Received: 9 November 2020 | Revised: 13 January 2021 | Accepted: 23 January 2021

DOI: 10.1111/dom.14329

BRIEF REPORT

WILEY

Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2

Simone Bastrup Israelsen MD[1,2] | Anton Pottegård DMSc[3] | Håkon Sandholdt MSc[1] | Sten Madsbad DMSc[2,4] | Reimar Wernich Thomsen PhD[5] | Thomas Benfield DMSc[1,2]

[1]Center of Research and Disruption of Infectious Diseases, Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark

[2]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[3]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

[4]Department of Endocrinology, Copenhagen University Hospital, Hvidovre, Denmark

[5]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Simone Bastrup Israelsen, MD, Center of Research and Disruption of Infectious Diseases, Department of Infectious Diseases, Copenhagen University Hospital, Amager and Hvidovre, Kettegaard Alle 30, DK-2650 Hvidovre, Denmark.
Email: simone.elisabeth.bastrup.israelsen.02@regionh.dk

Abstract

Incretin-based therapies, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4i), have been hypothesized to exert beneficial effects on COVID-19 outcomes due to anti-inflammatory properties. In this population-based cohort study, we retrieved data from nationwide registries on all individuals diagnosed with severe acute respiratory syndrome coronavirus 2 infection up to 1 November 2020. For individuals with diabetes, we examined the impact of use of GLP-1 RAs (n = 370) and DPP-4i (n = 284) compared with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) (n = 342) on risk of hospital admission and severe outcomes. Relative risks (RRs) were calculated after applying propensity score weighted methods to control for confounding. Current users of GLP-1 RAs had an adjusted RR of 0.89 (95% confidence interval 0.34-2.33), while users of DPP-4i had an adjusted RR of 2.42 (95% confidence interval 0.99-5.89) for 30-day mortality compared with SGLT-2i use. Further, use of GLP-1 RAs or DPP-4i compared with SGLT-2i was not associated with decreased risk of hospital admission. Thus, use of incretin-based therapies in individuals with diabetes and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was not associated with improved clinical outcomes.

KEYWORDS
antidiabetic drug, DPP-4 inhibitor, GLP-1 analogue, population study, SGLT-2 inhibitor

1 | INTRODUCTION

Diabetes is associated with up to two-fold increased risk of mortality for individuals with coronavirus disease 2019 (COVID-19).[1,2] Recent recommendations advise discontinuation of metformin and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in severe cases due to a risk of lactic acidosis or ketoacidosis and dehydration.[3] Meanwhile, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4i) are hypothesized to have a beneficial anti-inflammatory effect on COVID-19 mediated by cytokine inhibition.[4] Sitagliptin, the first approved agent of DPP-4i, has been associated with reduced mortality in patients with COVID-19 and with type 2 diabetes when administered at hospital admission.[5] However, most previous studies were restricted to hospitals and selected populations, and population-based evidence of an impact of current use of novel glucose-lowering drugs (GLDs) on COVID-19 outcomes is limited.

2 | METHODS

Data were retrieved from nationwide registries throughout Denmark on all individuals diagnosed with severe acute respiratory syndrome

coronavirus 2 infection (SARS-CoV-2; using the reverse transcriptase-polymerase chain reaction test) up to 1 November 2020.[6]

The current use of GLP-1 RA, DPP-4i or SGLT-2i was defined as redeemed prescriptions within 90 days before testing positive for SARS-CoV-2. The primary outcome was death within 30 days after a positive SARS-CoV-2 test, while secondary outcomes included hospital admission, intensive care unit (ICU) admission and mechanical ventilation. Patients were followed from the date of positive test for SARS-CoV-2 until death, migration or end of follow-up (30 days). We compared rates of outcomes in users of GLP-1 RA or DPP-4i with those among users of SGLT-2i. Individuals receiving combinations of these drugs and individuals with less than 1 year of available data were excluded from the analyses.

SGLT-2is were chosen as active comparators as they are generally used for similar medical indications, that is, second- or third-line GLD. Furthermore, GLP-1 RA and SGLT-2i users in Denmark have previously been shown to be comparable regarding age, duration of diabetes and GLD therapy, prevalence of diabetic complications and comorbidities.[7] Both drug groups can induce a weight loss, although this is more pronounced for GLP-1 RA. Finally, DDP-4i users are expected to be slightly older and experience more comorbidities compared with GLP-1 RA and SGLT-2i users.[8]

An individual propensity score of drug exposure was computed by using logistic regression based on age, sex, markers of diabetes severity, comorbidities and use of cardiovascular medication (Table 1). Propensity scores were used to calculate stabilized inverse probability of treatment weights, which were applied to account for differences in patient characteristics between treatment groups, that is, to control for confounding.

Descriptive statistics are reported as median with interquartile range for continuous variables or number with percentages for categorical variables. Baseline characteristics are presented for the unweighted and weighted patient cohort for both comparisons (GLP-1 RA vs. SGLT-2i and DPP-4i vs. SGLT-2i). The differences in risk factors between treatment groups were quantified by standardized mean differences. Relative risks were calculated by log binomial regression and presented as both crude (unweighted) and adjusted (weighted) estimates with 95% confidence intervals (CI).

3 | RESULTS

In total, 49 332 cases with SARS-CoV-2 infection were identified between 27 February and 1 November 2020. Of these, 1970 were current users of any GLDs, including 370 GLP-1 RA, 284 DPP-4i and 342 SGLT-2i users. Patients receiving both GLP-1 RA and SGLT-2i (n = 96) or both DPP-4i and SGLT-2i (n = 68) were excluded from the analyses. Individuals with <1 year of baseline data (n = 886) due to recent migration were excluded as well.

DPP-4i use was associated with older age (median 67 compared with 59 years for GLP-1 RA and SGLT-2i use) and higher Charlson's Comorbidity Index (CCI) scores (CCI ≥3: 9% vs. 6% and 5% in users of GLP-1 RA and SGLT-2i, respectively) (Table 1). In the GLP-1 RA and DPP-4i versus SGLT-2i analyses, 2.11% and 2.33% of the weights were >3, with 5-95% percentiles at 0.47-1.89 and 0.54-1.91, respectively. No weights were >10 after stabilization.

In weighted analyses, GLP-1 RA users had similar 30-day mortality to SGLT-2i users (3.3% vs. 3.7%) that both were lower than for DPP-4i users (8.6%) corresponding to an adjusted and weighted relative risk (RR) of 0.89 (95% CI 0.34-2.33) for GLP-1 RA and an adjusted and weighted RR of 2.42 (95% CI 0.99-5.89) for DPP-4i compared with SGLT-2i users, respectively (Table 2). Risks of hospital admission, ICU admission and mechanical ventilation were overall similar in GLP-1 RA and DPP-4i users compared with SGLT-2i users (Table 2). Risks of hospital admission and mechanical ventilation were increased across all treatment groups with adjusted RRs between 1.22 and 2.22, while adjusted RR for ICU admission was close to 1.0 for GLP-1 RA users and 1.30 for DPP-4i users (Table 2). However, all these estimates had low statistical precision (Table 2).

4 | DISCUSSION

Use of GLP-1 RA or DPP-4i was not associated with improved outcomes compared with SGLT-2i use in individuals infected with SARS-CoV-2. However, DPP-4i users had a more than a two-fold increased 30-day mortality compared with SGLT-2i users, although this result had low statistical precision. These findings do not support a preventive or attenuation effect of current use of DPP-4i or GLP-1 RA in patients with diabetes and SARS-CoV-2 infection including those admitted with COVID-19.[4] Indeed, they contradict the recent findings by Solerte et al.[5] concluding that treatment with sitagliptin at hospital admission is associated with reduced mortality in COVID-19 patients with diabetes. However, several aspects may limit the comparability of the studies. Our study differs in that less than 30% of individuals were hospitalized and in the timing of treatment, that is, individuals included in our study were users of DPP-4i before being infected with SARS-CoV-2. Owing to the retrospective design of both studies, the results are not definitive and require confirmation in a randomized controlled trial. Although we adjusted for diabetes severity markers, comorbidities and cardiovascular comedications, our results could still have been influenced by residual confounding from unmeasured or unknown factors driven by more comorbidities and less obesity in DPP-4i compared with SGLT-2i users. Finally, the generalizability of our study results may depend on the availability of novel GLD combination therapies and high-quality diabetes care in health care systems that may be overwhelmed by workload due to steep infection curves.

Overall, our findings that incretin-based therapies (GLP-1 RA and DDP-4i) in individuals with diabetes and COVID-19 were not associated with improved outcomes are consistent with previous reports on use of GLD before a diagnosis of SARS-CoV-2 infection.[9,10] The CORONADO study included 1317 patients with diabetes and did not find an association between type of GLD use and mechanical ventilation or death.[9] Dalan et al.[11] found an increased risk of ICU admission among 27 patients with diabetes and concomitant use of DDP-4i, within a cohort of 717 patients hospitalized with SARS-CoV-2

TABLE 1 Patient characteristics before and after inverse probability of treatment weighting

	GLP-1 RA (n = 370)	SGLT-2i (n = 246)	SMD	wGLP-1 RA (n = 373)	wSGLT-2i (n = 243)	wSMD	DPP-4i (n = 284)	SGLT-2i (n = 274)	SMD	wDPP-4i (n = 291)	wSGLT-2i (n = 266)	wSMD
Age, median (IQR)	59 (51-70)	59 (52-68)	0.02	60 (52-69)	59 (52-68)	0.00	67 (57-76)	58 (52-68)	0.57	63 (53-74)	62 (53-71)	0.08
Sex (male)	196 (53.0)	152 (61.8)	0.18	209 (55.9)	138 (56.8)	0.02	173 (60.9)	165 (60.2)	0.01	172 (59.0)	160 (60.2)	0.03
Other diabetes treatment												
Metformin	218 (58.9)	190 (77.2)	0.40	249 (66.8)	163 (67.2)	0.01	215 (75.7)	212 (77.4)	0.04	219 (75.2)	208 (78.0)	0.07
Insulin	141 (38.1)	43 (17.5)	0.47	113 (30.4)	72 (29.5)	0.02	40 (14.1)	77 (28.1)	0.35	64 (22.0)	58 (21.7)	0.01
Sulfonylureas	11 (3.0)	17 (6.9)	0.18	20 (5.3)	11 (4.6)	0.03	27 (9.5)	15 (5.5)	0.15	19 (6.6)	17 (6.2)	0.02
Diabetes markers												
Duration, median (IQR), years[a]	10 (5-15)	8 (4-13)	0.16	10 (5-15)	10 (5-15)	0.02	10 (6-14)	10 (5-14)	0.10	10 (6-15)	10 (6-15)	0.02
Microvascular complications[b]	112 (30.3)	41 (16.7)	0.33	95 (25.4)	59 (24.2)	0.03	65 (22.9)	60 (21.9)	0.02	69 (23.6)	60 (22.4)	0.03
Macrovascular complications[b]	97 (26.2)	62 (25.2)	0.02	98 (26.2)	64 (26.4)	0.01	92 (32.4)	76 (27.7)	0.10	92 (31.5)	80 (29.9)	0.04
Charlson's Comorbidity Index												
0	278 (75.1)	199 (80.9)	0.14	288 (77.2)	193 (79.3)	0.05	203 (71.5)	220 (80.3)	0.21	222 (76.5)	203 (76.1)	0.01
1-2	69 (18.6)	36 (14.6)	0.11	60 (16.1)	39 (16.1)	0.00	56 (19.7)	41 (15.0)	0.13	51 (17.5)	45 (17.0)	0.01
≥3	23 (6.2)	11 (4.5)	0.08	25 (6.6)	11 (4.7)	0.11	25 (8.8)	13 (4.7)	0.16	18 (6.1)	18 (6.9)	0.04
Diagnoses[b]												
Myocardial infarction	7 (1.9)	11 (4.5)	0.15	12 (3.3)	7 (3.1)	0.01	15 (5.3)	11 (4.0)	0.06	15 (5.2)	15 (5.8)	0.02
Heart failure	24 (6.5)	11 (4.5)	0.09	20 (5.3)	13 (5.2)	0.01	18 (6.3)	16 (5.8)	0.02	14 (4.8)	15 (5.6)	0.04
Obesity	108 (29.2)	38 (15.4)	0.33	88 (23.5)	55 (22.4)	0.03	35 (12.3)	62 (22.6)	0.27	51 (17.7)	47 (17.7)	0.00
Medication[c]												
Antihypertensives	208 (56.2)	122 (49.6)	0.13	194 (51.9)	133 (54.8)	0.06	175 (61.6)	145 (52.9)	0.18	166 (57.0)	150 (56.3)	0.01
Statins	185 (50.0)	124 (50.4)	0.01	186 (49.7)	123 (50.5)	0.02	151 (53.2)	149 (54.4)	0.02	150 (51.7)	141 (52.9)	0.02
Antiplatelets	117 (31.6)	59 (24.0)	0.17	102 (27.3)	65 (26.6)	0.02	94 (33.1)	79 (28.8)	0.09	79 (27.3)	76 (28.7)	0.03

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile ranges; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean differences; w, weighted.

[a]Years since first redeemed glucose-lowering drug prescription (registered since 2005).

[b]Complications or diagnoses within 10 years before inclusion.

[c]Use within 90 days before inclusion.

TABLE 2 Outcomes of SARS-CoV-2 infection in users of GLP-1 RA and DPP-4i compared with users of SGLT-2i before and after inverse probability of treatment weighting

	GLP-1 RA		SGLT-2i		GLP-1 RA vs. SGLT-2i	DPP-4i		SGLT-2i		DPP-4i vs. SGLT-2i
Outcome	Events	Risk (%)	Events	Risk (%)	Relative risk	Events	Risk (%)	Events	Risk (%)	Relative risk
Crude estimates										
30-day death	14/370	3.8 (1.8-5.7)	9/246	3.7 (1.3-6.0)	1.03 (0.45-2.35)	30/284	10.6 (7.0-14.1)	7/274	2.6 (0.7-4.4)	4.13 (1.85-9.26)
ICU admission	12/370	3.2 (1.4-5.1)	9/246	3.7 (1.3-6.0)	0.89 (0.38-2.07)	16/282	5.7 (3.0-8.4)	9/274	3.3 (1.2-5.4)	1.73 (0.78-3.85)
Mechanical ventilation	10/370	2.7 (1.0-4.4)	7/246	2.8 (0.8-4.9)	0.95 (0.37-2.46)	15/284	5.3 (2.7-7.9)	6/274	2.2 (0.5-3.9)	2.41 (0.95-6.13)
Hospital admission	94/362	26.0 (21.4-30.5)	54/243	22.2 (17.0-27.5)	1.17 (0.87-1.57)	85/276	30.8 (25.3-36.3)	55/273	20.1 (15.4-24.9)	1.53 (1.14-2.05)
Adjusted estimates[a]										
30-day death	12/373	3.3 (1.4-5.2)	9/243	3.7 (0.8-6.5)	0.89 (0.34-2.33)	25/291	8.6 (4.9-12.3)	9/266	3.6 (0.8-6.4)	2.42 (0.99-5.89)
ICU admission	10/373	2.7 (1.2-4.3)	8/243	3.2 (0.8-5.5)	0.87 (0.34-2.21)	12/290	4.1 (2.1-6.2)	8/266	3.2 (0.9-5.5)	1.30 (0.54-3.12)
Mechanical ventilation	13/373	3.5 (0.3-6.8)	5/243	2.1 (0.3-3.9)	1.65 (0.47-5.76)	14/291	4.8 (1.9-7.7)	6/266	2.2 (0.3-4.1)	2.22 (0.77-6.46)
Hospital admission	102/367	27.9 (21.7-34.1)	54/241	22.4 (16.0-28.8)	1.25 (0.87-1.79)	74/285	26.1 (20.0-32.2)	57/265	21.5 (16.0-27.0)	1.22 (0.86-1.72)

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ICU, intensive care unit; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

[a]Adjusted estimates obtained in an inverse probability of treatment weighted pseudo-population using stabilized weights. Factors included in the propensity score informing the weights were age, sex, duration of glucose-lowering drug (GLD) treatment, concomitant use of other GLDs (metformin, insulin, sulfonylureas), diabetic complications, medical obesity, myocardial infarction, chronic heart failure, chronic obstructive pulmonary disease, Charlson's Comorbidity Index without diabetes mellitus (0, 1-2, ≥3), and cardiovascular medications (antihypertensives, statins, antiplatelets).

infection, but did not include data on mortality. Other studies have reported a worse prognosis of insulin-treated versus non-insulin-treated patients with diabetes and COVID-19, but it is unclear whether this reflects insulin effects per se or the presence of more advanced or poorly controlled diabetes with additional comorbidity that is associated with both insulin use and more severe COVID-19.[1,10]

5 | CONCLUSION

In conclusion, neither current use of GLP-1 RA nor DPP-4i was associated with improved outcomes of individuals with diabetes infected with SARS-CoV-2 when compared with SGLT-2i use. Use of DPP-4i before infection with SARS-CoV-2 might even have a harmful effect, in contrast to the current anti-inflammation hypotheses and the possible association of sitagliptin treatment at hospital admission with reduced mortality. However, our study results should be interpreted cautiously due to the limited sample size.

ACKNOWLEDGMENTS

No funding was obtained for this study.

CONFLICT OF INTEREST

T.B. reports grants from Pfizer, Novo Nordisk Foundation, Simonsen Foundation, Lundbeck Foundation and Kai Hansen Foundation, grants and personal fees from GSK, Pfizer and Gilead, and personal fees from Boehringer Ingelheim and MSD, with no relation to the work reported in this paper. A.P. reports grants from Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, with no relation to the work reported in this paper. R.W.T. reports that the Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to and administered by Aarhus University. None of these studies have relation to the present study. S.M. reports grants and personal fees from Novo Nordisk A/S and Boehringer-Ingelheim, and personal fees from MSD and Sanofi, with no relation to the work reported in this paper. S.B.I. and H.S. report no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14329.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study

ORCID

Simone Bastrup Israelsen https://orcid.org/0000-0002-0653-1289

Anton Pottegård https://orcid.org/0000-0001-9314-5679

REFERENCES

1. Reilev M, Kristensen KB, Pottegård A, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *Int J Epidemiol*. 2020;49:1468-1481. https://doi.org/10.1093/ije/dyaa140.
2. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature*. 2020;584:430-436. https://doi.org/10.1038/s41586-020-2521-4.
3. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(6):546-550. https://doi.org/10.1016/S2213-8587(20)30152-2.
4. Mirabelli M, Chiefari E, Puccio L, Foti DP, Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. *Int J Environ Res Public Health*. 2020;17(10):3664. https://doi.org/10.3390/ijerph17103664.
5. Solerte SB, D'Addio F, Trevisan R, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. *Diabetes Care*. 2020;43:2999-3006. https://doi.org/10.2337/dc20-1521.
6. Pottegård A, Kristensen KB, Reilev M, et al. Existing data sources in clinical epidemiology: the Danish COVID-19 cohort. *Clin Epidemiol*. 2020;12:875-881. https://doi.org/10.2147/CLEP.S257519.
7. Knudsen JS, Baggesen LM, Lajer M, et al. Changes in SGLT2i and GLP-1RA real-world initiator profiles following cardiovascular outcome trials: a Danish nationwide population-based study. *PLoS One*. 2020;15(3):e0229621. https://doi.org/10.1371/journal.pone.0229621.
8. Pottegård A, Lund LC, Henriksen DP, et al. Use of dipeptidyl peptidase-4 inhibitors and risk of splanchnic vein thrombosis: a Danish nationwide new-user active comparator cohort study. *Diabetes Obes Metab*. 2020;23:648-652. https://doi.org/10.1111/dom.14253.
9. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. 2020;63(8):1500-1515. https://doi.org/10.1007/s00125-020-05180-x.
10. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care*. 2020;43(7):1399-1407. https://doi.org/10.2337/dc20-0660.
11. Dalan R, Ang LW, Tan WYT, et al. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. *Eur Heart J Cardiovasc Pharmacother*. 2020. https://doi.org/10.1093/ehjcvp/pvaa098.

How to cite this article: Israelsen SB, Pottegård A, Sandholdt H, Madsbad S, Thomsen RW, Benfield T. Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2. *Diabetes Obes Metab*. 2021;1–5. https://doi.org/10.1111/dom.14329