SUPPLEMENTARY MATERIAL

Association of premorbid GLP-1RA and SGLT-2i prescription alone and in combination with COVID-19 Severity

Authors

Klara R. Klein[1], Trine J. Abrahamsen[2], Anna R. Kahkoska[1,3], G. Caleb Alexander[4,5,6], Christopher G. Chute[7], Melissa Haendel[8], Stephanie S. Hong[6], Hemalkumar Mehta[5], Richard Moffitt[9], Til Stürmer[10], Kajsa Kvist[2], John B. Buse[1] on behalf of the N3C consortium

Affiliations

[1]Division of Endocrinology and Metabolism, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

[2]Trine Julie Abrahamsen, PhD: Novo Nordisk A/S, Søborg, Denmark

[3]Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill

[4]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[5]Department of Epidemiology, Johns Hopkins, Bloomberg School of Public Health, Baltimore, MD

[6]Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD

[7]Schools of Medicine, Public Health, and Nursing; Johns Hopkins University, Baltimore, MD 21287

[8]Center for Health AI, University of Colorado School of Medicine, Aurora, CO

[9] Department of Biomedical Informatics, Stony Brook University, Stony Brook, NY

[10]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Corresponding Author

Klara R. Klein, Division of Endocrinology and Metabolism, Campus Box #7172, 8072 Burnett Womack, 160 Dental Circle, Chapel Hill NC 27599, Tel: (919)-966-0134, Fax (919)-966-6025, E-mail: klara_klein@med.unc.edu

TABLES:

Supplementary Table S1. Crude primary and secondary outcomes, according to premorbid medication use of GLP-1RA, SGLT-2i, and DDP-4i**.**

Outcome	**All (N = 78,806)**	**GLP-1RA (N = 42,799)**	**SGLT-2i (N = 25,421)**	**DPP-4i (N = 20,200)**
60-day mortality* – E (%)	3,070 (3.90)	1,148 (2.68)	756 (2.97)	1,413 (7.00)
Emergency room visit‡ – E (%)	23,366 (29.65)	11,503 (26.88)	7,279 (28.63)	7,205 (35.67)
Hospitalization‡ – E (%)	18,109 (22.98)	7,975 (18.63)	5,556 (21.86)	6,425 (31.81)
Mechanical ventilation (Intubation or ventilation)‡ – E (%)	3,318 (4.21)	1,619 (3.78)	1,083 (4.26)	991 (4.91)

* Within 60 days after positive SARS-CoV-2 test, ‡ Within 14 days after a positive SARS-CoV-2 test, N: Total number of individuals, E: number of outcome events (first event only), %: proportion of individuals with the outcome

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT-2i. sodium glucose co-transporter 2 inhibitor

Supplementary Table S2. Odds ratios in age-restricted cohort for 60-day mortality and secondary outcomes for use of GLP-1RA vs. DPP-4i and use of SGLT-2i vs. DPP-4i[#].

Outcome	**Model**	**GLP-1RA vs DPP-4i OR (95% CI)**	**SGLT-2i vs DPP-4i OR (95% CI)**
60-day mortality*	TMLE	0.64 (0.59-0.69)	0.57 (0.52-0.63)
	IPTW	0.64 (0.59-0.70)	0.53 (0.49-0.58)
Emergency room visit‡	TMLE	0.78 (0.75-0.81)	0.80 (0.77-0.84)
	IPTW	0.79 (0.76-0.82)	0.80 (0.77-0.83)
Hospitalization‡	TMLE	0.70 (0.67-0.73)	0.74 (0.71-0.77)
	IPTW	0.69 (0.67-0.72)	0.72 (0.69-0.75)
Mechanical ventilation (Intubation or ventilation)‡	TMLE	1.01 (0.92-1.10)	0.99 (0.90-1.08)
	IPTW	1.02 (0.94-1.12)	0.97 (0.89-1.06)

[#] The age-restricted cohort included only individuals aged 45–80 years (33,579 GLP-1RA users, 21,625 SGLT-2i users, and 16,503 DPP-4i users).

* Within 60 days after positive SARS-CoV-2 test, ‡ Within 14 days after a positive SARS-CoV-2 test

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; IPTW, inverse probability treatment weighted; OR, odds ratio; SGLT-2i, sodium glucose co-transporter 2 inhibitor; TMLE, targeted maximum likelihood estimation

Supplementary Table S3. Odds ratios in eGFR-restricted cohort for 60-day mortality and secondary outcomes for use of GLP-1RA vs. DPP-4i and use of SGLT-2i vs. DPP-4i[#].

Outcome	**Model**	**GLP-1RA vs DPP-4i OR (95% CI)**	**SGLT-2i vs DPP-4i OR (95% CI)**
60-day mortality*	TMLE	0.58 (0.49 - 0.69)	0.59 (0.53 - 0.67)
	IPTW	0.60 (0.53 - 0.68)	0.53 (0.47 - 0.59)
Emergency room visit[‡]	TMLE	0.80 (0.75 - 0.86)	0.86 (0.82 - 0.90)
	IPTW	0.79 (0.76 - 0.83)	0.83 (0.79 - 0.87)
Hospitalization[‡]	TMLE	0.67 (0.62 - 0.72)	0.76 (0.72 - 0.80)
	IPTW	0.69 (0.65 - 0.72)	0.73 (0.70 - 0.77)
Mechanical ventilation (Intubation or ventilation)[‡]	TMLE	0.80 (0.64 - 1.00)	0.89 (0.79 - 1.01)
	IPTW	0.80 (0.71 - 0.89)	0.88 (0.78 - 0.98)

[#] The eGFR-restricted cohort included only individuals with eGFR ≥ 45 mL/min (38,730 GLP-1RA users, 23,128 SGLT-2i users, and 16,172 DPP-4i users).

* Within 60 days after positive SARS-CoV-2 test, [‡] Within 14 days after a positive SARS-CoV-2 test

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; IPTW, inverse probability treatment weighted; OR, odds ratio; SGLT-2i, sodium glucose co-transporter 2 inhibitor; TMLE, targeted maximum likelihood estimation

Supplementary Table S4. Odds ratios adjusted for age and sex (sensitivity analysis using a simple model) for 60-day mortality and secondary outcomes for use of GLP-1RA vs. DPP-4i and use of SGLT-2i vs. DPP-4i**.**

Outcome	**Model**	**GLP-1RA vs DDP-4i OR (95% CI)**	**SGLT-2i vs DDP-4i OR (95% CI)**
60-day mortality*	TMLE	0.64 (0.59 - 0.69)	0.57 (0.52 - 0.63)
	IPTW	0.64 (0.59 - 0.70)	0.53 (0.49 - 0.58)
Emergency room visit‡	TMLE	0.78 (0.75 - 0.81)	0.80 (0.77- 0.84)
	IPTW	0.79 (0.76 - 0.82)	0.80 (0.77 - 0.83)
Hospitalization‡	TMLE	0.70 (0.67 - 0.73)	0.74 (0.71 - 0.77)
	IPTW	0.69 (0.67 - 0.72)	0.72 (0.69 - 0.75)
Mechanical ventilation (Intubation or ventilation)‡	TMLE	1.01 (0.92 - 1.10)	0.99 (0.90 - 1.08)
	IPTW	1.02 (0.94 - 1.12)	0.97 (0.89 - 1.06)

* Within 60 days after positive SARS-CoV-2 test, ‡ Within 14 days after a positive SARS-CoV-2 test

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; IPTW, inverse probability treatment weighted; OR, odds ratio; SGLT-2i, sodium glucose co-transporter 2 inhibitor; TMLE, targeted maximum likelihood estimation

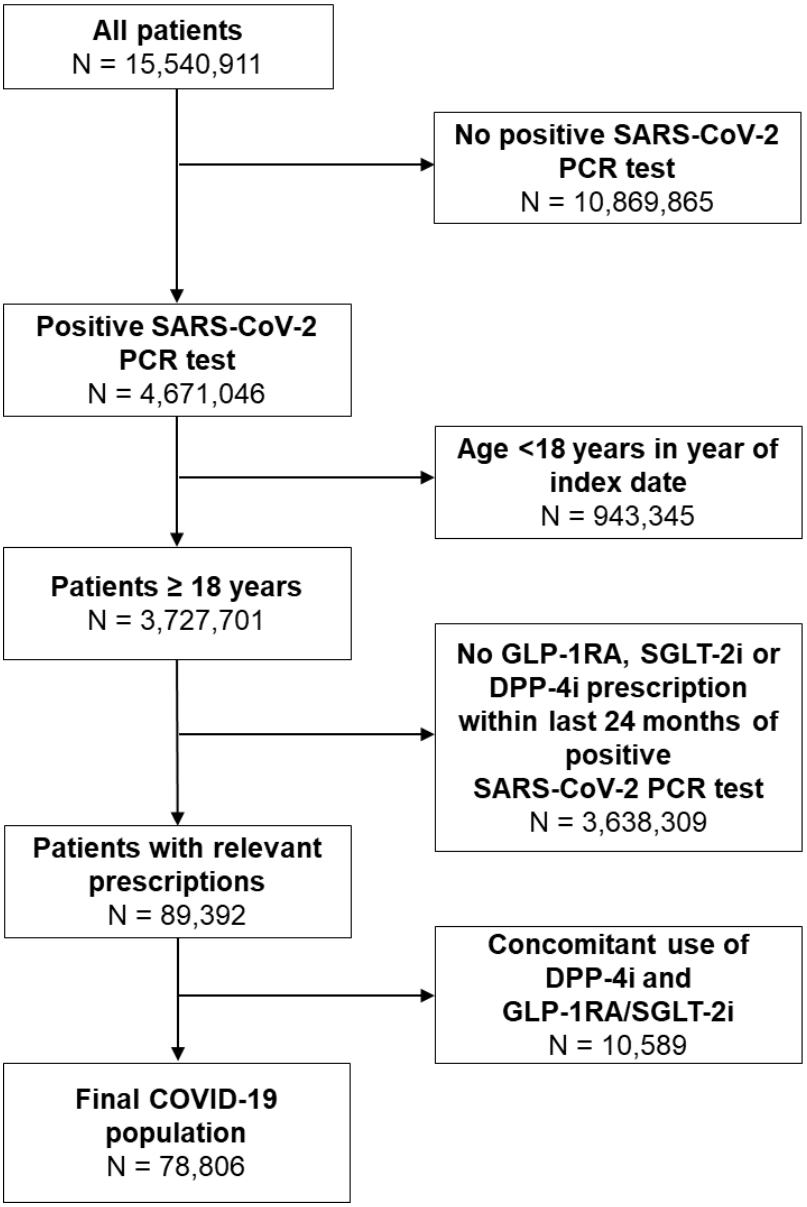
Supplementary Table S5. Crude primary and secondary outcomes, according to premorbid medication use of GLP-1RA mono, SGLT-2i mono, and GLP-1RA/ SGLT-2i.

Outcome	**GLP-1RA mono (N = 36,942)**	**SGLT-2i mono (N = 20,656)**	**GLP-1RA/ SGLT-2i (N = 11,594**
60-day mortality* – E (%)	1,044 (2.83)	669 (3.24)	299 (2.58)
Emergency room visit‡ – E (%)	10,040 (27.18)	6,054 (29.31)	3,193 (27.54)
Hospitalization‡ – E (%)	7,029 (19.03)	4,777 (23.13)	2,258 (19.48)
Mechanical ventilation (Intubation or ventilation)‡ – E (%)	1,393 (3.77)	884 (4.28)	447 (3.86)

* Within 60 days after positive SARS-CoV-2 test, ‡ Within 14 days after a positive SARS-CoV-2 test; N: Total number of individuals; E: number of outcome events (first event only), %: proportion of individuals with the outcome

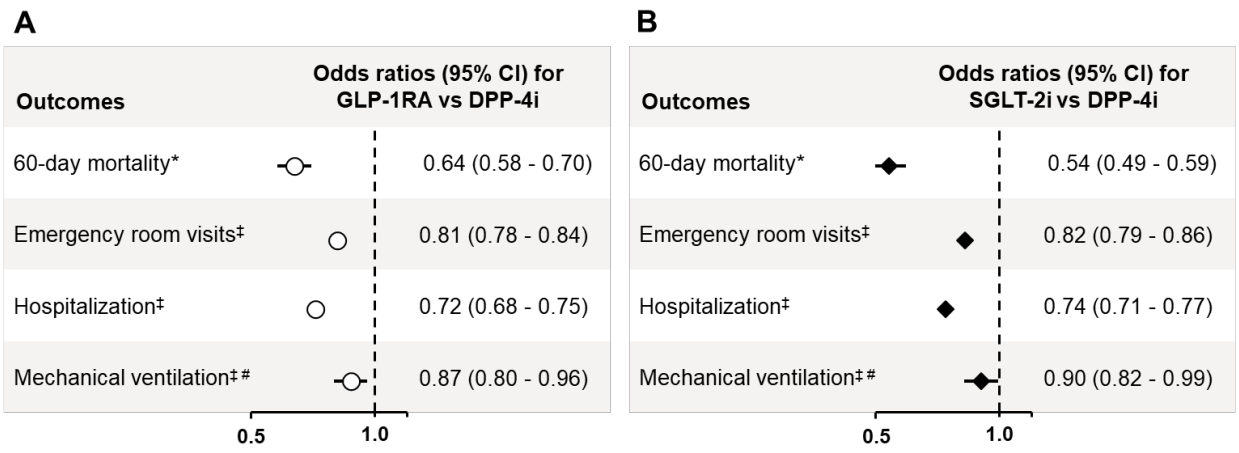
Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, sodium glucose co-transporter 2 inhibitor

FIGURES



Supplementary Figure S1. Overview of study population

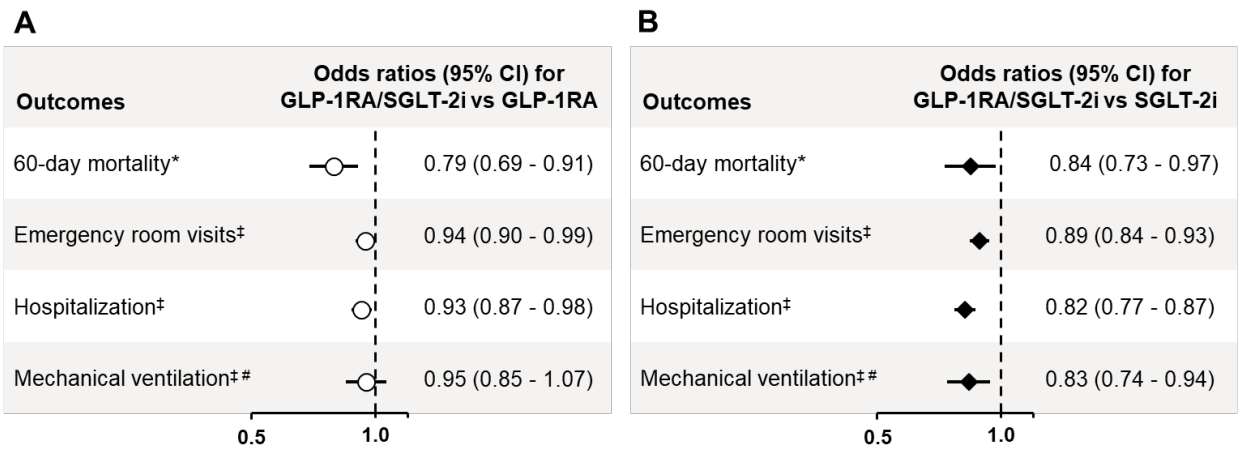
Abbreviations: COVID-19, coronavirus disease 2019; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; PCR, polymerase chain reaction; .SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGLT-2i, sodium glucose co-transporter 2



Supplementary Figure S2. Forest plot depicting IPTW-estimated ORs for primary and secondary outcomes for patients with a COVID-19 diagnosis and prescription for GLP-1RA (A) and SGLT-2i (B) use compared with DPP-4i use, respectively.

* Within 60 days after positive SARS-CoV-2 test, ‡ Within 14 days after positive SARS-CoV-2 test, # Mechanical ventilation (intubation or ventilation)

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; IPTW, inverse probability treatment weighted; OR, odds ratio; SGLT-2i, sodium glucose co-transporter 2 inhibitor



Supplementary Figure S3. Forest plot depicting IPTW-estimated ORs for primary and secondary outcomes for patients with a COVID-19 diagnosis and prescription for GLP-1RA and SGLT-2i combined use compared with GLP-1RA (A) and SGLT-2i (B) single use, respectively**.**

* Within 60 days after positive SARS-CoV-2 test, ‡ Within 14 days after positive SARS-CoV-2 test, # Mechanical ventilation (intubation or ventilation)

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; IPTW, inverse probability treatment weighted; OR, odds ratio; SGLT-2i, sodium glucose co-transporter 2 inhibitor