DIABETES

Glucose-lowering treatments and COVID-19 mortality in T2DM

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The poor prognosis in patients with diabetes mellitus who contract COVID-19 urged physicians to question routine drug treatment for people with type 2 diabetes mellitus. What treatment should we prioritize? So far only observational studies are available, although complementary interventional studies are needed to address this issue.

Refers to Khunti, K. et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol.* **9**, 293–303 (2021).

A paper by Kamlesh Khunti and colleagues recently examined the relationship between the prescription of glucose-lowering therapies and the risk of coronavirus disease 2019 (COVID-19)-related mortality among nearly 3 million people with type 2 diabetes mellitus (T2DM) in the nationwide National Diabetes Audit database in England[1], from February 2020 to August 2020. The key findings are a positive association between use of insulin therapy and dipeptidyl peptidase (DPP4) inhibitors and the risk of COVID-19-related death and a negative association between metformin, sodium–glucose co-transporter 2 (SGLT2) inhibitors and sulfonylureas and the risk of COVID-19-related death, which suggests a deleterious and a protective effect, respectively. By contrast, glucagon-like peptide 1 (GLP1) receptor agonists and thiazolidinediones were not significantly associated with risk of COVID-19-related death.

The question of the safety of the different glucose-lowering therapies in the context of COVID-19 is among the key questions that patients with T2DM and physicians have been asking since the beginning of the pandemic and the identification of the negative effect of diabetes mellitus in COVID-19 prognosis. The present study helps to consolidate previously reported findings, such as the beneficial association between use of metformin and decreased COVID-19-related mortality, from the French nationwide CORONADO study[2] and from a meta-analysis[3]. This study also consolidates the the deleterious association with insulin, which had already been suggested in a Chinese study[4].

Some limitations adequately acknowledged by Khunti and colleagues[1] are common to many observational studies. For example, the current analysis pooled drugs in their therapeutic class, ruling out possible specific effects of different molecules within the same class. However, assuming a class effect helped to gather large numbers and produce robust results. The study focused on routine prescription and did not consider potential changes or discontinuation of treatment; however, to ascertain drug intake is very complex, particularly in COVID-19 hospital settings.

It is always good to remind ourselves that association is not causation. As electronic health records and other medical administrative data are more widely and quickly available, they give researchers the opportunity to access nationwide data at low cost and to claim

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the findings are representative. However, in observational studies such as the present study, findings on medications are probably explained by an indication bias that statistical adjustments were not able to fully exclude. In other words, the association between medication and outcomes was rather due to the reason why a medication was prescribed than by the medication in itself. As an illustration, in patients with T2DM, metformin is usually a first-line therapy, whereas insulin is used later in the course of the disease after the occurrence of diabetic complications such as chronic kidney disease. This situation leads to different patient profiles being associated with different prescriptions. Importantly, data from the Scottish diabetes registry showed an increased odds ratio for COVID-19 severity according to the number of glucose-lowering drug classes prescribed, notwithstanding the classes themselves[5]. This approach examining the number of prescribed drugs is an elegant strategy, which is worth being tested using data from the present study[1] and other studies.

It is wise to temper the interpretation of statistical significance by looking more closely at the effect size, before thinking about drug discontinuation or change of glucose-lowering medications. As indicated by Rory Collins and colleagues[6], evidence of any effect of a medication derived from observational studies must be considered only if the association at least doubles the outcomes. This requirement

Table 1 | **Current COVID-19 prospective trials on glucose-lowering interventions in patients with T2DM**

Clinical trial number[a]	Drug tested	Placebo controlled	*N*
04510194	Metformin	Yes	750
04625985		Yes	20
04727424		Yes (metformin + 2 other IDs)	2,724
04604223	Pioglitazone	Yes	1,506
04535700		No	76
04473274		No	20
04542213	Linagliptin	No, linaglitpin + insulin vs insulin	70
04371978		No, linaglitpin + insulin vs insulin	100
04393246	Dapagliflozine	No, dapagliflozine + 2 other IDs vs SOC	1,407
04350593		Yes	1,250

The full version of this table, including inclusion criteria and primary outcomes, is available in the supplementary information. [a]Actively recruiting or completed trials registered on Clinicaltrial.gov (accessed on 13 April 2021). COVID-19, coronavirus disease 2019; ID, investigation drug; SOC, standard of care; T2DM, type 2 diabetes mellitus.

was neither consistently evidenced in the present study[1], even after looking at the low and high estimates of the hazard ratio, nor in most previous epidemiological studies[2–4].

As an external illustration, in the field of diabetes medication and cardiovascular disease, the safety of sulfonylureas was questioned for more than 50 years. This uncertainty started with the University Group Diabetes Program trial, which suggested that this drug class was associated with cardiovascular mortality. Numerous reports were generated from so-called real-life evidence that suggested that sulfonylureas were indeed deleterious regarding cardiovascular outcomes. The CAROLINA randomized controlled trial (RCT), an international non-inferiority trial including 6,042 participants with T2DM and a high cardiovascular risk, followed for 6.2 years, compared glimepiride and linagliptin, a DPP4 inhibitor previously reported as neutral for cardiovascular outcomes, versus placebo. This trial established the lack of difference between the two drugs regarding 3-point major adverse cardiovascular events (MACE): 356 of 3,023 participants (11.8%) in the linagliptin group versus 362 of 3,010 (12.0%) in the glimepiride group (HR 0.98 (95% CI 0.84–1.14); $P<0.001$ for noninferiority and $P=0.76$ for superiority). These findings remind us that mild to moderate effects in observational studies, such as what was consistently found for sulfonylureas, should not be taken for granted[7]. In this respect, an independent study tried to predict RCT findings from real-world evidence. They considered patients with T2DM and high cardiovascular risk and selected 24,131 propensity score-matched pairs of patients initiating linagliptin or glimepiride. Results were consistent with those of the CAROLINA trial after applying a propensity matching, taking more than 120 confounding factors into account[8] (HR for 3-point MACE = 0.91, CI 0.79–1.05).

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To further illustrate the difference between association and causation, a second example could be considered here in the context of COVID-19. An association between vitamin D deficiency and COVID-19 prognosis was suspected very early in the course of the pandemic and was later supported by observational findings. However, a RCT published in 2021 did not find any positive effect of vitamin D supplementation on hospital length of stay or any secondary end points, whereas plasma concentrations of vitamin D were higher in those randomized to supplementation than in those who received placebo[9].

Still, according to these observational findings, it can be argued that the switch from one drug with a potential deleterious association to another with a potential beneficial association is tempting. For instance, in patients with T2DM and COVID-19, why not substitute DPP4 inhibitors for SGLT2 inhibitors? Waiting until ongoing trials produce results seems rather conservative, even if results are expected rapidly. The current efforts on this topic are summarized in TABLE 1 and Supplementary Table 1. Obviously, current trials will not clearly answer all of these open questions.

Lastly, the interpretation of the present study[1] can be viewed in the light of the pathophysiological mechanisms linking drugs and outcomes. The fact that metformin and sulfonylureas were both associated with protective hazard ratios must be seen as supportive of a lack of causation, as the mechanisms of action of these two drugs are opposite. Sulfonylureas induce insulin secretion, whereas metformin decreases insulin resistance. Considering the effect of glucose-lowering therapies on decreasing inflammation[10], it is tempting to group metformin and SGLT2 inhibitors together owing to their common protective association with decreased inflammation; however, the lack of association between GLP1 receptor agonists, which are also associated with decreased inflammation, and mortality does not support this hypothesis and brings us back to indication bias.

In conclusion, the understanding of the association between glucose-lowering therapies and COVID-19-related death in people with T2DM is at an early stage. Well-conducted observational studies are not able to evidence strong protective or deleterious associations, which discourages a dramatic change in glucose handling in patients with T2DM. This weak effect illustrates how real-world evidence should be taken cautiously, even when data on a nationwide range are made available.

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Competing interests
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