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BRIEF REPORT

Effects of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes in women versus men

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Abstract

Sodium-glucose co-transporter-2 (SGLT2) inhibitors prevent cardiovascular complications in type 2 diabetes. We aimed to study whether they have similar effects in women and men by summarizing the effects of SGLT2 inhibitors compared to placebo on vascular and safety outcomes stratified by sex. We included patients with type 2 diabetes enrolled in the EMPA-REG OUTCOME, CANVAS Program, DECLARE TIMI-58 and CREDENCE trials. There were no differences in the risk ratios between men and women, SGLT2 versus control (placebo), for vascular efficacy outcomes or death (all *P* for interaction ≥.12), with clear protection shown against major adverse cardiovascular events, heart failure, vascular death and total mortality. SGLT2 inhibitor treatment was also associated with similar relative risks in women and men for the safety outcomes of amputation, fracture, genital infection and urinary tract infection (all *P* for interaction ≥.17). SGLT2 inhibition provided similar protection against vascular risks and death, and similar risks of serious adverse events, for women and men.

KEYWORDS
canagliflozin, dapagliflozin, empagliflozin, meta-analysis, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Treatment of type 2 diabetes with sodium-glucose co-transporter-2 (SGLT2) inhibitors has been shown to reduce the risk of cardiovascular events in patients at high cardiovascular risk.[1,2] Type 2 diabetes has been found to be associated with a greater relative risk of coronary heart disease in women compared to men,[3] but the assumption that disease outcomes are equivalent for men and women exposed to the same risks is still the norm.[4] This is reinforced by women being generally under-represented in clinical studies and by the limited power of analyses performed to explore potential differences in responses to treatments between sexes.[4] SGLT2 expression in rat models showed a sex difference, such that hormonal upregulation of SGLT2 takes place after puberty in female rats but not in male rats,[5] suggesting the potential for sex difference in SGLT2 function that warrants further evaluation.[5]

In the present study, we aimed to evaluate whether SGLT2 inhibitor treatment has similar clinical vascular and safety effects in women as in men with diabetes. To gain power for this subgroup analysis, especially as women are under-represented in trials, results by sex were pooled for the four recent reports on large-scale randomized controlled trials that investigated the effects of SGLT2 inhibitors on clinical vascular outcomes in diabetes.

2 | METHODS

This was a pooled analysis of outcomes for patients with type 2 diabetes, women versus men, treated with the SGLT2 inhibitors empagliflozin, canagliflozin or dapagliflozin, each compared to placebo. The CANVAS Program,[1] the EMPA-REG OUTCOME trial[2] and the CREDENCE trial[6] included patients with type 2 diabetes at high cardiovascular risk, with no differences in inclusion criteria for women versus men. The DECLARE TIMI-58 trial[7] also included patients at high cardiovascular risk but, amongst those without established cardiovascular disease, women were included if aged ≥60 years, while men were recruited if aged ≥55 years.

Individual participant data for canagliflozin were extracted directly from the CANVAS and CREDENCE databases. PubMed and clinicaltrials.gov were searched for all published articles on the EMPA-REG OUTCOME and DECLARE TIMI-58 trials. The articles were then screened by one author (K.R.) for results reported by sex. Data were extracted by the same investigator (K.R.). Data for empagliflozin were taken from three articles that described EMPA-REG OUTCOME trial results by sex,[8-10] as well as one article including pooled phase 1, 2 and 3 studies of empagliflozin, where results from the EMPA-REG OUTCOME trial were reported separately by sex.[11] Data for dapagliflozin came from the main report of the DECLARE TIMI-58 trial.[7] For the safety outcome fracture, empagliflozin data were obtained from a pooling study of phase 1, 2 and 3 studies, where the majority of data came from the EMPA-REG OUTCOME trial.[12]

The vascular outcomes of interest were: the composite of major adverse cardiovascular events (MACE), comprising cardiovascular (CV) death, non-fatal acute myocardial infarction and non-fatal stroke; CV death; hospitalization for heart failure; hospitalization for heart failure or CV death; fatal or non-fatal stroke; and fatal or non-fatal myocardial infarction. The safety outcomes studied were urinary tract infection, genital infection, lower limb amputation and fracture. We also studied all-cause mortality.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression models separately for each sex. Models were stratified for the presence of cardiovascular disease at baseline. As the CANVAS Program combined data from the CANVAS and CANVAS R trials. Their Cox model was stratified for the component studies. An intention-to-treat approach was used for efficacy outcomes and an on-treatment approach was used for safety outcomes except for amputation and fracture, which were assessed using intention-to-treat analyses.

The HRs and 95% CIs were sought for each outcome. Where only event numbers were available relative risks and 95% CIs were calculated with the number of patients randomized used as the denominator and the number of events as the numerator. This occurred for the outcomes hospitalization for heart failure, stroke, fracture and amputation from the EMPA-REG OUTCOME trial and for outcomes MACE and hospitalization for heart failure or CV death from the DECLARE TIMI-58 trial. HRs for hospitalization for heart failure or CV death from the EMPA-REG OUTCOME trial were estimated by use of the online tool "Web Plot Digitizer" from a forest plot figure.[13]

We assumed that relative risks and HRs could be considered equivalent,[14] denoted them as risk ratios, and pooled the results for both women and men, and overall, across the four studies using inverse variance weighted meta-analysis. A priori, we considered the effects would be consistent across the studies and so used fixed-effect models. Wald tests were used to test for sex differences (ie, interactions between sex and treatment) after log transformation.[3,15] To evaluate heterogenity, forest plots were drawn showing results for all trials, and Cochran's Q tests performed, for both women and men. As a result of multiple testing, results were considered significant when $P < .01$.

Statistical analyses were performed with SAS version 9.2, SAS Enterprise Guide 7.1 and STATA version 15.1.

3 | RESULTS

There were fewer women than men in all four trials: in the CANVAS Program 35.8% of participants were women, in the CREDENCE trial 33.9%, in the EMPA REG OUTCOME trial 28.8%, and in the DECLARE-TIMI 58 trial 37.4%. There were 3994 MACE events, affecting 10.3% of the total population but a slightly lesser proportion of women (1224 events, 9.0% of women) compared to men (2770 events, 11.0% of men).

Treatment with SGLT2 inhibitors was clearly beneficial for all efficacy outcomes except myocardial infarction and stroke (Figure 1 and Figure S1). There were no detectable sex differences for the effects of SGLT2 inhibition on any efficacy outcome (all P for interaction ≥.12), with a risk ratio for MACE of 0.86 (95% CI 0.76 to 0.97) for women and 0.88 (95% CI 0.82 to 0.95) for men (P for interaction 0.73).

For the safety outcomes studied there was also no evidence of sex differences. Both women and men had an increased risk from SGLT2 treatment of genital tract infection (women 3.68 [95% CI 2.71 to 5.00] vs. men 4.62 [95% CI 3.73 to 5.73]; P for interaction = .23), and amputation (1.30 [95% CI 1.06 to 1.59]). However there was no evidence of such increased risk for urinary tract infection or fracture, either overall or for either sex. The only variable that showed significant between-trial heterogenity in either sex was fracture in women (Q test $P = .004$).

4 | DISCUSSION

In this pooled analysis of the EMPA REG OUTCOME trial, CANVAS Program, DECLARE-TIMI 58 trial and CREDENCE trial, we showed

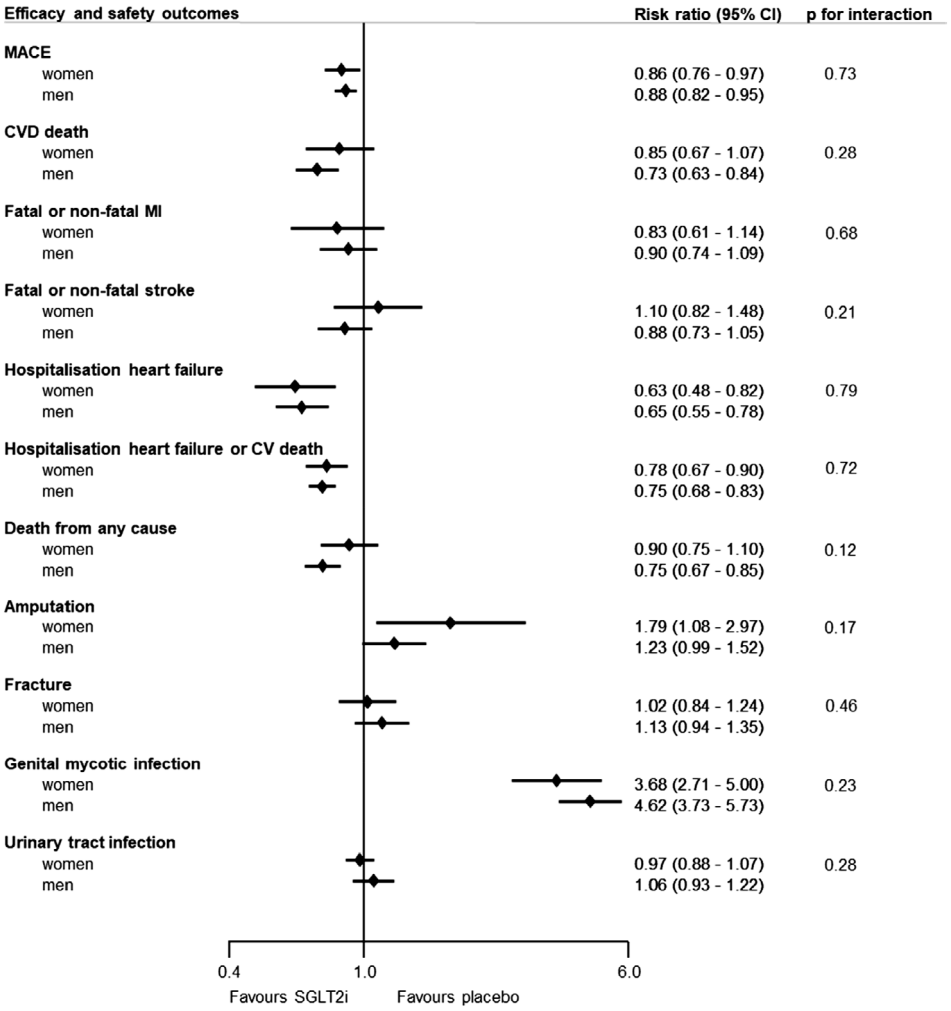

FIGURE 1 Risk ratios and 95% confidence intervals (CIs) for efficacy and safety outcomes by sex and overall, for participants with sodium-glucose co-transporter-2 (SGLT2) inhibitor treatment versus placebo. CVD, cardiovascular disease; MACE, major adverse cardiovascuar events; MI, myocardial infarction

that use of SGLT2 inhibitors produced similar relative effects for women and men for all cardiovascular outcomes, indicating important protective effects for both sexes. Further, because the absolute risks of women and men included in these studies were only marginally different, there would be similarly large absolute benefits of therapy for both women and men.

A key strength of these analyses is that, by combining the data from the four large trial programmes, it has been possible to provide reasonably precise estimates of effects for each sex and to compare more reliably the findings between women and men. The high quality of the underlying trial programmes provides significant reassurance about the likely validity of the findings. A limitation of our work is the inability to account for loss to follow-up for some outcomes in two trials, so that we pooled HRs and relative risks, which differ mathematically; however, as there is no reason to suppose that women and men would experience differing loss to follow-up, this is unlikely to have had a significant effect on our sex comparisons.

For the safety outcome amputation, we showed an increased risk with use of SGLT2 inhibitor overall, with no evidence of a sex difference. Detailed previous analyses of the CANVAS data had shown an increased risk but not identified any mechanism that would be likely to be modified by sex.[16] Whether the SGLT2 inhibitor class causes amputation, and whether any such effect is specific to a particular compound, remains uncertain.

In conclusion, these data suggest that both women and men will achieve significant cardiovascular protection with SGLT2 inhibition, with no sex differences with regard to the known risks of SGLT2 inhibition.

CONFLICT OF INTEREST

K.C. received a 2017 Diabetes Canada Junior Investigator Award funded by AstraZeneca outside of the submitted work. She has also received conference support from Merck Inc. B.N. reports grants for a clinical trial from Janssen, honoraria and travel reimbursement from Janssen and advisory board fees from Janssen outside of the submitted work, all of which were paid to his institution. No other potential conflict of interests were reported.

AUTHOR CONTRIBUTIONS

M.W. and B.N. conceived the project. K.R. and Z.Z. performed the statistical calculations. K.R. wrote the first manuscript draft. All authors read and approved the final draft.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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