Association Between DPP-4 Inhibitors and COVID-19–Related Outcomes Among Patients With Type 2 Diabetes

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Diabetes Care 2021;44:e64–e66 | https://doi.org/10.2337/dc20-1824

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), uses angiotensin-converting enzyme 2 to invade human cells. However, recent evidence suggested that dipeptidyl peptidase 4 (DPP-4) may be used as a coreceptor when SARS-CoV-2 enters the target cells (1). Interestingly, upregulation of DPP-4 is associated with older age, respiratory or cardiovascular disease, and diabetes (2), all of which were reported to exacerbate COVID-19. Given the pathophysiological evidence, DPP-4 inhibitors were suggested to have beneficial effects on COVID-19. Given the high fatality rate of COVID-19 among patients with diabetes, there is an urgent need to understand the effect DPP-4 inhibitors may have on COVID-19. Therefore, we aimed to determine whether use of DPP-4 inhibitors reduces the risk of adverse COVID-19–related outcomes among patients with type 2 diabetes (T2D).

We conducted a nationwide cohort study using the Health Insurance Review and Assessment Service database linked with the Korea Disease Control and Prevention Agency database, which covers the entire South Korean population of ≥50 million, from 1 January 2017 to 15 May 2020. We included patients who had a positive test result for COVID-19 as of 15 May 2020, had been diagnosed with T2D within the preceding 3 years before COVID-19 diagnosis (cohort entry), and had ≥1 antidiabetic prescription within the 180 days before cohort entry. We excluded patients aged <18 years; those prescribed metformin monotherapy only, to restrict inclusion to patients who were on second- or third-line therapy for T2D; those prescribed insulin monotherapy as they are likely to be patients with type 1 diabetes; those prescribed only insulin and metformin as they do not belong to either exposure group (described below); and women with polycystic ovarian syndrome or gestational diabetes mellitus as these conditions are alternative indications for antidiabetic drugs.

We measured exposure in the 180 days before cohort entry, classifying patients into two mutually exclusive exposure groups: users of DPP-4 inhibitors (alone or in combination with other antidiabetic drugs), and users of other noninsulin second- or third-line antidiabetic drugs (sulfonylureas, thiazolidinediones, sodium–glucose cotransporter 2 inhibitors, meglitinides, α-glucosidase inhibitors, and glucagon-like peptide 1 receptor agonists, each individually or in combination with other antidiabetic drugs [reference group]) (3). The primary outcome was all-cause mortality. The secondary outcome was a composite of an intensive care unit admission and use of noninvasive or invasive mechanical ventilation or extracorporeal membrane oxygenation, proxies for severe manifestation of COVID-19. All patients were followed up from cohort entry until the first occurrence of an outcome or end of the study period (15 May 2020). Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs, adjusted for 19 covariates. This study was approved by the institutional review board of Sungkyunkwan University, Suwon, South Korea (SKKU 2020-04-011).

Of 7,590 patients with confirmed cases of COVID-19, we identified 586 patients for our study cohort. There were 47 deaths among 453 users of DPP-4 inhibitors (incidence rate 1.73 per 1,000 person-days) and 22 deaths among 133 users of other second- or third-line

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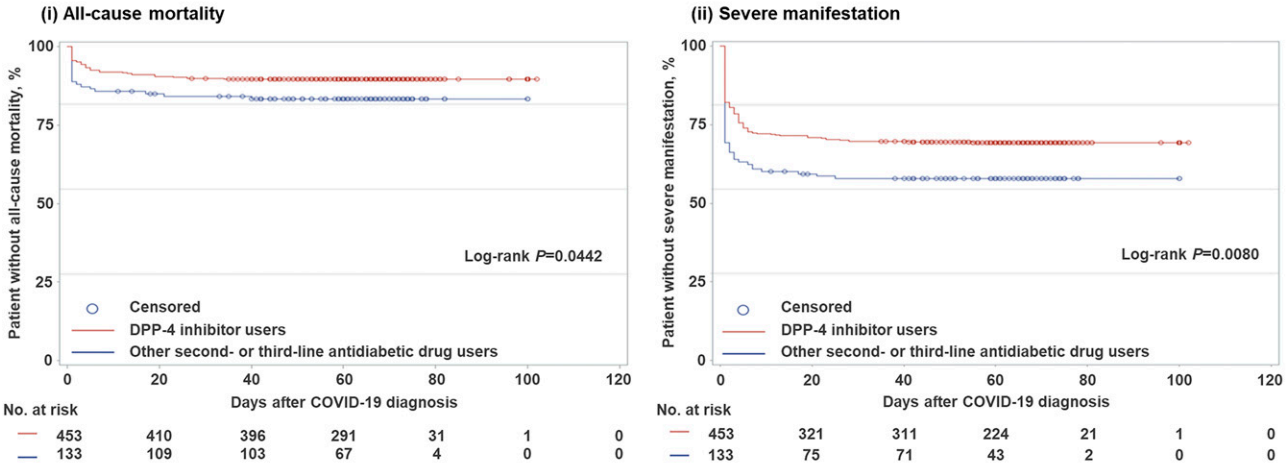
Received 20 July 2020 and accepted 3 January 2021

This article is part of a special article collection available at https://care.diabetesjournals.org/collection/diabetes-and-COVID19.

A Survival curves of adverse COVID-19-related outcomes



B Hazard ratios for the association between the use of DPP-4 inhibitors and the risk of adverse COVID-19-related outcomes

Analysis	DPP-4 inhibitors Events/ Patients	DPP-4 inhibitors Person-days	Other second- or third-line drugs Events/ Patients	Other second- or third-line drugs Person-days	HR (95% CI) Crude	HR (95% CI) Adjusted*
Primary outcome: All-cause mortality						
Main analysis	47/453	27,189	22/133	6,926	0.60 (0.36-0.99)	0.74 (0.43-1.26)
Subgroup analyses						
Aged <65 years	6/221	14,576	3/50	2,830	0.45 (0.11-1.79)	0.55 (0.13-2.24)
Aged ≥65 years	41/232	12,613	19/83	4,096	0.74 (0.43-1.28)	0.74 (0.43-1.28)
Male	27/223	13,040	10/74	3,920	0.89 (0.43-1.83)	0.95 (0.46-1.97)
Female	20/230	14,149	12/59	3,006	0.40 (0.20-0.82)	0.50 (0.25-1.04)
No cardiovascular disease	1/115	7,536	2/28	1,487	0.12 (0.01-1.33)	0.15 (0.01-1.95)
Cardiovascular disease	46/338	19,653	20/105	5,439	0.69 (0.41-1.16)	0.79 (0.46-1.34)
No respiratory disease	25/302	18,654	11/89	4,814	0.65 (0.32-1.32)	0.76 (0.37-1.57)
Respiratory disease	22/151	8,535	11/44	2,112	0.55 (0.27-1.14)	0.64 (0.31-1.31)
No renal disease	33/357	21,574	16/109	5,696	0.60 (0.33-1.10)	0.77 (0.42-1.41)
Renal disease	14/96	5,615	6/24	1,230	0.56 (0.21-1.45)	0.41 (0.15-1.12)
No liver disease	39/391	23,468	21/111	5,692	0.50 (0.30-0.85)	0.61 (0.35-1.04)
Liver disease	8/62	3,721	1/22	1,234	2.88 (0.36-23.01)	2.80 (0.34-22.83)
No cancer	42/410	24,720	19/121	6,345	0.63 (0.37-1.08)	0.72 (0.42-1.25)
Cancer	5/43	2,469	3/12	581	0.44 (0.11-1.85)	0.63 (0.15-2.78)
<2.5 years of antidiabetic treatment	6/94	6,042	5/31	1,491	0.37 (0.11-1.20)	0.41 (0.12-1.40)
≥2.5 years of antidiabetic treatment	41/359	21,147	17/102	5,435	0.67 (0.38-1.17)	0.72 (0.41-1.28)
<3 concomitant antidiabetic agents†	28/276	16,630	15/94	4,890	0.61 (0.33-1.15)	0.79 (0.42-1.49)
≥3 concomitant antidiabetic agents†	19/177	10,559	7/39	2,036	0.58 (0.24-1.37)	0.54 (0.23-1.30)
Sensitivity analyses						
SMRW approach‡	43/416	27,189	16/113	6,926	0.58 (0.26-1.31)	0.78 (0.33-1.83)
90-day exposure window§	45/441	26,507	22/134	7,022	0.60 (0.36-0.99)	0.73 (0.42-1.24)
30-day exposure window¶	45/432	25,853	21/130	6,931	0.62 (0.37-1.05)	0.71 (0.41-1.23)
Exclusion of patients who used insulin#	34/374	22,459	14/106	5,695	0.67 (0.36-1.25)	0.86 (0.44-1.69)
Secondary outcome: Severe manifestation**						
Main analysis	42/453	27,417	15/133	7,239	0.81 (0.45-1.45)	0.83 (0.45-1.53)

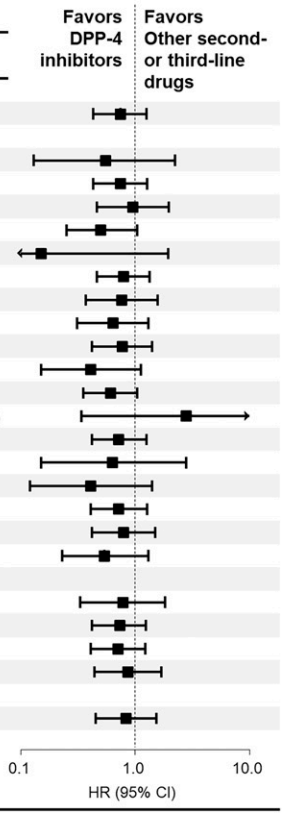


Figure 1—Risk of adverse COVID-19–related outcomes, presented as survival curves (*A*) and hazard ratios (*B*), in users of DPP-4 inhibitors compared with users of other second- or third-line antidiabetic drugs. SMRW, standardized mortality ratio weighting. *Adjusted for age and sex at cohort entry, Charlson comorbidity index, comorbid conditions (hypertension, ischemic heart disease, heart failure/cardiomyopathy, cerebrovascular disease, peripheral arterial disease, respiratory disease, chronic liver disease, chronic renal disease, cancer [excluding nonmelanoma skin cancer], end-stage illness), use of comedications (ACE inhibitors or angiotensin receptor blockers, other antihypertensives, antithrombotics, opioids, immunosuppressive therapy), and duration of antidiabetic treatment (<2.5 years, ≥2.5 years), measured in the 6–18 months before cohort entry. In the subgroup analyses, HRs were adjusted for age, sex, and Charlson comorbidity index because of limited sample sizes. †Number of antidiabetic medication classes used in the 30-day period before cohort entry. ‡Propensity score was estimated as the predicted probability of receiving DPP-4 inhibitors based on the above-mentioned covariates using a multivariable logistic regression model. To handle extreme weights, the lower and upper 5th percentiles were trimmed. §Redefined the exposure assessment window to 90 days. ¶Redefined the exposure assessment window to 30 days. #Excluding patients with concomitant use of insulin. **Composite outcome of admission to an intensive care unit and use of mechanical ventilation or extracorporeal membrane oxygenation.

antidiabetics (3.18 per 1,000 person-days) (Fig. 1). The unadjusted survival curves demonstrated a significantly lower probability of all-cause mortality ($P = 0.0442$) and severe manifestations of COVID-19 ($P = 0.0080$) among DPP-4 inhibitor users. In the adjusted model, DPP-4 inhibitor use was insignificantly associated with all-cause mortality (HR 0.74, 95% CI 0.43–1.26) and severe manifestations (HR 0.83, 95% CI 0.45–1.53) compared with the reference group. There was no evidence of effect modification between DPP-4 inhibitor use and the risk of all-cause mortality for all subgroup analyses except for history of cardiovascular disease, where a lower HR was observed among patients with no previous history of cardiovascular disease (P for interaction $= 0.0252$). Our main findings remained consistent in all sensitivity analyses that minimized potential confounding by using a propensity score approach that involved standardized mortality ratio weighting, varied the exposure ascertainment window, and excluded patients who concomitantly used insulin. Moreover, as >90% of patients continued their respective treatment after being hospitalized with COVID-19, impact of exposure misclassification is likely to be minimal.

In summary, compared with use of other second- or third-line antidiabetic drugs, use of DPP-4 inhibitors was not associated with adverse COVID-19-related outcomes among patients with T2D. However, our findings hint at clinical relevance as potential benefits associated with DPP-4 inhibitors were observed in this patient population, although our estimates had wide 95% CIs due to limited power; recent studies reported similar beneficial effects (4,5). While awaiting the results of ongoing randomized controlled trials investigating this issue, our findings provide further clinical insight for health care professionals in managing the ongoing pandemic.

Acknowledgments. The authors express their appreciation to the health care professionals dedicated to treating COVID-19 patients in South Korea and to the Ministry of Health and Welfare, the Health Insurance Review and Assessment Service, and Do-Yeon Cho of the Health Insurance Review and Assessment Service of South Korea for sharing invaluable national health insurance claims data in a prompt manner. I.-S.O. and H.E.J. report receiving research funding from the National Research Foundation of South Korea, outside the submitted work. K.B.F. is supported by a salary support award from the Fonds de recherche du Québec – Santé and a William Dawson Scholar award from McGill University. O.H.Y.Y. receives salary support from the Fonds de recherche du Québec – Santé. J.-Y.S. reports receiving grants from the Ministry of Food and Drug Safety, the Ministry of Health and Welfare, and the National Research Foundation of South Korea, outside the submitted work.

Funding. This study was supported by the Government-wide R&D Fund project for Infectious Disease Research (GFID) of South Korea (grant no. HG18C0068).

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Duality of Interest. J.-Y.S. reports grants from pharmaceutical companies including Amgen, Pfizer, Hoffmann-La Roche, Dong-A ST, and Yungjin outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. Y.N. and J.-Y.S. conceptualized and designed the study. Y.N., I.-S.O., H.E.J., K.B.F., O.H.Y.Y., and J.-Y.S. analyzed and interpreted data and contributed to the writing of the manuscript. K.B.F., O.H.Y.Y., and J.-Y.S. contributed to the critical revision of the manuscript for important intellectual content. I.-S.O. acquired data and performed the statistical analysis. J.-Y.S. obtained funding and supervised the study and had final responsibility for the decision to submit for publication. J.-Y.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Solerte SB, Di Sabatino A, Galli M, Fiorina P. Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. Acta Diabetol 2020;57:779–783

2. Bassendine MF, Bridge SH, McCaughan GW, Gorrell MD. COVID-19 and comorbidities: a role for dipeptidyl peptidase 4 (DPP4) in disease severity? J Diabetes 2020;12:649–658

3. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012;35:2665–2673

4. 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

5. Mirani M, Favacchio G, Carrone F, et al. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: a case series from an academic hospital in Lombardy, Italy. Diabetes Care 2020;43:3042–3049