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technological advances—such as the newer glucose monitoring devices—might reduce the higher relative mortality in women younger than 40 years with type 2 diabetes and men of all ages with type 1 diabetes. The high proportions of people younger than 40 years diagnosed with type 2 diabetes from ethnic minority groups, particularly those of South Asian heritage, and more socially deprived localities, highlight important target populations for primary and secondary prevention.

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## Dapagliflozin in patients with COVID-19: mind the kidneys

We read the DARE-19 trial by Mikhail Kosiborod and colleagues,[1] published in *The Lancet Diabetes and Endocrinology* with interest. The DARE-19 trial was a randomised, double-blind, placebo-controlled trial of patients hospitalised with COVID-19. Key inclusion criteria were hospitalisation with laboratory confirmed or clinically suspected SARS-CoV-2 infection no more than 4 days before screening, requirement of oxygen supplementation of 5 L/min or less to achieve an oxygen saturation of at least 94%, and one or more cardiometabolic risk factors including chronic kidney disease (estimated glomerular filtration rate [eGFR] between 25–60 mL/min per 1·73 $m^2$). Praiseworthy logistics were applied resulting in recruitment of 1250 patients from 95 sites in seven countries, with 60% of participants from Brazil.

Adding dapagliflozin 10 mg versus placebo to usual care did not affect the two primary outcomes: reduction in organ dysfunction or death and improvement in clinical recovery. Development of acute kidney injury was hierarchically the most important secondary outcome. The authors concluded that dapagliflozin did not increase the risk of acute kidney injury because there was no difference in the proportion of patients with serum creatinine concentrations two times that reported at baseline. However, doubling of serum creatinine represents acute kidney injury stage 2 according to current Kidney Disease: Improving Global Outcomes (KDIGO) criteria[2] and does not exclude stage 1 acute kidney injury or worse stages that manifest only as oliguria. A retrospective cohort study of patients hospitalised with COVID-19 confirmed that acute kidney injury occurred in 1835 (46%) of 3993 individuals.[3] Morality was significantly worse in those with acute kidney injury. Of note, 716 (39%) of 1835 patients with acute kidney injury cohort in the retrospective study would not have met the acute kidney injury criteria used in DARE-19 and would have been missed. In DARE-19, acute kidney injury occurred in only 62 (5%) of 1250 patients, but the true incidence of was likely much higher.

Dapagliflozin is a SGLT2 inhibitor associated with a haemodynamically driven reduction in eGFR.[4] Patients hospitalised with COVID-19 are at high risk of developing kidney injury for various reasons, such as dehydration and hypotension (70%), and viral sepsis (22%).[3,5] In this context, starting a drug that might reduce glomerular perfusion could have a detrimental effect. In our opinion, it is premature to claim that dapagliflozin is safe with respect to kidney function in patients who are acutely ill. To avoid potentially misleading conclusions and to prevent

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iatrogenic acute kidney injury in high risk patients, we strongly recommend that appropriate criteria are applied in future clinical trials. Furthermore, studying the effect of dapagliflozin using biomarkers of glomerular and tubular injury would add granularity to the functional criteria (serum creatinine elevation or urine output decline).[6] We strongly suggest that full KDIGO criteria be used (possibly with the inclusion of biomarkers of kidney damage) in upcoming investigations.

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## Authors' reply

We appreciate the correspondence from Thiago Reis and colleagues regarding the selection of criteria for acute kidney injury in the DARE-19 trial.[1] We used several definitions of kidney events in the trial, which were prespecified in the protocol approved by regulatory authorities in each participating country. The kidney organ dysfunction component of the primary efficacy endpoint of prevention included doubling of serum creatinine or initiation of renal replacement therapy during index hospitalisation; the first key secondary efficacy endpoint was a kidney composite, which also included serious adverse events of acute kidney injury after discharge and all-cause mortality until day 30; and acute kidney injury was also a key safety event (defined as doubling of serum creatinine during index hospitalisation or a serious adverse event of acute kidney injury after discharge until day 30). Regardless of the definitions used, there was no evidence for an increased risk of acute kidney injury with dapagliflozin compared with placebo. The number of kidney events was numerically lower in patients who received dapagliflozin across all these endpoints, although these findings did not reach statistical significance.

Reis and colleagues suggest that the definitions of acute kidney injury in the DARE-19 trial (which capture Kidney Disease: Improving Global Outcomes [KIDIGO] stage 2 and higher) were overly strict, and that all stages of acute kidney injury (including stage 1 acute kidney injury) should be used in the evaluation of SGLT2 inhibitors (which might cause an acute dip in estimated glomerular filtration rate) in patients hospitalised with acute COVID-19. The key argument behind this suggestion is that earlier stages of acute kidney injury are common, and have been shown to be of prognostic importance, but might have been missed because of our more restrictive definitions. We would like to point out that the prognostic implications of acute kidney injury referenced by Reis and colleagues typically refer to the incidence of hard clinical events, such as initiation of renal replacement therapy and death. The study by Chan and colleagues,[2] cited by Reis and colleagues, is a large study of acute kidney injury in patients hospitalised with COVID-19. Chan and colleagues,[3] specifically used the outcome of all-cause mortality when referring to the prognostic implications of different acute kidney injury stages. In the DARE-19 trial,[1] we observed no signal for a higher risk of renal replacement therapy, other prespecified events of organ failure, or death in patients who received dapagliflozin; and the number of these events, although not statistically different, were numerically lower in the dapagliflozin group compared with the placebo group. Thus, although inclusion of stage 1 acute kidney injury would have likely increased the number of acute kidney injury events by adding mild elevations in serum creatinine, it would have had no effect on the results of the DARE-19 trial as it pertains to the important clinical events.

In summary, we do not believe that inclusion of KIDIGO stage 1 acute kidney injury would have altered the key conclusions of the DARE-19 trial.

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