI, University of Colorado School of Medicine, Aurora, CO, USA

measured from the positive test date. Secondary outcomes included emergency room (ER) visits, hospitalization, and mechanical ventilation within 14 days. Using a super learner approach and accounting for baseline characteristics, associations were quantified with odds ratios (OR) estimated with targeted maximum likelihood estimation (TMLE).

Results: Use of GLP-1RA (OR 0.64, 95% confidence interval [CI] 0.56–0.72) and SGLT-2i (OR 0.62, 95% CI 0.57–0.68) were associated with lower odds of 60-day mortality compared to DPP-4i use. Additionally, the OR of ER visits and hospitalizations were similarly reduced with GLP1-RA and SGLT-2i use. Concomitant GLP-1RA/SGLT-2i use showed similar odds of 60-day mortality when compared to GLP-1RA or SGLT-2i use alone (OR 0.92, 95% CI 0.81–1.05 and OR 0.88, 95% CI 0.76–1.01, respectively). However, lower OR of all secondary outcomes were associated with concomitant GLP-1RA/SGLT-2i use when compared to SGLT-2i use alone.

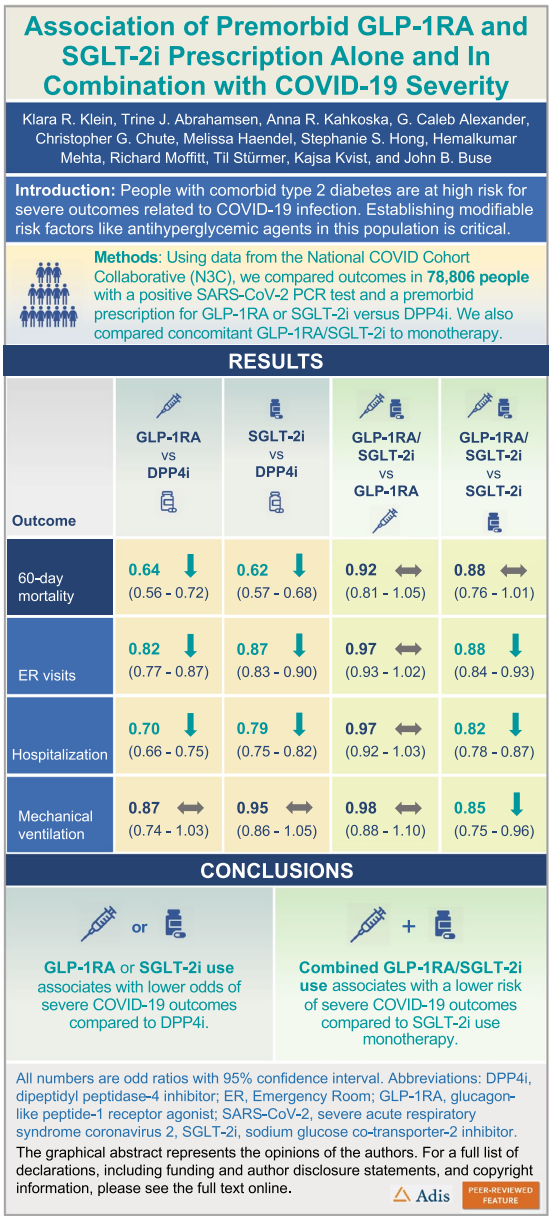
Conclusion: Among adults who tested positive for SARS-CoV-2, premorbid use of either GLP-1RA or SGLT-2i is associated with lower odds of mortality compared to DPP-4i. Furthermore, concomitant use of GLP-1RA and SGLT-2i is linked to lower odds of other severe COVID-19 outcomes, including ER visits, hospitalizations, and mechanical ventilation, compared to SGLT-2i use alone.

Graphical abstract available for this article.

R. Moffitt
Department of Biomedical Informatics, Stony Brook University, Stony Brook, NY, USA

T. Stürmer
Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Graphical Abstract:



Keywords: COVID-19; SARS-CoV-2; Type 2 diabetes; SGLT-2i; GLP-1RA; Observational data; National COVID Cohort Collaborative (N3C)

Key Summary Points

Why carry out this study?

We previously demonstrated that a premorbid prescription of either glucagon-like peptide-1 receptor agonists (GLP-1RA) or sodium-glucose cotransporter-2 inhibitors (SGLT-2i), compared to dipeptidyl peptidase 4 inhibitors (DPP-4i), is associated with reduced severity of COVID-19 through analyses of observational data from the National COVID Cohort Collaborative (N3C).

With access to a sixfold larger N3C cohort gathered over approximately 3 years of the pandemic (1 January 2020–15 September 2022), we reassessed the association of GLP-1RA or SGLT-2i prescriptions alone and in combination with COVID-19 severity.

What was learned from this study?

Prescriptions for GLP-1RA and SGLT-2i continue to be associated with lower COVID-19 mortality compared to prescriptions for DPP-4i.

When compared to the use of SGLT-2i alone, concomitant prescription of GLP-1RA/SGLT-2i is associated with lower odds of secondary outcomes, including emergency room visits, hospitalizations, and mechanical ventilation, suggesting that there may be additive, protective effects from the concomitant use of GLP-1RA/SGLT-2i in the context of COVID-19.

DIGITAL FEATURES

This article is published with digital features, including graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.25257022.

INTRODUCTION

Chronic comorbid conditions such as diabetes are a risk factor for severe adverse coronavirus disease 2019 (COVID-19) outcomes, including hospitalization, invasive mechanical ventilation, and death [1–3]. Early efforts aimed to identify modifiable risk factors to minimize COVID-19 severity in this population. Glycemic control is thought to be one high-risk factor associated with severity of COVID-19 infection in people living with diabetes [4, 5].

Using observational data from the National COVID Cohort Collaborative (N3C), we previously demonstrated that premorbid prescription of two antihyperglycemic medication classes, glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose-cotransporter 2 inhibitors (SGLT-2i), compared to dipeptidyl peptidase 4 inhibitors (DPP-4i) prescription, associate with lower odds of multiple adverse outcomes among people with diabetes diagnosed with COVID-19 prior to 25 February 2021 ($n = 12{,}446$) [6]. It is unknown whether this association remains robust to the development of new variants, natural immunity, and effective vaccines. We thus reevaluated the association of GLP-1RA and SGLT-2i prescriptions on severe COVID-19 outcomes in an approximately sixfold larger cohort ($n = 78{,}806$) that covered a longer period of the pandemic. Additionally, given increasing prescriptions of SGLT-2i and GLP-1RA in combination, two agents which operate through distinct mechanisms that may provide unique benefits in the setting of COVID-19, we examined the impact of concomitant GLP-1RA/SGLT-2i prescription on COVID-19 severity.

METHODS

Study Design

In this study, we analyzed real-world observational data of 78,806 adults from the N3C cohort [7], which includes individuals with at least one positive PCR test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after 1 January 2020 [6, 8, 9]. We gained permission to use the deidentified electronic medical health medical record data via the data-use request process through the National Covid Cohort Collaborative (N3C) enclave. Our general

study design and methods, including statistical analyses, have been previously described [6].

Briefly, we analyzed data through 15 September 2022 and included adults aged ≥ 18 years who had any prescription of GLP-1RA, SGLT-2i or DPP-4i within 24 months prior to a COVID-19 diagnosis. A diagnosis of type 2 diabetes was not required for inclusion in the study. Prescription information reflects prescriptions written during ambulatory visits and does not reflect dispensing or adherence. In analyses where DPP4i were used as the comparator, we excluded those persons with concomitant prescription of DPP-4i and GLP-1RA/SGLT-2i (Electronic Supplementary Material [ESM] Fig. S1). We did not exclude people who were included in our prior analysis ($n = 12,446$).

In this article, cohorts with a prescription for a particular drug will be referred to as arms (e.g., "GLP-1RA arm"). To ensure consistency with our prior analysis, individuals with prescriptions for both GLP-1RA and SGLT-2i ($n = 11,594$) contributed to both exposure arms in the comparison with individuals with prescriptions for DPP-4i. Additional analyses compared concomitant GLP-1RA/SGLT-2i prescription ("GLP-1RA/SGLT-2i arm") to prescription with GLP-1RA or SGLT-2i alone.

We defined the first positive SARS-CoV-2 PCR as the index date and the primary outcome as 60-day mortality following a positive PCR. Secondary outcomes included emergency room (ER) visits, hospitalization, and mechanical ventilation (intubation or ventilation) within 14 days of a positive PCR test. We used data up to 24 months before the index date to identify drug exposure, continuous variables, medical history, and demographics.

Statistical Analysis

Standardized mean differences (SMD) were used to compare baseline characteristics before and after propensity score weighting (PSW) [10, 11]. In the primary analysis, we used targeted maximum likelihood estimation (TMLE) to estimate odds ratios (ORs) and 95% confidence interval (CI) [10, 11]. For sensitivity analyses, we used inverse probability treatment-weighted (IPTW) logistic regression. We performed post-hoc analyses on two restricted cohorts (individuals aged 45–80 years and individuals with an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min) and a sensitivity analysis using only sex and age as covariates to evaluate the impact of imputing missing data in covariates. Analyses were performed using Palantir Foundry hosted within the N3C enclave, a cloud-based FedRAMP moderate secure enclave [7], and statistical programs Python and R.

Ethics Compliance

The protocol of this study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) on 5 October 2020 (Number 37860). The University of North Carolina at Chapel Hill Office of Human Research Ethics determined that the study protocol did not constitute research on human subjects.

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave (https://covid.cd2h.org) and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NCATS U24 TR002306 and Axle Informatics Subcontract NCATS-P00438-B. The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol IRB00249128 or individual site agreements with NIH.

This study research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories), and scientists who have contributed to the ongoing development of this community resource [7]. The study was performed in accordance with the Declaration of Helsinki (1964) and its later amendments [12].

RESULTS

By 15 September 2022, 75 sites across the USA had contributed data on 15,540,911 individuals to the N3C database, of whom 4,671,046

had a positive SARS-CoV-2 PCR test. The present study included 78,806 individuals across 63 sites. While the first analysis evaluated 13 months (January 2020 to February 2021), this subsequent analysis extends to 33 months during the evolving pandemic (January 2020 to September 2022). Table 1 presents crude and weighted characteristics of the study sample. The total study population had a mean (± standard deviation [SD]) age of 58.7 (± 13.3) years. Those individuals in the DPP-4i arm were older and had a lower mean body mass index (BMI) than those in the GLP-1RA and SGLT-2i arms, respectively. The prevalence of most comorbid conditions was higher in the DPP-4i arm, but the prevalence of comorbid cardiovascular-related diseases was highest in the SGLT-2i arm. The subpopulations of interest were similar following PSW (Table 1). Where PSW exposure arms remained imbalanced, TMLE analysis improved the chance of correct model specification.

Crude primary and secondary outcomes are summarized in ESM Table S1. The GLP-1RA and SGLT-2i arms associated with a lower 60-day mortality, with proportions of 2.68% and 2.97%, respectively, compared to 7.00% in the DPP-4i arm. Figure 1 provides ORs (95% CI) for all outcomes estimated by TMLE comparing the GLP-1RA or SGLT-2i arms to the DPP-4i arm. ORs for the primary outcome 60-day mortality were lower for the GLP-1RA (OR 0.64, 95% CI 0.56–0.72) and SGLT-2i (OR 0.62, 95% CI 0.57–0.68) arms compared to the DPP-4i arm. ORs were also significantly lower for all secondary outcomes with GLP-1RA and SGLT-2i prescription, with the exception of mechanical ventilation. IPTW analyses are presented in ESM Fig. S2. ORs for 60-day mortality were lower for the GLP1-RA (OR 0.64, 95% CI 0.56–0.72) and SGLT2i (OR 0.62, 95% CI 0.57–0.68) arms compared to the DPP4i arm. GLP1-RA and SGLT2i use was also associated with lower ORs for all secondary outcomes, including ER visits, hospitalization, and mechanical ventilation. Two post-hoc cohort analyses (age restricted: 45–80 years and eGFR restricted: ≥ 45 mL/min/1.73 m^2; ESM Tables S2, S3) and a sensitivity analysis for age and sex adjustment (ESM Table S4) yielded results similar to the primary analysis with lower odds for all outcomes, except for mechanical ventilation.

Crude and weighted baseline information for individuals prescribed GLP-1RA and SGLT-2i alone and in combination are presented in Table 2. The percentage of individuals with comorbid conditions, including renal, hepatic and cardiovascular-related disease, was slightly lower in the concomitant GLP-1RA/SGLT-2i arm compared to the monotherapy arms. Conversely, use of other antihyperglycemic agents was higher in the GLP-1RA/SGLT-2i arm. Exposure arms were similar following PSW.

Comparison of crude primary and secondary outcomes for the GLP-1RA/SGLT-2i arm and the GLP-1RA and SGLT-2i arms (ESM Table S5) indicated that concomitant GLP-1RA/SGLT-2i prescription was associated with lower 60-day mortality (2.58%) compared to monotherapy (2.83% for GLP-1RA and 3.24% for SGLT-2i). The concomitant GLP-1RA/SGLT-2i prescription arm showed lower rates for secondary outcomes than the SGLT-2i arm, but similar rates when compared to the GLP-1RA arm.

TMLE-estimated ORs comparing the GLP-1RA and SGLT-2i arms, respectively, with the concomitant GLP-1RA/SGLT-2i arm (Fig. 2) resulted in similar odds for 60-day mortality for the GLP-1RA/SGLT-2i co-prescription arm compared to the GLP-1RA (OR 0.92, 95% CI 0.81–1.05) and SGLT-2i (OR 0.88, 95% CI 0.76–1.01) monotherapy arms. Lower odds were observed for all secondary outcomes, including ER visits, hospitalization, and mechanical ventilation in the concomitant GLP-1RA/SGLT-2i arm compared to the SGLT-2i monotherapy arm, whereas similar odds were observed when concomitant GLP-1RA/SGLT-2i use was compared to GLP-1RA use alone. IPTW-estimated ORs comparing the GLP-1RA and SGLT-2i arms with the concomitant GLP-1RA/SGLT-2i arm (ESM Fig. S3) demonstrated lower rates for 60-day mortality for both comparisons. Concomitant GLP-1RA/SGLT-2i prescription was also associated with lower odds for all secondary outcomes, although mechanical ventilation only trended toward lower odds in the comparison to GLP-1RA alone.

Table 1 Demographics and clinical characteristics before and after propensity score weighting, according to premorbid prescription for total study population and for glucagon-like peptide-1 receptor agonist, sodium-glucose cotransporter-2 inhibitor, and dipeptidyl peptidase-4 inhibitor arms

Demographics and clinical characteristics	Crude characteristics				Weighted characteristics[a]					
	All (*N* = 78,806)	GLP-1RA users (*N* = 42,799)	SGLT-2i users (*N* = 25,421)	DPP-4i users (*N* = 20,200)	GLP-1RA users (*N* = 41,703)	DPP-4i users (*N* = 17,931)	SMD	SGLT-2i users (*N* = 24,752)	DPP-4i users (*N* = 19,633)	SMD
Age[b], years (*N* = 78,806)	58.7 ± 13.3	55.6 ± 12.8	58.6 ± 12.0	64.4 ± 12.8	57.87 ± 12.93	60.11 ± 13.44	0.17	60.59 ± 11.93	61.45 ± 13.31	0.07
Sex[b], Female (*N* = 78,804)	43,618 (55.35)	26,474 (61.86)	11,492 (45.21)	10,500 (51.98)	24,534 (58.83)	9943 (55.45)	0.07	11,795 (47.66)	9571 (48.75)	0.02
Race[b], White (*N* = 69,668)	51,352 (65.16)	28,536 (66.67)	17,341 (68.22)	12,113 (59.97)	31,871 (76.42)	13,584 (75.76)	0.02	19,143 (77.34)	15,015 (76.48)	0.02
Ethnicity[b], Hispanic or Latino (*N* = 71,382)	9689 (12.29)	4705 (10.99)	2971 (11.69)	3087 (15.28)	5059 (12.13)	2402 (13.39)	0.04	3252 (13.14)	2710 (13.80)	0.02
Current smoker[b] (*N* = 78,806)	15,657 (19.87)	8078 (18.87)	5144 (20.24)	4275 (21.16)	8116 (19.46)	3605 (20.11)	0.02	5070 (20.48)	4065 (20.71)	0.01
BMI[b], kg/m^2 (*N* = 48,807)	34.8 ± 8.6	36.7 ± 8.6	34.3 ± 8.2	31.8 ± 7.8	35.40 ± 6.94	34.04 ± 6.93	0.20	33.39 ± 6.43	32.96 ± 6.64	0.07
Body weight, kg (*N* = 49,851)	104.2 ± 36.8	109.1 ± 36.9	103.5 ± 34.8	96.5 ± 37.5	105.86 ± 29.89	102.20 ± 31.39	0.12	100.35 ± 28.09	100.48 ± 31.34	0.00
Glycated hemoglobin[b], % (*N* = 61,142)	7.8 ± 2.0	7.8 ± 2.0	8.0 ± 1.8	7.8 ± 1.9	7.82 ± 1.79	7.90 ± 1.69	0.04	7.99 ± 1.61	7.96 ± 1.74	0.02
Heart rate[b], bpm (*N* = 27,459)	84.8 ± 15.7	86.0 ± 15.2	84.6 ± 15.7	83.2 ± 16.6	85.39 ± 9.46	84.78 ± 10.12	0.06	84.36 ± 9.85	84.19 ± 9.99	0.02
Systolic blood pressure[b], mmHg (*N* = 44,132)	131.3 ± 19.6	131.1 ± 18.7	129.6 ± 19.3	133.4 ± 21.0	131.78 ± 14.66	132.47 ± 14.89	0.05	131.03 ± 15.52	131.82 ± 14.97	0.05
Diastolic blood pressure[b], mmHg (*N* = 43,590)	76.0 ± 11.8	76.9 ± 11.4	75.6 ± 11.5	74.5 ± 12.3	76.28 ± 8.83	75.69 9.30	0.06	75.33 ± 9.11	75.18 ± 9.24	0.02
eGFR[b], mL/min/1.73 m^2 (*N* = 61,803)	77.1 ± 29.0	81.3 ± 28.1	79.4 ± 26.3	67.5 ± 30.7	78.13 ± 26.50	74.64 ± 28.55	0.13	75.94 ± 24.66	74.13 ± 27.86	0.07

Table 1 continued

Demographics and clinical characteristics	Crude characteristics				Weighted characteristics[a]					
	All (*N* = 78,806)	GLP-1RA users (*N* = 42,799)	SGLT-2i users (*N* = 25,421)	DPP-4i users (*N* = 20,200)	GLP-1RA users (*N* = 41,703)	DPP-4i users (*N* = 17,931)	SMD	SGLT-2i users (*N* = 24,752)	DPP-4i users (*N* = 19,633)	SMD
Creatinine, mg/dL (*N* = 70,055)	1.2 ± 1.2	1.1 ± 1.1	1.1 ± 0.8	1.5 ± 1.6	1.17 ± 1.10	1.35 ± 1.43	0.15	1.13 ± 0.84	1.34 ± 1.37	0.19
Alanine aminotransferase, U/L (*N* = 64,967)	30.7 ± 62.2	30.1 ± 38.9	31.7 ± 50.2	30.7 ± 94.5	29.92 ± 37.90	31.88 ± 79.27	0.03	31.00 ± 44.46	31.98 ± 81.54	0.01
Aspartate aminotransferase, U/L (*N* = 64,535)	31.0 ± 98.4	29.0 ± 56.3	30.4 ± 62.7	34.6 ± 161.0	29.37 ± 57.19	34.02 ± 135.05	0.04	30.52 ± 55.41	34.18 ± 139.07	0.03
Medication										
Metformin[b]	48,645 (61.73)	25,501 (59.58)	17,433 (68.58)	12,843 (63.58)	25,515 (61.18)	11,422 (63.70)	0.05	16,711 (67.52)	13,123 (66.84)	0.01
Sulfonylurea[b]	20,850 (26.46)	9167 (21.42)	7287 (28.67)	7230 (35.79)	10,639 (25.51)	5328 (29.72)	0.09	7819 (31.59)	6441 (32.81)	0.03
Insulin[a]	38,185 (48.45)	21,835 (51.02)	12,807 (50.38)	9449 (46.78)	21,025 (50.41)	9067 (50.56)	0.00	12,027 (48.59)	9381 (47.78)	0.02
Statin[b]	53,377 (67.73)	27,198 (63.55)	18,823 (74.05)	14,850 (73.51)	27,779 (66.61)	12,603 (70.29)	0.08	18,211 (73.58)	14,383 (73.26)	0.01
ACEi/ARB[b]	49,458 (62.76)	25,572 (59.75)	17,713 (69.68)	13,084 (64.77)	25,595 (61.37)	11,415 (63.66)	0.05	16,803 (67.89)	13,113 (66.79)	0.02
Remdesivir	399 (0.51)	182 (0.43)	145 (0.57)	111 (0.55)	186 (0.45)	96 (0.53)	0.01	142 (0.57)	106 (0.54)	0.00
Medical history										
Myocardial infarction[b,c]	7337 (9.31)	3152 (7.36)	3083 (12.13)	2035 (10.07)	3408 (8.17)	1616 (9.01)	0.03	2774 (11.21)	2092 (10.65)	0.02
Congestive heart failure[b,c]	13,943 (17.69)	5993 (14.00)	5463 (21.49)	4051 (20.05)	6518 (15.63)	3091 (17.24)	0.04	5087 (20.55)	3905 (19.89)	0.02
Cancer or metastatic cancer[b,c]	7881 (10.00)	3743 (8.75)	2470 (9.72)	2466 (12.21)	4043 (9.70)	1904 (10.62)	0.03	2642 (10.68)	2169 (11.05)	0.01
Dementia or stroke[b,c]	10,917 (13.85)	4834 (11.29)	3482 (13.70)	3769 (18.66)	5536 (13.27)	2718 (15.16)	0.05	3792 (15.32)	3168 (16.13)	0.02

Table 1 continued

Demographics and clinical characteristics	Crude characteristics				Weighted characteristics[a]					
	All (*N* = 78,806)	GLP-1RA users (*N* = 42,799)	SGLT-2i users (*N* = 25,421)	DPP-4i users (*N* = 20,200)	GLP-1RA users (*N* = 41,703)	DPP-4i users (*N* = 17,931)	SMD	SGLT-2i users (*N* = 24,752)	DPP-4i users (*N* = 19,633)	SMD
Chronic kidney disease or end-stage renal disease[b]	17,294 (21.95)	8080 (18.88)	5031 (19.79)	5992 (29.66)	9139 (21.91)	4466 (24.91)	0.07	5669 (22.90)	4810 (24.50)	0.04
Peripheral vascular disease[c]	17,775 (22.56)	9063 (21.18)	5766 (22.68)	5048 (24.99)	9514 (22.81)	4063 (22.66)	0.00	5915 (23.90)	4589 (23.37)	0.01
Mild liver disease[c]	11,332 (14.38)	6625 (15.48)	3860 (15.18)	2457 (12.16)	6307 (15.12)	2372 (13.23)	0.05	3649 (14.74)	2492 (12.69)	0.06
Severe liver disease[c]	1484 (1.88)	669 (1.56)	523 (2.06)	451 (2.23)	702 (1.68)	392 (2.18)	0.04	518 (2.09)	412 (2.10)	0.00
Pulmonary disease	21,325 (27.06)	11,991 (28.02)	6609 (26.00)	5309 (26.28)	11,523 (27.63)	4907 (27.36)	0.01	6401 (25.86)	5245 (26.72)	0.02
Coronary artery disease	16,531 (20.98)	7493 (17.51)	6455 (25.39)	4742 (23.48)	8230 (19.73)	3638 (20.29)	0.01	6331 (25.58)	4434 (22.58)	0.07
Heart failure	13,232 (16.79)	5617 (13.12)	5201 (20.46)	3876 (19.19)	6107 (14.64)	2956 (16.48)	0.05	4870 (19.68)	3697 (18.83)	0.02
Hypertension	57,543 (73.02)	30,595 (71.49)	19,365 (76.18)	15,146 (74.98)	30,644 (73.48)	13,110 (73.11)	0.01	18,953 (76.57)	14,534 (74.03)	0.06
Liver disease	4694 (5.96)	2418 (5.65)	1627 (6.40)	1242 (6.15)	2428 (5.82)	1105 (6.16)	0.01	1595 (6.45)	1179 (6.01)	0.02

Values are presented in table as the number of subjects with the percentage in parentheses (categorical parameters) or as the mean ± standard deviation (continuous parameters)

To ensure consistency with our prior analysis [6], individuals with prescriptions for both GLP-1RA and SGLT-2i ($n = 11,594$) contributed to both exposure arms in the comparison with DPP-4i

ACEi ACE inhibitors, *ARB* angiotensin receptor blockers, *bpm* beats per minute, *BMI* body mass index, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *eGFR* estimated glomerular filtration rate, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *SGLT-2i* sodium glucose co-transporter 2 inhibitor, *SMD* standard mean deviation

[a]For weighted characteristics, data are shown after imputation of missing values

[b]Characteristics included in model

[c]Comorbidities were defined based on the individual categories of diseases or diagnoses used to generate the updated Charlson Comorbidity Index [33]

DISCUSSION

Since the COVID-19 pandemic began, diabetes has emerged as a risk factor for severe COVID-19, with results from meta-analyses suggesting a nearly twofold increased mortality risk [1]. Given that COVID-19 was the fourth leading cause of death in the USA in 2022 [6, 13], effective strategies to improve COVID-19 outcomes among people with diabetes are needed. To this end, antihyperglycemic medication use presents an attractive target with plausible biological mechanisms. GLP-1RA and SGLT2i inhibitors have garnered particular attention due to their anti-inflammatory effects and well-established cardiovascular risk reduction in high-risk individuals [14, 15]. We and others have demonstrated an association between the use of GLP-1RA and SGLT-2i and reduced adverse outcomes of COVID-19 [6, 16–22]. Whether this association remained as the pandemic progressed, with novel variants and increasing natural and vaccine-induced immunity, has not been established. Using a sixfold larger cohort than our original analysis [6] and data from a timepoint (15 September 2022) further into the pandemic, the present study provides further evidence supporting the association of GLP-1RA and SGLT-2i with improved COVID-19 outcomes compared to premorbid DPP-4i prescription.

In contrast, the DARE-19 study examined acute prescription of SGLT-2i in the setting of COVID-19. This double-blind randomized controlled trial investigated whether the SGLT-2i dapagliflozin provided organ protection in non-critically ill hospitalized people with COVID-19 and at least one cardiometabolic risk factor when initiated within 4 days of SARS-CoV-2 infection. A trend toward benefit was observed in the composite outcome of organ dysfunction or death but was not statistically significant [23]. It is plausible that premorbid SGLT-2i use, as examined in our study, provides more protection than initiation after SARS-CoV-2 infection. Consistently, results from other studies suggest that SGLT2i and GLP-1RA monotherapy confer lower risk of outcomes compared to DPP4i monotherapy when prescribed prior to hospitalization for COVID-19 [19].

Additionally, we found that concomitant GLP-1RA/SGLT-2i prescription trended toward improved 60-day mortality when compared to GLP-1RA or SGLT2i monotherapy but did not reach statistical significance. Dual therapy was associated with similar odds of secondary outcomes as GLP-1RA monotherapy but was

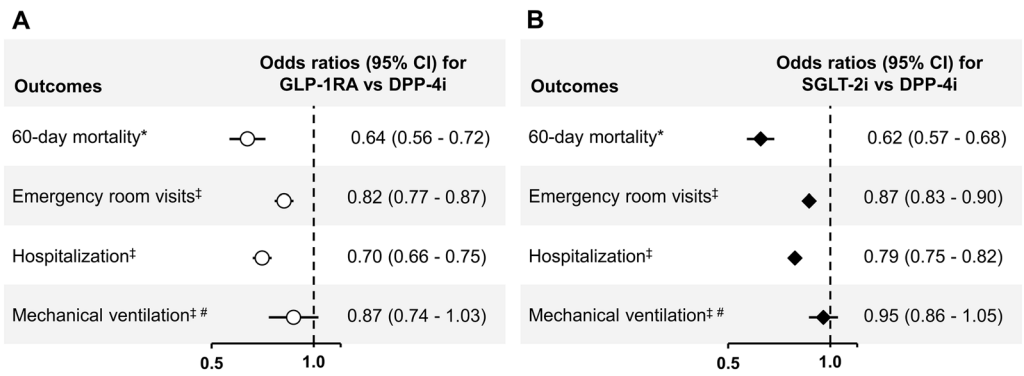


Fig. 1 Forest plot depicting TMLE-estimated ORs for primary and secondary outcomes for people with a COVID-19 diagnosis and prescription for GLP-1RA (**A**) and SGLT-2i (**B**) use compared with DPP-4i use, respectively. Single asterisk (*) indicates within 60 days after positive SARS-CoV-2 PCR test; double dagger sign (†) indicates within 14 days after positive SARS-CoV-2 test; hash sign (#) indicates mechanical ventilation (intubation or ventilation). *CI* Confidence interval, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *OR* odds ratio, *SGLT-2i* sodium glucose co-transporter 2 inhibitor, *TMLE* targeted maximum likelihood estimation

Table 2 Demographics and clinical characteristics before and after propensity score weighting, according to premorbid prescription for total, glucagon-like peptide-1 receptor agonist (GLP-1RA) monotherapy, sodium-glucose cotransporter-2 inhibitor (SGLT-2i) monotherapy, and concomitant GLP-1RA/SGLT-2i arms

Characteristics, mean ± standard deviation or *n* (%)	Crude characteristics			Weighted characteristics[a]					
	GLP-1RA mono (*N* = 36,942)	SGLT-2i mono (*N* = 20,656)	GLP-1RA/SGLT-2i (*N* = 11,594)	GLP-1RA mono users (*N* = 36,885)	GLP-1RA/SGLT-2i (*N* = 10,644)	SMD	SGLT-2i mono (*N* = 20,427)	GLP-1RA/SGLT-2i (*N* = 11,161)	SMD
Age[b], years (*N* = 69,192)	55.6 ± 13.2	59.9 ± 12.2	57.0 ± 11.3	55.99 (13.08)	56.79 (11.51)	0.07	58.96 (12.27)	58.29 ± 11.22	0.06
Sex[b], female (*N* = 38,664)	23,857 (64.58)	8874 (42.96)	5933 (51.17)	22,659 (61.43)	6075 (57.07)	0.09	9326 (45.66)	5283 (47.34)	0.03
Race[b], White (*N* = 46,336)	24,351 (65.92)	13,968 (67.62)	8017 (69.15)	28,431 (77.08)	8267 (77.67)	0.01	16,209 (79.35)	8877 (79.54)	0,00
Ethnicity[b], Hispanic or Latino (*N* = 8242)	4163 (11.27)	2718 (13.16)	1361 (11.74)	4206 (11.40)	1241 (11.66)	0.01	2601 (12.73)	1399 (12.53)	0.01
Current smoker[b] (*N* = 13,420)	6968 (18.86)	4228 (20.47)	2224 (19.18)	6984 (18.94)	2035 (19.12)	0.00	4121 (20.18)	2242 (20.09)	0.00
BMI[b], kg/m^2 (*N* = 42,681)	36.8 ± 8.7	33.1 ± 7.8	35.7 ± 8.2	36.54 ± 6.96	36.13 ± 6.79	0.06	33.96 ± 6.79	34.58 ± 6.33	0.09
Body weight, kg (*N* = 44.037)	109.3 ± 37.7	99.8 ± 33.4	107.5 ± 35.8	109.10 ±30.52	107.89 ±29.30	0.04	101.62 ± 28.09	105.32 ± 29.17	0.13
Glycated hemoglobin[b], % (*N* = 54,300)	7.7 ± 2.1	8.0 ± 1.8	8.3 ± 1.8	7.86 ± 1.89	8.12 ± 1.60	0.15	8.09 ± 1.68	8.16 ± 1.60	0.04
Heart rate[b], bpm (*N* = 24,393)	85.9 ± 15.2	83.4 ± 15.8	86.2 ± 15.0	85.91 ± 9.46	86.03 ± 9.24	0.01	84.55 ± 9.99	85.17 ± 9.20	0.06
Systolic blood pressure[b], mmHg (*N* = 39,179)	131.5 ± 18.8	129.6 ± 19.5	130.1 ± 18.7	131.28 ± 13.97	130.99 ± 14.67	0.02	129.71 ± 14.91	129.87 ± 14.33	0.01
Diastolic blood pressure[b], mmHg (*N* = 38,721)	77.1 ± 11.5	75.3 ± 11.6	76.0 ± 11.2	76.80 ± 8.70	76.44 ± 8.75	0.04	75.63 ± 9.08	75.77 ± 8.63	0.02
eGFR[b], mL/min/1.73 m^2 (*N* = 54,712)	80.4 ± 28.9	77.8 ± 26.4	82.0 ± 25.7	81.19 ± 26.51	81.23 ± 24.61	0.00	79.55 ± 24.37	80.42 ± 23.58	0.04
Creatinine, mg/dL (*N* = 61,411)	1.1 ± 1.1	1.1 ± 0.8	1.0 ± 0.8	1.12 ± 1.04	1.05 ± 0.79	0.08	1.08 ± 0.78	1.06 ± 0.78)	0.02
Alanine aminotransferase, U/L (*N* = 56,871)	30.2 ± 41.1	32.2 ± 62.1	30.8 ± 27.5	30.56 ± 37.16	30.35 ± 24.65	0.01	32.37 ± 55.79	30.84 ± 26.54	0.04
Aspartate aminotransferase, U/L (*N* = 56,465)	29.4 ± 60.3	31.7 ± 87.4	28.3 ± 28.7	29.66 ± 55.05	28.20 ± 27.26	0.03	31.56 ± 77.54	28.40 ± 27.67	0.05
Medication									
Metformin[b]	21,148 (57.25)	14,058 (68.06)	8676 (74.83)	22,676 (61.48)	7247 (68.08)	0.14	14,373 (70.36)	8057 (72.19)	0.04

Table 2 continued

Characteristics, mean ± standard deviation or *n* (%)	Crude characteristics			Weighted characteristics[a]					
	GLP-1RA mono (*N* = 36,942)	SGLT-2i mono (*N* = 20,656)	GLP-1RA/SGLT-2i (*N* = 11,594)	GLP-1RA mono users (*N* = 36,885)	GLP-1RA/SGLT-2i (*N* = 10,644)	SMD	SGLT-2i mono (*N* = 20,427)	GLP-1RA/SGLT-2i (*N* = 11,161)	SMD
Sulfonylurea[b]	7921 (21.44)	6587 (31.89)	3744 (32.29)	8873 (24.06)	2997 (28.16)	0.09	6566 (32.14)	3661 (32.80)	0.01
Insulin[b]	18,063 (48.90)	8823 (42.71)	6981 (60.21)	19,084 (51.74)	6117 (57.47)	0.12	9918 (48.55)	5747 (51.49)	0.06
Statin[b]	22,629 (61.26)	15,193 (73.55)	9131 (78.76)	24,142 (65.45)	7682 (72.18)	0.15	15,371 (75.25)	8514 (76.29)	0.02
ACEi/ARB[b]	21,287 (57.62)	14,231 (68.90)	8382 (72.30)	22,538 (61.10)	7086 (66.58)	0.11	14,280 (69.91)	7859 (70.41)	0.01
Remdesivir	161 (0.44)	135 (0.65)	43 (0.37)	169 (0.46)	38 (0.36)	0.02	137 (0.67)	42 (0.37)	0.04
Medical history									
Myocardial infarction[b,c]	2494 (6.75)	2575 (12.47)	1125 (9.70)	2729 (7.40)	895 (8.41)	0.04	2364 (11.57)	1205 (10.80)	0.02
Congestive heart failure[b,c]	4997 (13.53)	4596 (22.25)	1870 (16.13)	5198 (14.09)	1615 (15.18)	0.03	4118 (20.16)	2054 (18.40)	0.04
Cancer or metastatic cancer[b,c]	3353 (9.08)	2168 (10.50)	975 (8.41)	3301 (8.95)	957 (8.99)	0.00	2006 (9.82)	1044 (9.35)	0.02
Dementia or stroke[b,c]	4222 (11.43)	2943 (14.25)	1442 (12.44)	4306 (11.67)	1305 (12.26)	0.02	2785 (13.63)	1471 (13.18)	0.01
Chronic kidney disease or end-stage renal disease[b]	7232 (19.58)	4122 (19.96)	2179 (18.79)	7162 (19.42)	2099 (19.72)	0.01	4009 (19.63)	2151 (19.27)	0.01
Peripheral vascular disease[c]	7763 (21.01)	4641 (22.47)	2543 (21.93)	7832 (21.23)	2310 (21.70)	0.01	4496 (22.01)	2546 (22.81)	0.02
Mild liver disease[c]	5621 (15.22)	2905 (14.06)	1962 (16.92)	5635 (15.28)	1827 (17.16)	0.05	2971 (14.54)	1825 (16.35)	0.05
Severe liver disease[c]	578 (1.56)	436 (2.11)	194 (1.67)	580 (1.57)	180 (1.69)	0.01	422 (2.07)	193 (1.73)	0.02
Pulmonary disease[c]	10,480 (28.37)	5139 (24.88)	3132 (27.01)	10,420 (28.25)	2946 (27.68)	0.01	5195 (25.43)	2937 (26.32)	0.02
Coronary artery disease	6074 (16.44)	5309 (25.70)	2599 (22.42)	6405 (17.37)	2207 (20.74)	0.09	4964 (24.30)	2691 (24.11)	0.00
Heart failure	4698 (12.72)	4392 (21.26)	1747 (15.07)	4877 (13.22)	1,524 (14.31)	0.03	3,952 (19.35)	1,903 (17.05)	0.06
Hypertension	25,942 (70.22)	15,440 (74.75)	9105 (78.53)	26,475 (71.78)	8196 (77.00)	0.12	15,345 (75.12)	8709 (78.03)	0.07
Liver disease	2060 (5.58)	1286 (6.23)	713 (6.15)	2061 (5.59)	678 (6.37)	0.03	1273 (6.23)	687 (6.16)	0.00

Values are presented in table as the number of subjects with the percentage in parentheses (categorical parameters) or as the mean ± standard deviation (continuous parameters)

ACEi ACE inhibitors, *ARB* angiotensin receptor blockers, *bpm* beats per minute, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *mono* monotherapy, *SGLT-2i* sodium glucose co-transporter 2 inhibitor, *SMD* standard mean deviation

[a]For weighted characteristics, data are shown after imputation of missing values

[b]Characteristics included in model

[c]Comorbidities were defined based on the individual categories of diseases or diagnoses used to generate the updated Charlson Comorbidity Index [33]

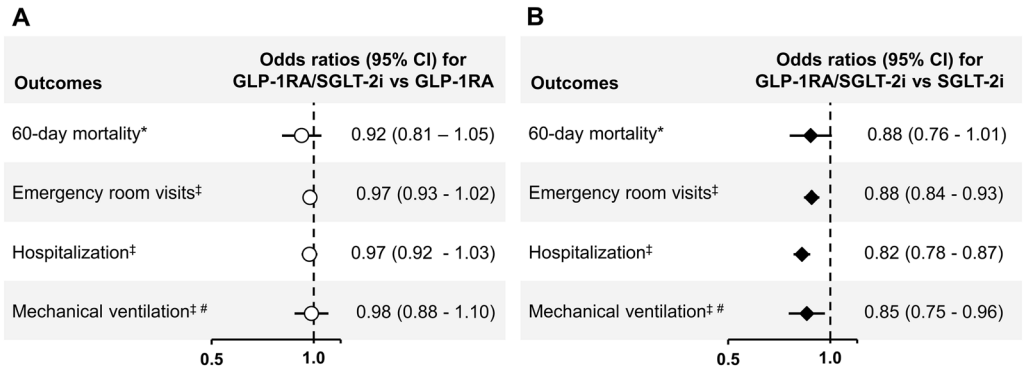


Fig. 2 Forest plot depicting TMLE-estimated ORs for primary and secondary outcomes for people with a COVID-19 diagnosis and prescription for GLP-1RA and SGLT-2i combined use compared with GLP-1RA monotherapy (**A**) and SGLT-2i (**B**) monotherapy, respectively. Single asterisk (*) indicates within 60 days after positive SARS-CoV-2 PCR test; double dagger sign (‡) indicates within 14 days after positive SARS-CoV-2 test; hash sign (#) indicates mechanical ventilation (intubation or ventilation). *CI* confidence interval, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *OR* odds ratio, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SGLT-2i* sodium glucose co-transporter 2 inhibitor, *TMLE* targeted maximum likelihood estimation

associated with statistically significantly lower odds of all secondary outcomes when compared with SGLT-2i monotherapy. These findings are consistent with those from randomized trials suggesting that the cardiorenal benefits of GLP-1RA and SGLT-2i are independent of each other [24]. The impact of dual therapy is encouraging given that users of GLP-1RA/SGLT-2i combination therapy were more likely to be treated with additional antihyperglycemic agents, particularly insulin, as many studies have suggested that insulin use is associated with a higher risk of adverse outcomes and may indicate more advanced diabetes [19–21].

DPP-4i, which was chosen as a comparator, also has hypothesized immunomodulatory qualities that solicited attention as a potential COVID-19 therapeutic [25]. Yet, the results of observational studies of DPP-4i-related impact on COVID-19 have been inconclusive. The findings of a recent small randomized-controlled trial suggest improvement in COVID-19 severity in hospitalized people with hyperglycemia treated with DPP-4i compared to those receiving insulin alone [26]. The results of meta-analyses also suggest improved outcomes with DPP-4i compared to non-users [27]. Our data suggest that GLP-1RA and SGLT-2i outperform DPP-4i, although prospective data are limited.

The mechanism by which GLP-1RA and SGLT-2i protect against severe COVID-19 outcomes is unknown but may relate to established anti-inflammatory, immunomodulatory, cardiorenal, and metabolic effects [28, 29]. While their effects are likely multifactorial, future studies should examine whether these agents modulate innate or vaccine-induced immunity in people living with diabetes. The results from several studies indicate an association between lower effectiveness of COVID-19 vaccines for severe COVID-19-related outcomes in people with diabetes [30, 31]. Consistently, low anti-SARS-CoV-2 antibody levels on hospital admission associate with severe COVID-19-related outcomes in people with type 2 diabetes [32]. Whether the use of GLP-1RA, SGLT2i, or GLP-1RA/SGLT2i in combination modulate innate or vaccine-induced antibody response should be explored as a potential mechanism for their benefit in the setting of COVID-19.

Our observational study is limited by the potential of residual confounding, with particular attention to the socioeconomic demographic receiving these agents.

Nevertheless, our findings are consistent with randomized-controlled trials that have repeatedly demonstrated the cardiorenal and mortality benefits of these two classes of medications.

CONCLUSION

Our study supports earlier findings that premorbid GLP-1RA or SGLT-2i prescribing was associated with lower mortality and other secondary outcomes in the setting of COVID-19 compared to DPP-4i prescribing. Furthermore, we provide the first evidence of potential synergistic effects from concomitant GLP-1RA/SGLT-2i use on COVID-19 severity.

ACKNOWLEDGEMENTS

We are grateful for the vision of the National Centers for Advancing Translational Science to support the development of N3C as a freely available resource, to the dozens of healthcare system leaders who generously agreed to participate in this audacious effort by sharing their data, to the hundreds of people who enabled the data sharing, to the thousands of healthcare workers and their supporters who collected the data, and to the millions of patients and their families whose peril in this pandemic is reflected herein. The authors gained permission to use the data via the data-use request process through the National Covid Cohort Collaborative (N3C) enclave. We gratefully acknowledge the following core contributors to N3C: Adam B. Wilcox, Adam M. Lee, Alexis Graves, Alfred (Jerrod) Anzalone, Amin Manna, Amit Saha, Amy Olex, Andrea Zhou, Andrew E. Williams, Andrew Southerland, Andrew T. Girvin, Anita Walden, Anjali A. Sharathkumar, Benjamin Amor, Benjamin Bates, Brian Hendricks, Brijesh Patel, Caleb Alexander, Carolyn Bramante, Cavin Ward-Caviness, Charisse Madlock-Brown, Christine Suver, Christopher Chute, Christopher Dillon, Chunlei Wu, Clare Schmitt, Cliff Takemoto, Dan Housman, Davera Gabriel, David A. Eichmann, Diego Mazzotti, Don Brown, Eilis Boudreau, Elaine Hill, Elizabeth Zampino, Emily Carlson Marti, Emily R. Pfaff, Evan French, Farrukh M Koraishy, Federico Mariona, Fred Prior, George Sokos, Greg Martin, Harold Lehmann, Heidi Spratt, Hemalkumar Mehta, Hongfang Liu, Hythem Sidky, J.W. Awori Hayanga, Jami Pincavitch, Jaylyn Clark, Jeremy Richard Harper, Jessica Islam, Jin Ge, Joel Gagnier, Joel H. Saltz, Joel Saltz, Johanna Loomba, John Buse, Jomol Mathew, Joni L. Rutter, Julie A. McMurry, Justin Guinney, Justin Starren, Karen Crowley, Katie Rebecca Bradwell, Kellie M. Walters, Ken Wilkins, Kenneth R. Gersing, Kenrick Dwain Cato, Kimberly Murray, Kristin Kostka, Lavance Northington, Lee Allan Pyles, Leonie Misquitta, Lesley Cottrell, Lili Portilla, Mariam Deacy, Mark M. Bissell, Marshall Clark, Mary Emmett, Mary Morrison Saltz, Matvey B. Palchuk, Melissa A. Haendel, Meredith Adams, Meredith Temple-O'Connor, Michael G. Kurilla, Michele Morris, Nabeel Qureshi, Nasia Safdar, Nicole Garbarini, Noha Sharafeldin, Ofer Sadan, Patricia A. Francis, Penny Wung Burgoon, Peter Robinson, Philip R.O. Payne, Rafael Fuentes, Randeep Jawa, Rebecca Erwin-Cohen, Rena Patel, Richard A. Moffitt, Richard L. Zhu, Rishi Kamaleswaran, Robert Hurley, Robert T. Miller, Saiju Pyarajan, Sam G. Michael, Samuel Bozzette, Sandeep Mallipattu, Satyanarayana Vedula, Scott Chapman, Shawn T. O'Neil, Soko Setoguchi, Stephanie S. Hong, Steve Johnson, Tellen D. Bennett, Tiffany Callahan, Umit Topaloglu, Usman Sheikh, Valery Gordon, Vignesh Subbian, Warren A. Kibbe, Wenndy Hernandez, Will Beasley, Will Cooper, William Hillegass, and Xiaohan Tanner Zhang. Details of all contributions are available at https://covid.cd2h.org/core-contributors.

Medical Writing, Editorial, and Other Assistance. The authors thank Kati Rehberg and Greg R. Markby from Novo Nordisk A/S (Denmark) for medical writing and editorial assistance with the preparation of this article.

Author Contributions. John Buse is the guarantor of this article. Klara Klein and John Buse led the writing of this article. Klara Klein, Anna Kahkoska, Trine Abrahamsen, Kajsa Kvist, and John Buse contributed to the study concept and design. Christopher Chute contributed to data curation, data integration, data quality assurance, clinical data model expertise, and N3C phenotype definition. Trine Abrahamsen performed data analysis through full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Klara Klein drafted the manuscript. All authors, including Caleb Alexander, Melissa Haendel, Stephanie S. Hong, Hemalkumar Mehta, Richard Moffitt, and Til Stürmer, provided input in relation to clinical context, data analysis, contributed to manuscript review and editing, and approved the final version.

Funding. Klara Klein was supported by the University of North Carolina Department of Medicine and School of Medicine Physician Scientist Training Program. Anna Kahkoska was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant KL2TR002490. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Anna Kahkoska received research grants from the Diabetes Research Connection and the American Diabetes Association, and a prize from the National Academy of Medicine, outside the submitted work. Til Stürmer received investigator-initiated research funding and support as Principal Investigator (R01 AG056479) from the National Institute on Aging (NIA), and as Co-Investigator (R01 HL118255, R01 MD011680), National Institutes of Health (NIH). Hemalkumar Mehta was supported by the National Institute on Aging (K01AG070329). John Buse was supported by grants from the National Institutes of Health's National Center for Advancing Translational Sciences (UL1TR002489, UM1TR004406). The journal's Rapid Service Fee was funded by Novo Nordisk.

Data Availability. The data that support the findings of this study are available with permission from https://covid.cd2h.org/, but as privacy and/ or ethical restrictions apply, they are not publicly available. Some or all datasets generated and analyzed during the current study are available on reasonable request from the corresponding author.

Declarations

Conflict of Interest. Klara Klein has received personal compensation for consultation from Novo Nordisk. Trine Abrahamsen and Kajsa Kvist are full-time employees and stockholder of Novo Nordisk. Anna Kahkoska has received support from Novo Nordisk for travel to present data. G. Caleb Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics, a healthcare consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Melissa Haendel is a founder of Pryzm Health and is supported by grants from the National Institutes of Health and the Patient-Centered Outcomes Research Institute. Til Stürmer received salary support as Director of Comparative Effectiveness Research (CER), NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR002489), the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim), from pharmaceutical companies (Novo Nordisk), and from a contribution from Dr. Nancy A. Dreyer to the Department of Epidemiology, University of North Carolina at Chapel Hill. He does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, and Novo Nordisk. John B. Buse has received grant support from Bayer, Boehringer-Ingelheim, Carmot, Corcept, Dexcom, Eli Lilly, Insulet, MannKind, Novo

Nordisk, and vTv Therapeutics; consulting contracts from Alkahest, Altimmune, Anji, Aqua Medical Inc, AstraZeneca, Boehringer-Ingelheim, CeQur, Corcept Therapeutics, Dasman Diabetes Center (Kuwait), Eli Lilly, embecta, Fortress Biotech, GentiBio, Glyscend, Insulet, Mediflix, Medscape, Mellitus Health, Metsera, Moderna, Novo Nordisk, Pendulum Therapeutics, Praetego, ReachMD, Stability Health, Tandem, Terns Inc, and Vertex; expert witness service for Medtronic MiniMed; and stock options from Glyscend, Mellitus Health, Pendulum Therapeutics, Praetego, and Stability Health. Christopher G. Chute, Stephanie S Hong, Hemalkumar Mehta and Richard Moffitt have no conflicts of interest to declare.

Ethical Approval. The N3C Data Enclave is managed under the authority of the U.S. National Institutes of Health (NIH); information can be found at https://ncats.nih.gov/n3c/resources. The N3C Publication Committee confirmed that this manuscript is in accordance with N3C data use and attribution policies; however, this content is solely the responsibility of the authors and does not necessarily represent official views of NIH or the N3C program. The protocol of this study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) on 5 October 2020 (Number 37860), and the University of North Carolina at Chapel Hill Office of Human Research Ethics determined that the study protocol did not constitute research on human subjects. The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave (https://covid.cd2h.org) and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NCATS U24 TR002306 and Axle Informatics Subcontract: NCATS-P00438-B. The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol IRB00249128 or individual site agreements with NIH. This study research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists who have contributed to the ongoing development of this community resource [7]. The study was performed in accordance with the Declaration of Helsinki (1964) and its later amendments [12].

REFERENCES

1. Hartmann-Boyce J, Rees K, Perring JC, et al. Risks of and from SARS-CoV-2 infection and COVID-19 in people with diabetes: a systematic review of reviews. Diabetes Care. 2021;44(12):2790–811.

2. Floyd JS, Walker RL, Kuntz JL, et al. Association between diabetes severity and risks of COVID-19 infection and outcomes. J Gen Intern Med. 2023;38(6):1484–92.

3. de Almeida-Pititto B, Dualib PM, Zajdenverg L, et al. Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. Diabetol Metab Syndr. 2020;12:75.

4. Singh AK, Khunti K. COVID-19 and diabetes. Annu Rev Med. 2022;73:129–47.

5. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff DC. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol. 2020;14(4):813–21.

6. Kahkoska AR, Abrahamsen TJ, Alexander GC, et al. Association between glucagon-like peptide 1 receptor agonist and sodium-glucose cotransporter 2 inhibitor use and COVID-19 outcomes. Diabetes Care. 2021;44(7):1564–72.

7. Haendel MA, Chute CG, Bennett TD, et al. The national COVID cohort collaborative (N3C): rationale, design, infrastructure, and deployment. J Am Med Inf Assoc. 2021;28(3):427–43.

8. Bennett TD, Moffitt RA, Hajagos JG, et al. Clinical characterization and prediction of clinical severity of SARS-CoV-2 infection among US adults using data from the US National COVID Cohort Collaborative. JAMA Netw Open. 2021;4(7): e2116901.

9. National COVID Cohort Collaborative. https://github.com/National-COVID-Cohort-Collaborative. Accessed 4 Apr 2023.

10. Pang M, Schuster T, Filion KB, Eberg M, Platt RW. Targeted maximum likelihood estimation for pharmacoepidemiologic research. Epidemiology. 2016;27(4):570–7.

11. Schuler MS, Rose S. Targeted maximum likelihood estimation for causal inference in observational studies. Am J Epidemiol. 2017;185(1):65–73.

12. World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed 4 Apr 2023.

13. Ahmad FB, Cisewski JA, Xu J, Anderson RN. Provisional mortality data—United States, 2022. MMWR Morb Mortal Wkly Rep. 2023;72(18):488–92.

14. Scheen AJ. SGLT2 inhibition during the COVID-19 epidemic: friend or foe? Diabetes Metab. 2020;46(5):343–4.

15. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020;41(3):bnaa011. https://doi.org/10.1210/endrev/bnaa011.

16. Heald AH, Jenkins DA, Williams R, et al. Mortality in people with type 2 diabetes following SARS-CoV-2 infection: a population level analysis of potential risk factors. Diabetes Ther. 2022;13(5):1037–51.

17. Nyland JE, Raja-Khan NT, Bettermann K, et al. Diabetes, drug treatment, and mortality in COVID-19: a multinational retrospective cohort study. Diabetes. 2021;70(12):2903–16.

18. Wander PL, Lowy E, Beste LA, et al. Prior glucose-lowering medication use and 30-day outcomes among 64,892 veterans with diabetes and COVID-19. Diabetes Care. 2021;44(12):2708–13.

19. Zhu Z, Zeng Q, Liu Q, Wen J, Chen G. Association of glucose-lowering drugs with outcomes in patients with diabetes before hospitalization for COVID-19: a systematic review and network meta-analysis. JAMA Netw Open. 2022;5(12): e2244652.

20. Nguyen NN, Ho DS, Nguyen HS, et al. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: a meta-analysis. Metabolism. 2022;131: 155196.

21. Chen Y, Lv X, Lin S, Arshad M, Dai M. The association between antidiabetic agents and clinical outcomes of COVID-19 patients with diabetes: a Bayesian network meta-analysis. Front Endocrinol (Lausanne). 2022;13:895458.

22. Zhan K, Weng L, Qi L, et al. Effect of antidiabetic therapy on clinical outcomes of COVID-19 patients with type 2 diabetes: a systematic review and meta-analysis. Ann Pharmacother. 2022;57:776–86.

23. Kosiborod MN, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021;9(9):586–94.

24. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med. 2021;385(10):896–907.

25. Narayanan N, Naik D, Sahoo J, Kamalanathan S. Dipeptidyl peptidase 4 inhibitors in COVID-19: beyond glycemic control. World J Virol. 2022;11(6):399–410.

26. Guardado-Mendoza R, Garcia-Magana MA, Martinez-Navarro LJ, et al. Effect of linagliptin plus insulin in comparison to insulin alone on metabolic control and prognosis in hospitalized patients with SARS-CoV-2 infection. Sci Rep. 2022;12(1):536.

27. Pal R, Banerjee M, Mukherjee S, Bhogal RS, Kaur A, Bhadada SK. Dipeptidyl peptidase-4 inhibitor use and mortality in COVID-19 patients with diabetes mellitus: an updated systematic review and meta-analysis. Ther Adv Endocrinol Metab. 2021;12:2042018821996482.

28. Banerjee Y, Pantea Stoian A, Silva-Nunes J, et al. The role of GLP-1 receptor agonists

during COVID-19 pandemia: a hypothetical molecular mechanism. Expert Opin Drug Saf. 2021;20(11):1309–15.

29. Salmen T, Pietroșel VA, Mihai BM, et al. Non-insulin novel antidiabetic drugs mechanisms in the pathogenesis of COVID-19. Biomedicines. 2022;10(10):2624.

30. van den Berg JM, Remmelzwaal S, Blom MT, et al. Effectiveness of COVID-19 vaccines in adults with diabetes mellitus: a systematic review. Vaccines (Basel). 2022;11(1):24.

31. Agrawal U, Katikireddi SV, McCowan C, et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): a prospective cohort study. Lancet Respir Med. 2021;9(12):1439–49.

32. Mink S, Saely CH, Leiherer A, et al. Anti-SARS-CoV-2 antibody levels predict outcome in COVID-19 patients with type 2 diabetes: a prospective cohort study. Sci Rep. 2023;13(1):18326.

33. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–82.