Letter

Diabetes Metab J 2021;45:615-616
https://doi.org/10.4093/dmj.2021.0081
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Effects of a DPP-4 Inhibitor and RAS Blockade on Clinical Outcomes of Patients with Diabetes and COVID-19 (*Diabetes Metab J* 2021;45:251-9)

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People with diabetes are at increased risk of severe coronavirus disease 2019 (COVID-19) complications, and COVID-19-related mortality in this population is two to three times higher than that in people without diabetes [1]. Glucose-lowering drugs used in the treatment of patients with diabetes might have significant effects on COVID-19 pathophysiology, potentially affecting the risk of progression to severe disease and mortality. Rhee et al. [2] reported data suggesting that dipeptidyl peptidase-4 inhibitors (DPP-4is) are significantly associated with a better clinical outcome in patients with COVID-19. The unadjusted odds ratio (OR) of severe/lethal cases among DPP-4i users was 0.77 (95% confidence interval [CI], 0.35 to 1.68); after some adjustment, the OR changed to 0.36 (95% CI, 0.13 to 0.97). This enourmous discrepancy—between the unadjusted and adjusted ORs—is difficult to understand.

The authors have compared relatively small cohorts not matched for critical factors. While DPP-4i users (n=263) and non-DPP-4i users (n=569) had a similar baseline risk for some mortality-linked comorbidities (e.g., cardiovascular disease, 26% vs. 28%; chronic kidney disease, 16% vs. 11%; and cancer, 18% vs. 24%), no information was given about heart failure, which is now one of the leading risk factors for mortality in diabetic patients. By contrast, treatment quality was extremely different and significantly better in the group receiving DPP-4i compared with non-users (metformin, 82% vs. 15%; statins, 61% vs. 29%; renin-angiotensin system blockade, 49% vs. 24%; and angiotensin receptor blocker inhibitors, 47% vs. 23%). Thus, it is extremely likely that the use of metformin and cardioprotective drugs have strongly influenced relative clinical outcomes for patients using DPP-4i. Indeed, a recent meta-analysis [3] of five studies encompassing 8,121 patients with diabetes who were admitted to hospital for COVID-19 showed a significantly reduced mortality rate associated with the use of metformin (OR, 0.62; 95% CI, 0.43 to 0.89). In addition, a recent population-based cohort study from Korea [4] showed that the use of statins was associated with lower mortality in patients with COVID-19 (hazard ratio [HR], 0.64; 95% CI, 0.42 to 0.95).

Very recently, several large population studies were published analyzing the effect of different glucose-lowering drugs on mortality in patients with diabetes during the COVID-19 pandemic (Table 1). In the UK, the pre-infection prescription of glucose-lowering therapies and risk of COVID-19 mortality was analysed in 2.85 million people with type 2 diabetes mellitus [5]. Overall, a COVID-19-related death occurred in 13,479 (0.5%) subjects. Metformin, sodium glucose co-transporter 2 (SGLT2) inhibitors, and sulfonylureas were associated with reduced risks of COVID-19-related mortality, whereas insulin and DPP-4is were associated with increases in risk; neutral results were found for glucagon-like peptide-1 (GLP-1) receptor agonists and thiazolidinediones. Interestingly, the use of SGLT2 inhibitors (HR, 0.82; 95% CI, 0.74 to 0.91) compared with DPP-4is (HR, 1.07; 95% CI, 1.01 to 1.13) was associated with significantly lower COVID-19 mortality risk [2]. However, as expected from treatment recommendations [6,7], pa-

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Table 1. Effect of DPP-4is on COVID-19 related mortality/severe outcome in population based studies

Country	No. of patients using DPP-4i	No. of patients not using DPP-4i	HR (95% CI)
UK (5)	479,555	2,371,910	1.07 (1.01–1.13)[a]
France (9)	285	1,032	0.85 (0.55–1.32)[a]
Denmark (8)	575	540[c]	2.42 (0.99–5.88)[a]
Korea (3)	263	569	0.36 (0.13–0.97)[b]

DPP-4i, dipeptidyl peptidase-4 inhibitor; COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval.
[a]Mortality, [b]Severe/lethal cases, [c]Patients in the control arm received sodium glucose co-transporter 2 inhibitors.

tients using DPP-4i in the UK study were older and were more likely to have chronic kidney disease [5].

In a Danish population-based study [8], the impact of current use of novel glucose-lowering drugs on COVID-19 was studied and relative risks (RR) were calculated after applying propensity score weighted methods to control for confounding. Current users of GLP-1 receptor agonists had an adjusted RR of 0.89 (95% CI, 0.34 to 2.33), while users of DPP-4i had an adjusted RR of 2.42 (95% CI, 0.99 to 5.89), for 30-day mortality compared with SGLT2 inhibitor use. In the French population-based Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study [9], the use of metformin was associated with a significantly reduced mortality in diabetic patients with COVID-19 (OR, 0.63; 95% CI, 0.52 to 0.77), whereas the use of DPP-4i had a neutral effect (OR, 0.83; 95% CI, 0.65 to 1.05). In a recent meta-analysis of seven studies [10], death occurred in 111 of 612 (18%) patients treated with DPP-4i and in 335 of 1,703 (20%) patients treated with other glucose-lowering medication, again suggesting a neutral effect (RR, 0.81; 95% CI, 0.57 to 1.15).

Several randomized controlled trials (NCT04365517, NCT04371978, and NCT04341935) are being conducted with DPP-4is in patients with type 2 diabetes mellitus and COVID-19. Until we have evidence from prospective, randomized studies such as these, data on the effectiveness or safety of DPP-4i in patients with COVID-19 should be interpreted with caution.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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