COMMENTARY

Initiation and Continuation of Sodium–Glucose Cotransporter 2 Inhibitors in Hospital Inpatients: Ready for Prime Time?

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Regular readers of this and many other diabetes journals will be aware of the almost-daily appearance of publications showing that the use of the sodium–glucose cotransporter 2 inhibitor (SGLT2i) class of oral hypoglycemic drugs is associated with improvements in cardiovascular and renal outcomes in those with diabetes and in those without. These data have led to these drugs being promoted as co–first-line agents in the management of type 2 diabetes in those with, or at high risk of developing, cardiovascular or renal disease (1,2). However, almost all of these studies, and subsequent benefits, have been in outpatient populations. There are fewer data on their acute use in the inpatient population.

In this issue of *Diabetes Care*, Khunti et al. (3) attempt to address the issue of safety of inpatient use of SGLT2i by using data from a nationwide audit carried out across 40 centers in the U.K. by the Association of British Clinical Diabetologists (ABCD). They looked at SGLT2i use and subsequent risk of diabetic ketoacidosis (DKA) or death in people with type 2 diabetes admitted to hospital with coronavirus 2019 disease (COVID-19) infection (3). They showed low rates of DKA in those using SGLT2i prior to hospitalization for COVID-19 infection. This article, together with another recent article from Khunti et al. (4), challenges the adage that SGLT2i should be stopped at the time of acute hospital admission. If the benefits exhibited in outpatients can be extended to the inpatient population, SGLT2i administration may provide added benefit because of the well-recognized harms caused by inpatient dysglycemia (5). However, is this the right thing to do, and do we have enough data to support this change in practice?

There are several things that need to be considered when discussing SGLT2i use in the inpatient population. As Khunti et al. (3) and others point out, there are good theoretical reasons why their use can be beneficial in acute illness. These include, but are not limited to, reductions in oxidative stress, endothelial dysfunction, and sympathetic function (4,6). However, the argument against the use of SGLT2i in the hospitalized inpatient is based predominantly on the fear of precipitating DKA, as well as hypovolemia or genital yeast infections, in those with diabetes.

In those with diabetes who are fasting or have low carbohydrate intake, insulin concentrations drop. Indeed, being on an SGLT2i may lower glucose concentrations, further lowering the drive to secrete insulin. Raised counterregulatory hormone concentrations in acute illness drive lipolysis and, together with the low insulin concentrations, allow the formation of ketones. If this is uncontrolled, then DKA may be precipitated (7). To date, very few cases of DKA have occurred in those without diabetes in the outpatient studies, and it is probable, because insulin concentrations in this population will be sufficient to inhibit ketosis, that DKA will not occur unless the individual is in extremis or on a ketogenic diet (8).

A recent systematic review and meta-analysis of the rate of DKA with SGLTi use suggested that the absolute rate across several randomized controlled trials ranged from 0.6 to 2.2 events per 1,000 person-years (9), with other, real-world insurance-based data from the U.S. suggesting rates of 6.0 to 6.3 per 1,000 person-years (10). These are rates in outpatients, most of whom have underlying atherosclerotic cardiovascular disease or chronic kidney disease but have no acute physiological trespass, i.e., are not acutely unwell. Can these outpatient data be translated to inpatients who, by the nature of their need for acute hospital admission, are unwell and already at potentially higher risk of developing DKA?

The two studies that have looked at the use of SGLT2i in acutely unwell inpatients were designed to assess efficacy and safety (11,12). However, with the benefit of hindsight it can be argued that, just on the basis of the trial design, they would fail to show a safety signal. The Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) study

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had 625 people in the dapagliflozin arm followed for 30 days, a total of 51.4 patient-years, with 2 cases of DKA. Similarly, the Empagliflozin in Patients Hospitalized for Acute Heart Failure (EMPULSE) trial had 125 people with diabetes on empagliflozin followed for a maximum of 90 days, a total of 30.6 patient-years. While there were no cases of DKA in the EMPULSE trial, the DARE-19 study data equated to a rate of almost 39 cases of DKA per 1,000 patient-years. Of course, this risk is potentially increased by the change in the concentration of counterregulatory hormones, in the insulin-to-glucagon ratio, and change in diet with a reduction in carbohydrate intake, thus increasing the risk of ketogenesis. This underpowering may also be the case with the ongoing SGLT2i arm of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial in the care of people hospitalized for COVID-19 disease, but those results are awaited (13). The ongoing Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack (DAPA-MI) study is aiming to recruit 6,400 people within 7 to 10 days of an acute myocardial infarction and may help answer some of these questions, but even then, the acute phase of the cardiovascular event may have subsided (14). Therefore, even with the ongoing real-world audit from ABCD, it will take time to collect enough data to demonstrate a sufficient safety signal for people to feel more comfortable prescribing these agents in acutely unwell inpatients.

One of the strengths of the ABCD data is that across the U.K., almost all hospitals use the same definition of DKA (15,16). This is not the case with many of the SGLT2i outcome trials, making it more difficult to make direct comparisons of rates of DKA (17). There are, however, some limitations of the article by Khunti et al. (3), which they acknowledge. By the nature of the data collection tool, it was unknown how many of those people admitted to the hospital had been on SGLT2i and had stopped them prior to coming into the hospital. Indeed, it could be argued that because they had longer duration of diabetes and more were on insulin, they would have had greater numbers of contacts with diabetes specialists and then would have had greater provision of "sick day rules," one of which says that if you are admitted to hospital, then these drugs should be stopped (18). This suggests that SGLT2i use is safe if the incidence of DKA is no higher in those using the drugs on admission and those who had stopped it prior to admission.

Readers of this journal may experience the heuristic principle, i.e., if we hear or see rare conditions, we are more likely to recall it. However, the vast majority of people eligible for SGLT2i will be looked after by nonspecialists who may not have an awareness of these potential dangers. Are SGLT2i ready for primetime use in inpatients? Given the data available to date, I suggest that the jury is still out. This is why the ongoing work by ABCD and others is so important. Without these real-world data, we will never get the answers we all seek.

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