Are SGLT2 Inhibitors Safe and Effective in Advanced Diabetic Kidney Disease?

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A substantial portion of health care use and cost related to CKD occurs with the development of kidney failure and the requirement for KRT with dialysis and/or kidney transplantation. Current estimates suggest that hospitalization rates for diabetes and CKD will increase more than for all other causes of CKD (1).

Measures of kidney function and damage assessed by the eGFR and the urinary albumin-creatinine ratio (ACR), respectively, are independent predictors of progression of diabetic kidney disease and currently provide the greatest opportunity to identify those at greatest need of interventions to preserve kidney function (2). However, until recently there have been very few treatment options aside from inhibition of the renin-angiotensin system, intensive glycemic control, and strict control of BP. Indeed, until now, the mainstay of management of patients with very low eGFR (late stage 4 and stage 5 CKD) has been close monitoring and/or preparation for KRT.

Large outcome trials of inhibitors of sodium-glucose cotransporter 2 (SGLT2is) or gliptins among patients with type 2 diabetes at high cardiovascular or kidney risk now provide a growing evidence base for cardiovascular and kidney benefits (3). Of these, the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial, which studied 4401 patients with type 2 diabetes, proteinuria (ACR of >300 mg/g), and eGFR>30 ml/min per m², was the first to demonstrate that canagliflozin 100 mg reduced risk of major kidney (a composite of ESKD, a doubling of the creatinine level, or death from kidney causes) and cardiovascular events (cardiovascular death, myocardial infarction or stroke, and heart failure hospitalization) (4). This resulted in the US Food and Drug Administration approving canagliflozin for prevention of kidney failure among patients with type 2 diabetes with eGFR>30 ml/min per m². However, the question of whether SGLT2i is similarly beneficial among patients with lower eGFR (<30 ml/min per m²) remains, particularly as the glucose-lowering and natriuretic effects of SGLT2i may diminish with markedly reduced glomerular filtration.

In this issue of CJASN, Bakris et al. (5) present a compelling post hoc analysis from the CREDENCE trial assessing the efficacy and safety of canagliflozin among trial participants who had eGFR<30 ml/min per 1.73 m² at study randomization in comparison with those who had eGFR≥30 ml/min per 1.73 m².

Overall, 174 of the 4401 (4%) participants had an eGFR<30 ml/min per 1.73 m² (mean [SD] eGFR: 26.5 [2.9] ml/min per 1.73 m²) at randomization, a fall that occurred during the interval from initial screening to the randomization visit over a range of 3–8 weeks for most participants (median 29 days). As per the study protocol, all participants, including those with eGFR<30 ml/min per 1.73 m², were receiving treatment with a stable maximum labeled or tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥4 weeks prior to randomization and advised to continue study treatment (canagliflozin 100 mg or matching placebo) until the commencement of dialysis, receipt of a kidney transplant, occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy, or study conclusion. During a median follow-up of 2.62 years, adverse events and eGFR were assessed at week 3, 12 weeks, 6 months, and every 6 months, including study closeout, allowing assessment of the original study primary outcomes and quantification of short-term acute change in eGFR (baseline to week 3), annualized chronic change in eGFR from week 3 to the end of treatment, and the total change in eGFR from baseline to the end of treatment.

Despite the very small number of participants with eGFR<30 ml/min per 1.73 m², the baseline characteristics were generally balanced across the canagliflozin and placebo groups, most notably for diabetes duration, hemoglobin A1c, BP, and albuminuria levels. At the end of follow-up, hemoglobin A1c and BP were numerically lower but not significantly different in the canagliflozin versus placebo groups.

In terms of efficacy, no heterogeneity in the effects across eGFR categories (i.e., <30 versus ≥30 ml/min per 1.73 m²) for any of the clinical outcomes, including development of kidney failure and major cardiovascular events, was observed. However, all effect estimates in the <30- versus ≥30-ml/min per 1.73 m² group were closer to the null with wide and overlapping 95% confidence intervals, suggesting uncertainty in the results due to the small sample size and low event numbers. The mean rate of decline in eGFR was 66% lower (−1.30 versus −3.83 ml/min per 1.73 m² per year) in the canagliflozin group, whereas the ACR was

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33% lower (95% confidence interval, 10% to 49%) in the canagliflozin group in keeping with the effects for the overall trial population over the study period. Importantly, the incidence of AKI was not different in the canagliflozin versus placebo group, and an acute reversible decline in eGFR (3 weeks after drug commencement) was not observed.

As one might expect, greater proportions of overall serious adverse events, drug discontinuations, and discontinuations due to adverse events were observed in the <30- versus >30-ml/min per 1.73 m² eGFR groups. An important omission was the number of ketoacidosis events. In the main CREDENCE trial, a ten-fold greater risk of ketoacidosis was reported. Understanding the risk of this serious complication for this vulnerable patient population (already at risk of uremic acidosis) will be critical for safe prescribing. Further trials and real-world observational studies will hopefully address this concern. In the interim, detailed patient education on appropriate use of SGLT2i with fasting, procedures, and sick day management will assist in minimizing any risk of harm.

The recently completed Dapagliflozin in Patients with CKD trial, which recruited participants with eGFR down to 25 ml/min per 1.73 m², has yet to report the effects of dapagliflozin versus placebo in those with eGFR<30 ml/min per 1.73 m² (13.8% of the total study population) (6). However, intriguingly, it has demonstrated similar benefits of dapagliflozin 10 mg versus placebo in participants with diabetic and nondiabetic proteinuric kidney disease. Meanwhile, the ongoing Study of Heart and Kidney Protection With Empagliflozin-Kidney trial is examining the effects of empagliflozin 10 mg in participants with an eGFR down to 20 ml/min per 1.73 m² with or without proteinuria (7). Data from these two trials will provide additional insight into the safety and efficacy of SGLT2is in people with very low eGFR and no proteinuria.

Until then, it would seem reasonable for clinicians to commence SGLT2i on the basis of current indication (patients with type 2 diabetes and proteinuric kidney disease with eGFR>30 ml/min per 1.73 m²), to monitor closely, and to continue treatment on the basis of individual tolerability, even when eGFR drops below 30 ml/min per 1.73 m² or until the commencement of maintenance dialysis or receipt of a kidney transplant.

Disclosures
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See related article, “Effects of Canagliflozin in Patients with Baseline eGFR <30 ml/min per 1.73 m²: Subgroup Analysis of the Randomized CREDECE Trial,” on pages 1705–1714.