Short Communication

Surrogate cardiovascular outcomes with sodium-glucose co-transporter-2 inhibitors in women: An updated meta-analysis

Dimitrios Patoulias a,*, Christodoulos Papadopoulos b, Michael Doumas a, c

a Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, General Hospital “Hippokration”, Greece
b Third Department of Cardiology, Aristotle University of Thessaloniki, General Hospital “Hippokration”, Greece
c Veterans Affairs Medical Center, George Washington University, Washington, DC, USA

ABSTRACT

The burden of cardiovascular disease morbidity and mortality among women with type 2 diabetes mellitus remains high, despite the improvement in therapeutic management over the recent years. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have revolutionized treatment of cardiovascular disease in subjects with diabetes. However, previous meta-analyses of cardiovascular outcome trials failed to prove a significant effect on surrogate cardiovascular outcomes among female participants. Therefore, we sought to update these results, by incorporating data from the most recently published trials. We pooled available data from all available trials (EMPA-REG OUTCOME, DECLARE-TIMI 58, VERTIS CV, DAPA-HF, EMPEROR-Reduced), except for the CANVAS trial. In the present updated meta-analysis we document that SGLT-2 inhibitors do not confer a significant decrease in the risk for major adverse cardiovascular events among women; however, they provide significant results in terms of reduction in the risk for cardiovascular death or hospitalization for heart failure, primarily driven by the results observed in the heart failure with reduced ejection fraction population. Better representation of women in future trials will provide further insights into the question whether there are true gender differences in the cardiovascular efficacy with this drug class.

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Cardiovascular disease represents the leading cause of death among women in the United States.1 The control rates of cardiovascular risk factors remain suboptimal, despite the fact that a slight improvement has been observed during the last two decades.2 Unfortunately, women are still underrepresented in cardiovascular clinical trials, leading to a significant lack of adequate evidence for this population.3

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are classified among those drugs that promise to revolutionize the field of therapeutics in diabetes and cardiovascular disease. Two previous meta-analyses of the relevant cardiovascular outcome trials with SGLT-2 inhibitors have demonstrated that this drug class provides a non-significant decrease in the risk for major adverse cardiovascular events (MACEs) in women,4,5 which raises doubts whether this finding is a class-effect or just a matter of underrepresentation of women.6

Therefore, we sought to update the previously published meta-analyses, incorporating data from the recently published Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial7, the ertugliflozin cardiovascular outcome trial (VERTIS CV)8 and EMPEROR-Reduced trial.9 Unfortunately, we excluded from our quantitative synthesis the Canagliflozin Cardiovascular Assessment Study (CANVAS)10, which did not provide numeric data regarding the events in each study arm, but generated results in the form of number of participants with the event of interest per 1000 patient-years.

Two independent reviewers extracted the data from the eligible reports, by using a pilot tested, data extraction form. We preferred
utilizing data from intention-to-treat analyses. We set as primary efficacy outcome the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as defined across all the selected cardiovascular outcome trials, and as secondary efficacy outcome the composite of hospitalization for heart failure worsening and cardiovascular death. No safety outcomes were assessed.

As we assessed only dichotomous variables, difference was calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel (M-H) random effects formula. Statistical heterogeneity among studies was assessed by using I² statistics. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.

Two independent reviewers assessed the quality of the included randomized controlled trials, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary safety outcome. Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer.

SGLT-2 inhibitor treatment resulted in a non-significant decrease in the risk for MACE (RR = 0.91, 95% CI; 0.80 to 1.04, I² = 0%), as shown in Fig. 1a. Regarding the secondary efficacy outcome, it was shown that SGLT-2 inhibitor treatment led to a significant decrease equal to 21% (RR = 0.79, 95% CI; 0.69 to 0.91, I² = 8%), which was primarily driven by the results observed in the dedicated HFrEF trials, as shown in Fig. 1b. More specifically, we demonstrated that SGLT-2 inhibitor treatment did not induce a significant decrease in the risk for heart failure hospitalization or cardiovascular death across the cardiovascular outcome trials (RR = 0.87, 95% CI; 0.73 to 1.03, I² = 0%), while it produced a significant result when we pooled the data from the DAPA-HF and the EMPEROR-Reduced trials (RR = 0.71, 95% CI; 0.58 to 0.88, I² = 15%). Risk of bias is considered as low across all included trials.

To sum up, the present updated meta-analysis documented that SGLT-2 inhibitors do not confer significant decrease in the risk for MACE among women; however, they provide significant results in terms of reduction in the risk for cardiovascular death or hospitalization for heart failure, primarily driven by the results observed in the HFrEF population. Based on the high mortality risk among patients with HFrEF and the fact that no sex-specific guideline therapy for HFrEF women patients exists so far, these results may have significant implications in clinical practice. Better representation of women in future trials will provide further insights and elucidate whether there are any gender disparities with the use of this novel drug class.

**Declaration of competing interest**

None to declare.
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