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Dear Editor and Reviewers,

Thank you for your time and efforts in reviewing our manuscript. Below are our point-by-point responses to your commentary with included text we added to the revised manuscript.

**Reviewer #1**

***Comment 1.***

***1.In the section of result, eGFR, proteinuria, blood pressure and other data are listed tediously, you could improve the key results, and conduct targeted discussion according to the described results.***

Thank you for this comment. In the results section, we have revised our listing in a less tedious manner as well as conducting a targeted discussion as demonstrated below:

**RESULTS**

In this sample, empagliflozin (n = 241 ) was the most prescribed SGLT2i followed by dapagliflozin (n = 85) and canagliflozin (n = 74). Median time from transplant for initiating SGLT2i was 3 years (range 0.88 -9.6 years post-transplant). Median baseline eGFR was 66.7 ml/min/1.73m$^2$ (range 50.4-75.8). Median Hgb A1c at initiation was 7.7% (range 6.9-9.3).

The following results were seen and are summarized in Table 1.

*Hgb A1c*

Hgb A1c generally improved with changes between 0.2-1% in the reported studies. Notably, in the study by AlKindi et al., which included a cohort with a mean A1c of 9.3 at initiation as well as excellent allograft function, Hgb A1c decreased by 2.3% at 12 months. As is described by Halden et al., more robust impacts on glycemic control were observed in those with higher Hgb A1c and eGFR.

*eGFR*

eGFR was preserved in most studies over a period of 6-12 months. Lim et al. observed a 10% eGFR dip in 15.6% of their cohort with SGLT2 initiation, though eGFR did recover from this and stabilize. After month 5, there was no significant difference in eGFR between dippers and non-dippers. At last follow up (8 months post-SGLT2i initiation), eGFR in the dippers (67.9 ± 13.9, n = 24) was comparable to that of the non-dippers (67.9 ± 13.9 ml/min/1.73m$^2$ ,[n = 24] vs 69.8 ± 19.0 ml/min/1.73m$^2$ [n = 106], p = 0.358).

Though specific data on long term eGFR are lacking, Lim et al. did report a significant reduction in terms of SCr doubling in the SGLT2i cohort vs non-SGLT2i users in both unadjusted (HR = 0.49, 95% CI: 0.29-0.85) , adjusted (across multiple models: aHR 0.37-0.41,

95% CI 0.22-0.90, all p <0.05) , and propensity-score matching (aHR 0.45, 95% CI 0.23-0.88, p = 0.019) at 72 months of follow up.

*Proteinuria*

Proteinuria was not assessed in these studies. As proteinuria is a major risk factor for and driver of progressive CKD, this is certainly an area that needs further studying.

*Weight*

Weight decreased in 8 studies with a median weight decrease of 1.95 kg (range 0.7 – 3.2 kg).

*Blood pressure*

Blood pressure changes were reported in 4 studies, with mixed results. The magnitude of these changes was on the order of 7-9 mmHg, which are likely clinically significant. This is reaffirmed by findings in the ADVANCE trial, whereby Heerspink et al. showed that randomization to perindopril-indapamide compared to placebo in CKD ≥3 patients with diabetes for 5 years prevented 12 cardiovascular events with reductions in systolic blood pressure on the order of 4.5 mmHg.

*Immunosuppression drug interactions*

Though data on drug interactions with immunosuppression were limited, four studies did not observe clinically nor statistically significantly differences in drug trough levels after SGLT2i initiation.

*Adverse events*

Urinary tract infections (UTI) were the most common adverse event observed across the various studies. When reported, these ranged from none observed up to 36%. 4 studies reported rates between 13-15%.

Genital infections (GI) occurred but less commonly than UTI in KTRs with only a few GI occurring in studies where it was distinctly described.

Graft function remained stable throughout these studies despite high ACEi/ARB utilization and the observed eGFR dip at the 4-6 weeks mark.

Leg amputation was not observed in any of the studies described. Schwaiger et al. reported on this in their study with empagliflozin. As is aptly described by Heyward et al. in their systematic review and meta-analysis, the risk for lower extremity amputation for SGLT2i use in the non-transplant population has only been observed with canagliflozin.

In these small studies, no episodes of euglycemic diabetic ketoacidosis were reported. Song et al. noted a wide range of insulin dose reductions post-SGLT2i incorporation. Hypoglycemia was noted infrequently in these studies (n = 2 per Lemke et al. This risk for hypoglycemia is highest for those with well controlled diabetes (Hgb A1c <8) as well as those on insulin and/or sulfonylurea-class medications, as was the case in the Lemke study.

*Cost*

Lemke et al. identified cost as the highest reported reason for SGLT2i discontinuation (35%, n = 6). Over time, SGLT2i have become more affordable. Aggarwal et al. recently described out-of-pocket expenses for SGLT2i, noting that for most insured patients, median cost for 30 days of SGLT2i therapy cost around $38.43 (range $3.87 – $49.42).

*Novel findings*

In their comprehensive randomized controlled trial, Halden et al. observed increased hemoglobin/hematocrit and decreased uric acid levels with SGLT2i use. Song et al. observed an improvement in serum magnesium levels after SGLT2i initiation.

*Long term outcomes*

Lim et al. showed a significant reduction at five years in their composite outcome of all-cause mortality, death-censored graft failure (DCGF), and serum creatinine doubling with SGLT2i use in both multivariate (adjusted hazard ratio [aHR] (0.43; 95% CI = 0.24-0.78, p = 0.006) and propensity score-matched aHR (0.45; 95% CI = 0.24-0.85, p = 0.013). Otherwise, these studies lacked long term outcome data.

Our discussion is designed to parallel this section and address these issues."

***Comment 2.***

***2.The content of the limitation could be simplified. The discussion of irrelevant content can be reduced, and the limitation of the research content can be highlighted.***

Thank you for this insightful feedback. We have simplified the limitations section with pertinent content as demonstrated below.

"Though early data on SGLT2i implementation in KTRs is promising, it is albeit limited.

There are 3 main limitations in the data on use of SGLT2i in KTRs. Lengthy studies with large enrollment volume are absent. The longest follow up was around 8.5 years with most having far less. This leaves cardiovascular, graft and mortality outcomes unexplored. Rare adverse events like euglycemic DKA or osteoporosis are also not explored. RCTs are necessary to establish causality and bolsters clinical practice recommendations. Most of the studies in SGLT2i are limited to retrospective, observational or case series.

The SGLT2i story is one that is well underway. There appears to be substantial evidence supporting their use in terms of safety and short-term efficacy based on the studies we described and their antecedents. What lies ahead regarding long-term SGLT2i therapy is unknown. With SGLT2i, we are not working *ab initio* (from the beginning). Rather, as is precedent in some of the greatest epics and sagas (i.e., the *Mahābhārata,* Homer's *Iliad* and *Odyssey*, Virgil's *Aeneid,* Dante's *Divine Comedy),* we can and ought to forge ahead into the unknown *in medias res* – into the middle of things.

**Reviewer #2**

***Comment 1.***

1. ***The authors describe their concerns on urinary tract infections (UTI) with the use of SGLT2i; actually, more genital infections (GI) have been reported in people with***

***diabetes on treatment with SGLT2i , most commonly in women. I would suggest to separate UTI from GI in this mini review***

Thank you for noting this. We have separated UTI from GI and describe that these occur at different frequencies/rate as demonstrated below:

"Urinary tract infections (UTI) were the most common adverse event observed across the various studies. When reported, these ranged from none observed up to 36%. 4 studies reported rates between 13-15%.

Genital infections (GI) occurred but less commonly than UTI in KTRs with only a few GI occurring in studies where it was distinctly described.

We also commented on genital infection in the discussion as shown below:

"Genital infections were observed but at a fairly low rate compared to UTI as described above."

Genital mycotic infection was changed to genital infection in the Table as well.

***Comment 2.***

2. ***Concerns regarding amputations in people with diabetes have been reported only with canagliflozin; I suggest keeping the concerns for risk of amputations only for canagliflozin.***

Thank you for this excellent comment. In the study by Schwaiger et al., they discuss amputation, which they did not see when comparing KTRs on empagliflozin vs placebo. We have omitted amputations from the table in the row corresponding to that study.

We have also added this section to clarify:

"Leg amputation was not observed in any of the studies described. Schwaiger et al. reported on this in their study with empagliflozin. As is aptly described by Heyward et al. in their systematic review and meta-analysis, the risk for lower extremity amputation for SGLT2i use in the non-transplant population has only been observed with canagliflozin."

On behalf of my co-authors and myself, thank you for your time and efforts reviewing our manuscript.

Sincerely,

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