Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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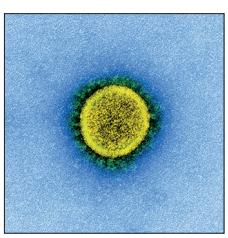
Can glucose-lowering drugs affect the prognosis of COVID-19 in patients with type 2 diabetes?

The emergence of a novel coronavirus, SARS-CoV-2, in December, 2019, has had devastating consequences on health, social, and economic systems around the world. Of the estimated 115 million people (about 10% with diabetes) who have been infected with SARS-CoV-2, more than 2·5 million patients had died due to COVID-19 at the time of writing (data from the Johns Hopkins Coronavirus Research Center). People with diabetes and related comorbidities are at increased risk of severe COVID-19 complications, and COVID-19-related mortality in this population is two to three times higher than that in people without diabetes.[1] Various mechanisms might explain why patients with diabetes are over-represented among those admitted to hospital with severe COVID-19 and have an increased risk for death. Metabolic inflammation is common in patients with diabetes and predisposes them to an enhanced release of cytokines.[2] For COVID-19, a cytokine storm has been implicated in the multiorgan failure reported in patients with severe disease. Inflammatory-driven processes are probably primary drivers of coagulopathy in COVID-19. Venous thromboembolism, arterial thrombosis, and thrombotic microangiopathy substantially contribute to increased morbidity and mortality in patients with COVID-19.[3] The chronic inflammation and hypercoagulable state common in diabetes could contribute to the high mortality risk associated with COVID-19 and diabetes.

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. In *The Lancet Diabetes & Endocrinology*, Kamlesh Khunti and colleagues[4] report COVID-19 mortality rates for patients with type 2 diabetes on different glucose-lowering therapies, in an observational nationwide study in England. 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, covering almost the whole population of people with type 2 diabetes who were registered with a general practice in England (irrespective of whether or not patients had been admitted to hospital). Overall, a COVID-19-related death occurred in 13 479 (0·5%) of the 2 851 465 patients during the study period (Feb 16 to Aug 31, 2020). Metformin, SGLT2 inhibitors, and sulfonylureas were associated with reduced risks of the COVID-19-related mortality, whereas insulin and DPP-4 inhibitors were associated with increases in risk; neutral results were found for GLP-1 receptor agonists and thiazolidinediones. Unfortunately, data were not available to allow the researchers to identify when the drugs were stopped during the progression of COVID-19, and it was not possible to establish whether the combination therapies that are widely used to control diabetes in England had any effect on mortality.

Khunti and colleagues' findings[4] are in line with a recent update from the nationwide CORONADO study in France,[5] which also showed that, in patients admitted to hospital with COVID-19 and diabetes, metformin use was associated with a decrease and insulin was associated with an increase in mortality risk. A significantly reduced mortality rate associated with the use of metformin (odds ratio 0·62 [95% CI 0·43–0·89]) was also reported in a recent meta-analysis of five studies[6] including 8121 patients with diabetes who were admitted to hospital for COVID-19. The findings of these studies, including the study by Khunti and colleagues,[4-6] are probably related at least in part to confounding by indication, as metformin is used early in the disease course of type 2 diabetes, whereas insulin



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Published **Online** March 30, 2021 https://doi.org/10.1016/S2213-8587(21)00059-0

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is initiated later. The use of SGLT2 inhibitors compared with DPP-4 inhibitors was associated with significantly lower mortality risk associated with COVID-19 in both Khunti and colleagues' study in England[4] and another recent study in Denmark.[7] However, in Khunti and colleagues' study,[4] 47% of the patients receiving a DPP-4 inhibitor were aged 70 years or older, compared with only 18% taking an SGLT2 inhibitor. Patients with an eGFR between 15 mL/min per 1·73 m² and less than 60 mL/min per 1·73 m² had a very high mortality risk in univariate analyses (hazard ratio 3·7 [95% CI 3·5–3·9] for 45 to <60 mL/min per 1·73 m² to 9·1 [8·4–9·9] for 15 to <30 mL/min per 1·73 m²). Notably, almost 25% of patients on a DPP-4 inhibitor had eGFR of less than 60 mL/min per 1·73 m², compared with only 4·1% of patients on an SGLT2 inhibitor.

How might these findings inform clinical practice? On the basis of evidence from smaller studies, Lim and colleagues[8] recommended that DPP-4 inhibitors be used across a broad spectrum of COVID-19 severity, but that SGLT2 inhibitors should only be used with caution, and metformin should be stopped in severe cases. Because positive results with respect to all-cause mortality have previously been reported for metformin and SGLT2 inhibitors,[9] withdrawal or non-use of these drugs could have a negative effect on the prognosis of patients with type 2 diabetes and COVID-19. Given the large cohort in Khunti and colleagues' study[4] and the absence of evidence for risk with these drugs, recommendations on the use of glucose-lowering drugs by people with type 2 diabetes during the COVID-19 pandemic might now become more liberal, allowing use of all glucose-lowering drugs in stable situations. However, because of the limitations of such real-world studies, prospective randomised clinical trials are necessary to more meaningfully explore which glucose-lowering agents, if any, induce benefit or harm in patients with COVID-19. Irrespective of therapy choice, strict management of cardiovascular risk factors and tight glycaemic control are crucial for patients with diabetes and COVID-19. Antithrombotic therapy for the prevention and treatment of COVID-19-associated thrombosis[3] as well as anti-inflammatory therapy[10] will hopefully translate into improved outcomes.[3] Finally, vaccination prioritisation of patients with type 2 diabetes who are at very high risk of severe COVID-19 could help protect this vulnerable population.

I have received personal fees for lectures and advisory board memberships from Boehringer Ingelheim, Eli Lilly, Mundipharma, AstraZeneca, and Takeda.

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Semaglutide for obesity: four STEPs forward, but more to come

Semaglutide 2·4 mg once weekly, an anti-obesity medication now submitted to regulators across the USA and Europe, is generating much excitement and attention about the amount of weight loss it produced in the phase 3 studies. Five phase 3 STEP (Semaglutide Treatment Effect in People with obesity) trials have now been completed,[1] and four have been published.[2–5] Reasons for the enthusiastic reception of these findings