Sodium-Glucose Cotransporter 2 Inhibitors & Kidney Transplantation: What Are We Waiting For?

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In recent robust randomized clinical trials (RCT), sodium-glucose cotransporter 2 (SGLT2) inhibitors, (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin), have been shown to dramatically decrease both kidney and cardiovascular (CV) adverse outcomes in patients with diabetic kidney disease (DKD), non-diabetic proteinuric kidney disease, and heart failure (HF) with reduced ejection fraction - with and without the presence of diabetes.\textsuperscript{1-6} For decades, both the nephrologist and transplant nephrologist’s arsenal for the management of proteinuric kidney disease has been limited to renin-angiotensin-aldosterone system blockade.\textsuperscript{7} Though SGLT2 inhibitors have taken the nephrology community by storm, patients with kidney transplants (KT) have been notably excluded from large RCT.\textsuperscript{8-10} Pathophysiologically, it seems likely they would also benefit from these apparent wonder drugs, particularly as many patients with KT have proteinuric kidney disease or heart failure. Similar to patients with native kidney disease, CV mortality is the leading cause of death in the KT population.\textsuperscript{11} Is it time to allow patients with KT to benefit from proposed SGLT2 inhibitor mechanisms including tubuloglomerular feedback restoration, decreased inflammation and fibrosis, and alteration in energy metabolism that all culminate in improved CV and kidney outcomes?\textsuperscript{12} Here, we review the available data for SGLT2 inhibitor use in patients with kidney transplants and discuss potential benefits and risk of their use in this population.

**Cardiovascular and Native Kidney Outcomes**

Since 2015, sequential RCTs have demonstrated efficacy of SGLT2 inhibitors in improving both kidney and CV outcomes. A 2020 meta-analysis included 6 of these RCTs that studied SGLT2 inhibitor use (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) in close to 47,000 patients with diabetes.\textsuperscript{2} In all the studies included in the meta-analysis, SGLT2 inhibitor use led to a reduction in HF hospitalizations, with empagliflozin being the only drug with significant CV death risk reduction. A reduction in kidney outcomes was seen with all agents except ertugliflozin, despite its similar pharmacology to other drugs in the class.

Via selective SGLT2 cotransporter inhibition in the proximal convoluted tubule (PCT), these medications inhibit filtered glucose reabsorption. Interestingly, early SGLT2 inhibitor RCTs, CANVAS and EMPA-REG, reported a mean glycated hemoglobin (HbA1c) improvement of only 0.5-0.6%.\textsuperscript{3,4} Thus, the
mechanism portending favorable CV and nephroprotective effects of SGLT2 inhibitors extend well beyond the anti-glycemic effects and include the restoration of tubuloglomerular feedback and natriuretic effects as well as proposed direct effects on myocardial tissue and the pathogenesis of fibrosis.\textsuperscript{13}

Early RCT results suggested positive kidney effects of SGLT2 inhibitors, however, the primary endpoints of these studies were cardiovascular and not kidney outcomes.\textsuperscript{4,8} Moreover, they included patients with mean estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73m\textsuperscript{2} and only 8-11\% of patients had albuminuria. The 2019 CREDENCE trial included 4,400 patients with type 2 diabetes and albuminuria with or without CKD (eGFR > 30 mL/min/1.73 m\textsuperscript{2}) and showed a 30\% relative risk reduction (p=0.00001) in end-stage kidney disease, doubling of the serum creatinine, or kidney or CV death with the use of canagliflozin as compared to placebo.\textsuperscript{9} This study also showed a mean 31\% decrease in albuminuria.\textsuperscript{5} Serious adverse events were not seen in patients on canagliflozin. More recently, the DAPA-CKD trial showed improved kidney outcomes with dapagliflozin in patients with and without diabetes and CKD (eGFR > 25 mL/min/1.73 m\textsuperscript{2}) and albuminuria.\textsuperscript{6} This study showed an improved primary composite outcome (≥50\% eGFR decline, new end stage kidney disease, kidney or CV mortality) in the dapagliflozin group compared to placebo (HR 0.61; 95\% CI 0.51-0.72; p <0.001).

While exclusion criteria of previous RCTs have been limited, those with KT on immunosuppressants have not been included. Further, patients with KT have a high prevalence of diabetes and CV disease, with subsequent overall morbidity and mortality.\textsuperscript{11}

**Potential Risks of SGLT2 inhibitor Use in Patients with KT**

Clinical studies have clearly showcased the benefits of SGLT2 inhibitors, but have simultaneously been accompanied by concern for urinary tract infection (UTI), acute kidney injury (AKI), genital infections including both mycotic and Fournier’s gangrene, lower extremity amputations, and euglycemic ketoacidosis (Figure 1).\textsuperscript{14}
Infectious Risks

Infection clearly raises additional concern for patients with KT on immunosuppression. These patients are at increased risk of bacterial and fungal infections, particularly earlier in the post-transplantation period, due to the risk of leukopenia from immunosuppressant use coupled with concomitant viral prophylaxis.\textsuperscript{15} SGLT2 inhibitor-induced glucosuria may provide a substrate for bacteria and fungi growth and increase the risk of urogenital infections, including potentially life-threatening Fournier’s gangrene (necrotizing fasciitis of the perineum). Of note, a recent study found that treatment with SGLT2 inhibitors, when compared to treatment with two or more non-SGLT2 inhibitor anti-hyperglycemic agents or insulin alone, was not associated with an increased risk of hospitalization for Fournier’s gangrene.\textsuperscript{16}

Though RCTs have not shown a significantly increased risk of UTI associated with SGLT2 inhibitor use, UTIs already present a significant challenge in patients with KT as the most common infectious complication that accounts for 30% of hospitalizations for sepsis.\textsuperscript{17} Even without the use of SGLT2 inhibitors, approximately one quarter of transplant recipients develop a UTI within the first year of transplant. Risk factors include female sex, history of frequent UTI prior to transplantation, urological abnormalities, and ureteral stent use.\textsuperscript{18} Similarly, SGLT2 inhibitor-induced glucosuria has been associated with an increased risk of mycotic genital infection (candida vaginitis, vulvovaginitis, or balanitis), with increased risk reported for women and those with a history of prior infection.\textsuperscript{14} Compared to individuals enrolled in these studies, patients with KT differ in both their genitourinary anatomy and use of chronic immunosuppression, thus begging the question of whether SGLT2 inhibitors will lead to a more pronounced adverse effect profile in this population.

Non-Infectious Risks

As in the non-KT population, AKI, ketoacidosis, and distal limb amputations present potential risks for patients with kidney transplants. Physiologically, SGLT2 inhibitors cause afferent arterial vasoconstriction and subsequently can precipitate an acute drop in GFR.\textsuperscript{8,9} This reduction in GFR, coupled with the natriuretic and diuretic effect, has led to concern that SGLT2 inhibitors can increase the risk of
hemodynamic AKI. It is plausible that this impact may be more profound in the early post-transplantation period, particularly when polyuria is common. In patients without KT, a recent meta-analysis of over 150,000 patients and found that regardless of the type of SGLT2 inhibitor used, the odds of AKI was actually lower in the treatment group.\textsuperscript{19} Reports of euglycemic ketoacidosis have underscored the importance of SGLT2 inhibitor avoidance in those with type 1 diabetes as well as during episodes of illness. Further, patients with KT are already at increased risk of diabetic ketoacidosis that has been associated with higher mortality.\textsuperscript{20} Although an increased risk of lower extremity amputation was seen in CANVAS with canagliflozin use, subsequent studies of both canagliflozin and other SGLT2 inhibitors suggest this is not a class effect.\textsuperscript{2,9,10}

**Efficacy and Safety of SGLT2 inhibitors in Patients with KT: What We Know**

Though large enough studies have not yet been completed to answer the question of long-term efficacy, limited studies have begun to try to answer that of short-term efficacy and safety of SGLT2 inhibitors in patients with KT and type 2 diabetes. These studies, consisting one small RCT, case series, and retrospective analyses, are summarized in Table 1. As has been reported in non-KT SGLT2 inhibitor clinical trials, patients with kidney transplants also experienced only modest improvements in glycemic control.

The only RCT including patients with KT enrolled 49 patients with new onset diabetes after transplantation (NODAT) that were randomized to either empagliflozin or placebo.\textsuperscript{21} This study found that after 6 months, patients in the empagliflozin group had minimal change in glycated hemoglobin (HbA1c), fasting plasma glucose, or 2-hour oral glucose tolerance test. Similarly, a prospective study in which 8 patients with diabetes and KT were switched from insulin to empagliflozin monotherapy found higher oral glucose tolerance test results, home blood glucose levels, and HbA1c - suggesting that empagliflozin should be used as an add-on agent, rather than monotherapy.\textsuperscript{22} In addition, several case series have also shown modest changes in HbA1c with SGLT2 inhibitor use.\textsuperscript{23–27} Overall, these studies did not find significantly higher rates of infection with SGLT2 inhibitor use, though inclusion criteria were generally limited to those without a significant history of UTI or genital mycotic infections. In some cases, however, UTI did lead to
SGLT2 inhibitor discontinuation. Inclusion criteria for many of these studies also selected for those patients at least one-year post-transplantation with well-controlled diabetes and stable kidney function. Two studies (both with canagliflozin use) reported no episodes of UTI or genital infections.\textsuperscript{23,24} Thus far, there have been no reports of FG in patients with KT with SGLT2 inhibitor use. Apart from one study, SGLT2 inhibitors were administered at least 1 year after kidney transplantation.\textsuperscript{28}

From the only KT RCT mentioned earlier, three episodes of UTI occurred in both treatment and control arms, and 1 genital mycotic infection was reported in the empagliflozin group.\textsuperscript{21} This study excluded patients with a history of recurrent UTI, urosepsis, and genital mycosis. Several other studies employed similar exclusion criteria, with some requiring a UTI-free period of 6 months prior to SGLT2 inhibitor initiation.\textsuperscript{23,25}

As immunosuppression is typically more intense during the first year after transplantation, the majority of reports examining the use of SGLT2 inhibitors in kidney transplantation thus far have excluded patients during this time period. The largest retrospective study to date includes 50 patients with KT (mostly on empagliflozin), half of which were initiated on SGLT2 inhibitors within the first year of transplantation.\textsuperscript{28} In this cohort, there were no reports of AKI, amputations, or DKA. There were 7 UTIs (14%), similar to the prevalence of UTI in this population without SGLT2 inhibitor use. There was a statistically significant decrease of 0.13 mg/dL in magnesium concentration, without clear clinical significance.

Due to their diuretic effect, it is not surprising that SGLT2 inhibitors may affect volume status. One study of patients with KT on empagliflozin used bioimpedance spectroscopy to show a transient loss of total body water, without significant decreases in blood pressure.\textsuperscript{22} Similarly, the RCT did not show significant blood pressure changes between empagliflozin and placebo groups.\textsuperscript{21} Both studies reported statistically significant weight loss in patients taking empagliflozin, an average of 1.6 kg (p = 0.02)\textsuperscript{22} and 2.5 kg (p = 0.01)\textsuperscript{21} from their baseline.
Summary and Recommendations

The anti-glycemic effect of SGLT2 inhibitors in patients with KT appears to be comparable to the modest effect previously demonstrated in large RCT in non-KT patients, though data are limited. While long-term CV and kidney outcomes remain to be evaluated in this specific patient population, it seems probable that similar effects will be seen as in the non-transplant population given hypothesized mechanisms of CV efficacy. Current data in this group suggests few cases of infections, only 1 episode of AKI, and thus far no reports of ketoacidosis, amputations, or Fournier’s gangrene. Empagliflozin or canagliflozin may be reasonable options, as they have been the most studied in the KT population within the drug class. With no current guidelines in place, we suggest that transplant nephrologist’s screen patients with KT based on criteria in Table 2 to assess candidacy and consider SGLT2 inhibitor prescription in select patients. Of utmost importance is the assessment for prior history of recurrent UTI and genital infections, and close follow-up after initiation. Blood pressure and diuretics may require adjustment prior to SGLT2 inhibitor initiation. Like those without KT, patients with KT should also receive effective counseling prior to starting SGLT2 inhibitors, including education of SGLT2 inhibitor avoidance on “sick day rules” to lower the risk of AKI and ketoacidosis, checking of blood pressure, maintenance of genital hygiene, and lower extremity surveillance. Similar to waiting 6-12 months post-transplantation, it seems prudent to delay or hold SGLT2 inhibitor administration the setting allograft rejection treatment during which immunosuppression is increased. Although SGLT2 inhibitor use is growing, cost and insurance approvals have been barriers in prescribing them. Of course, the transplant community eagerly awaits RCTs to definitively explore efficacy and safety of this promising drug class. It remains to be seen how SGLT2 inhibitors will perform in those with pancreas transplants, as well as recipients with gastroparesis and bariatric surgery. In medicine, one size has never fit all. It is time for a cautious, thoughtful, and personalized approach to select the best candidates with KT for safe SGLT2 inhibitor use to allow our patients to benefit from this shiny new tool in the nephrologist’s armamentarium.
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S Farouk: Conceptualization; Supervision; Writing - original draft; Writing - review and editing
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Table 1. Summary studies of patients with kidney transplants and sodium glucose cotransporter 2 inhibitor (SGLT2i) use (Ref: reference group; Empa: empagliflozin; dapa: dapagliflozin; cana: canagliflozin; RCT: randomized control trial; PS: prospective study; CS: case series; RS: retrospective study; UTI: urinary tract infection; NR: not reported; AKI: acute kidney injury; KA: ketoacidosis; Amp: amputation; FG: Fournier's gangrene)

<table>
<thead>
<tr>
<th>Author (Drug)</th>
<th>Design</th>
<th>SGLT2i (n)</th>
<th>Control/Ref (n)</th>
<th>UTI</th>
<th>Genital Mycotic Infection</th>
<th>Other Adverse Event (AKI, KA, Amp, FG)</th>
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<tr>
<td>Halden (Empa) 21</td>
<td>RCT</td>
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<td>3 (Control)</td>
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<td>3 (Empa)</td>
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<tr>
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<td>24</td>
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<td>1</td>
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<tr>
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<tr>
<td>Alkindi (Dapa/Empa) 27</td>
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Table 2. Characteristics of the “Ideal” SGLT2 inhibitor candidate with a kidney transplant (KT: kidney transplantation; UTI: urinary tract infection)

<table>
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<tr>
<th>Proposed Characteristics for the “Ideal” SGLT2 inhibitors Candidate with Kidney Transplant</th>
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<tr>
<td>At least 6-12 months after KT with stable kidney function</td>
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<tr>
<td>No recent episode of KT rejection or need for increased immunosuppression within 6-12 months</td>
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<tr>
<td>No history of recurrent UTI or genital infection, and 6 months of UTI-free period prior to initiation</td>
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<tr>
<td>No history of recurrent or persistent hypotension or recurrent episodes of volume depletion</td>
</tr>
<tr>
<td>No history of peripheral vascular disease</td>
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<td>Stable blood pressure</td>
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Figure Legend

Figure 1. Reported adverse effects associated with sodium-glucose cotransporter 2 inhibitor (SGLT2 inhibitors) use. (UTI: urinary tract infection; DKA: diabetic ketoacidosis). This figure was created with biorender.com.