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Letter to the Editor

Do we have enough evidence to support the use of SGLT2 inhibitors for MACE reduction in patients with advance kidney disease?

Sodium-Glucose co-transporter 2 inhibitors (SGLT2i) are novel therapeutic agents used for the treatment of type 2 diabetes mellitus (T2DM) and have reno-protective effects in patients with T2DM with or without renal impairment [1]. One of the previous meta-analysis included only 3 trials which showed reduction in major adverse cardiac events by 11% [2]. There were new trials published showing beneficial effects of SGLT2 inhibitors after this meta-analysis. Therefore, we have performed a meta-analysis including those trials to analyze if beneficial effects of SGLT2i still persist. We have also performed trial sequential analysis (TSA) to analyze whether we have enough evidence to support these beneficial effects of SGLT2i.

We aimed to perform a systematic review and meta-analysis of PubMed database on relevant studies to assess the effects of SGLT2 inhibitors in patients with T2DM and chronic kidney disease (CKD) defined as glomerular filtration rate (GFR) <60 ml/min/1.73 m^2, or GFR <90 ml/min/1.73 m^2 with albuminuria (ratio of albumin to creatinine, $>300–\leq 5000$ mg/g). The primary outcome was major adverse cardiovascular events (MACE), consisting of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. We performed TSA on MACE outcome to accommodate for increased risk of type I error resulting from repeated significance testing because of the addition of new trials in this meta-analysis. Ergo trails sequential analysis was performed to eliminate the possibility of type I error from the final estimate.

We used Mantel-Haenszel method with random effect model to compute risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was assessed using the I^2 test $>50\%$ or χ^2, p-value <0.05. Treatment with SGLT2 inhibitor was associated with a lower risk of three-point classical MACE in patients with T2DM and CKD [Risk ratio: 0.85, Confidence interval: 0.76–0.94, P value <0.05, $I^2 = 0\%$, χ^2 p-value = 0.93] [Fig. 1, Panel A]. Furthermore, it also demonstrated that we now have gathered enough evidence to support this risk reduction with SGLT2i in patients with chronic kidney disease as the Z-curve crosses the futility boundary for benefit [Fig. 1, Panel B].

Our present meta-analysis analyzed 6 trials which were all randomized, placebo-controlled, analyzing the effects of SGLT2 inhibitors on cardiovascular outcomes in patients with T2DM and CKD [2] as the aggregate of our data makes the results more reliable. SGLT2 inhibitors reduced MACE by 15% in this study. This is supported by TSA analysis indicating the fact that this result is associated with acceptable level of type I error. The exact mechanism for MACE reduction is not clear and none have been unequivocally explaining the benefits seen in RCTs. Previous analysis demonstrated modest reduction in HbA1c which in turn reduces microvascular complications [2]. SGLT2i also has natriuresis effects reducing heart failure hospitalizations [2]. It was also observed that SGLT2 inhibitors have direct effect on cardiomyocytes to improve myocardial function and reduce rhythm disturbances [3,4]. Other effects of SGLT2i were noted to reduce weight, decrease in

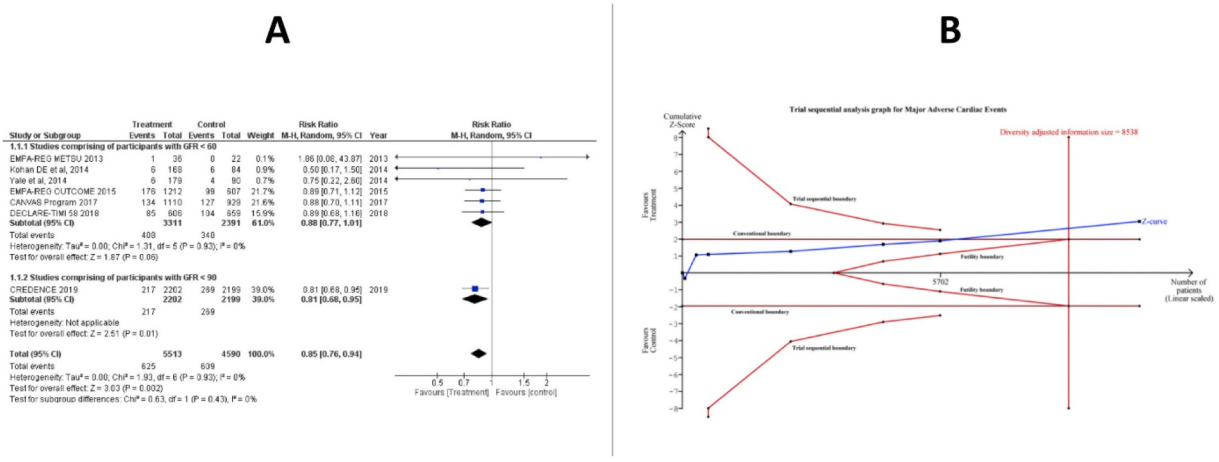

Fig. 1. Panel A: Association of SGLT2 inhibitors with Major Adverse Cardiovascular Events. **Panel B:** Trial Sequential Analysis showing sufficient evidence supporting beneficial effects of SGLT 2 inhibitors.

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arterial stiffness and vascular resistance, and reduction in oxidative stress [3–5]. These effects might combinedly reduce MACE as shown in this study.

We acknowledge several limitations of our study as with any other meta-analysis. The data used was at study level rather than individual participant data and the inclusion criteria and definition of endpoints slightly varied among the included trials. The broader generalizability of these results might also be affected by the characteristics of participants included in this study. Different agents may have slightly different effect on cardiovascular outcomes.

In conclusion, with increasing prevalence of T2DM and elevated risk of cardiovascular events, these data provide substantial evidence supporting the use of SGLT2I inhibitors to prevent clinically important MACE in people with T2DM and CKD. Therefore, use of SGLT2I inhibitors should be highly encouraged in patients with T2DM and CKD, especially in patients with established atherosclerotic cardiovascular disease.

Disclosure: The authors have nothing to disclose.

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