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Is it Time to Expand the Use of SGLT2 Inhibitors in Kidney Transplant Recipients?

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The emergence of sodium-glucose cotransporter-2 inhibitors (SGLT2i) over the past decade has revolutionized the management of patients with chronic kidney disease (CKD). SGLT2i have multiple effects on the kidney, including reducing intraglomerular pressure, leading to renal protective benefits for patients with CKD who are independent of improved glycemic control. Multiple studies have demonstrated a reduced risk of progressive decline in estimated glomerular filtration rate (eGFR) and progression to end-stage kidney disease in patients with diabetes and albuminuria treated with SGLT2i. These studies have also demonstrated a reduced risk of death from cardiovascular causes in this population.[1] Based on the data from the diabetes trials, the Kidney Disease Improving Global Outcomes guidelines were updated to recommend the use of SGLT2i for all patients with diabetes, CKD, and eGFR $\geq$ 20 ml/min.[2] However, the recommendations did not extend to kidney transplant recipients, because they were excluded from the trials and there were limited data on safety and efficacy in this population. Of notable concern was the increased risk of infection in immunosuppressed patients given the increased risk of genital mycosis associated with SGLT2i use in the general population. The DAPA-CKD trial showed that the kidney and cardiac benefits of SGLT2i extended to patients with nondiabetic CKD.[3] The Kidney Disease Improving Global Outcomes guidelines for CKD management now endorse the use of SGLT2i in all patients with CKD and albuminuria, although kidney transplant recipients (KTRs) were not included given the paucity of data in this population.[4]

Given the renal and cardiac protection seen in the general population, there is growing interest in the use of SGLT2i in KTRs, in whom long-term graft survival remains suboptimal and cardiovascular disease remains the leading cause of death. Nevertheless, until recently there were few data on the use of SGLT2i in this population. In this issue of Kidney International Reports, Maigret *et al*. report outcomes from the French GREAT-ASTRE (Gliflozin in Renal Transplantation) database that included 347 KTRs initiated on an SGLT2i from June 2021 to March 2023.[5] Importantly, 121 KTRs in the cohort did not have a history of diabetes. SGLT2i were prescribed based on local practice rather than prespecified criteria, although in general they were not started within the first 3 months of transplant and use was avoided in patients with a history of recurrent urinary tract infections. The baseline characteristics of the cohort (mean eGFR: 45 ml/min, mean proteinuria: 520 mg/d) suggest that most patients had an indication for SGLTi use based on CKD guidelines for native kidney disease.

The authors' primary objective was to provide real-world safety data, and over a median follow-up period of 1-year they found that SGLT2i use was generally well tolerated. Urinary tract infection was the most frequent adverse event (5%); however, reassuringly there were only 2 cases of genital mycosis and there were no signs of an increase in the risk of other infections despite the baseline immunosuppression. SGLT2i discontinuation, which was more frequent in patients with baseline eGFR $<$ 45 ml/min, occurred in 16% at 12months, a rate which was comparable with the DAPA-CKD study. The safety profile did not differ in patients with and without diabetes. The impact on renal function was similar to what is seen in native kidney disease, with slight but significant decreases in eGFR, proteinuria, and blood pressure reported in the

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short-term, findings which were irrespective of baseline diabetes status.

There are several limitations to this study, including the short duration of follow-up which limits the ability to comment on the long-term safety and efficacy of SGLT2i in KTRs. Majority of patients were several years posttransplant at the time of SGLT2i initiation. It is possible that the rate of infectious complications would be higher in the early posttransplant period, when levels of immunosuppression are high. Similarly, the discontinuation rate might be high if SGLT2i are initiated early post-transplant, because even small declines in kidney function during this period may lead to intervention by the transplant team. Although the benefits of SGLT2i in the general population are due to a class effect, most patients were prescribed dapagliflozin and it is possible that the effects seen in this study may not apply to other SGLT2i. In addition, the authors did not include data on graft failure, death, and cardiovascular outcomes, which might be expected to improve with SGLT2i use based on data from the general population.

Maigret *et al*. add to the emerging literature on the safety and efficacy of SGLT2i use in KTRs. Their findings are similar to those reported in other recent large cohorts of diabetic KTRS from Korea, Spain, and the United States.[6-8] Most importantly, Maigret *et al*. are the first to report on a sizable population of nondiabetic KTRs treated with SGLT2 inhibitors, providing reassuring safety data for use in a group of patients who will likely be prescribed these medications in increasing numbers based on benefits seen in the non-transplant population.

Although Maigret *et al*. did not report cardiovascular outcomes, 2 recent studies have found that the benefits of SGLT2i in the general population appear to extend to KTRs. In a large cohort of Korean KTRs with diabetes treated with SGLT2i, Lim *et al*. found a significant reduction in the rate of major adverse cardiac events (myocardial infarction, death from cardiovascular cause, stroke, or hospitalization for heart failure; hazard ratio [HR]: 0.37) and myocardial infarction (HR: 0.15).[9] Sheu *et al*., examining a large international database of electronic health records, found that use of SGLT2 in diabetic KTRs was associated with a significantly lower rate of mortality (adjusted HR: 0.32), major adverse cardiac events (death, myocardial infarction, stroke, hemorrhagic stroke, and cardiac arrest) (adjusted HR: 0.48), and major adverse kidney events (death and initiation of dialysis) (adjusted HR: 0.52).[10] Nevertheless, several lingering questions remain, including when SGLT2i can be initiated after transplant (because most studies have reported KRTs who are more than 1-year posttransplant) and whether the cardiovascular and kidney benefits found by Lim *et al*. and Sheu *et al*. will extend to the nondiabetic KTR population.

Cardiovascular disease remains the leading cause of death following kidney transplant, thereby contributing to suboptimal long-term graft survival. Historically, many cardioprotective interventions have been underutilized in KTRs. Maigret *et al*. add to the growing literature that we can use SGLT2i safely in diabetic KTRs and provide important data on the safe use of SGLT2i in nondiabetic KTRs. Based on the emerging data, it might be time for the transplant community to fully embrace the use of SGTL2i and prescribe them in all KTRs with an indication, irrespective of diabetes status.

DISCLOSURE

All the authors declared no competing interests.

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