Effects of SGLT2 inhibitors in type 2 diabetes, comparing women to men

Karin Rådholm[1,2], Zien Zhou[2], Kristin Clemens[3,4,5], Bruce Neal[2,6,7], Mark Woodward[2,8,9]

[1]Division of Community Medicine, Primary Care, Department of Medicine and Health Sciences, Faculty of Health Sciences, Linköping University, Department of Local Care West, County Council of Östergötland, Linköping, Sweden

[2]The George Institute for Global Health, University of New South Wales, Sydney, Australia

[3]Division of Endocrinology and Metabolism, Department of Medicine, Western University, London Ontario Canada

[4]Department of Epidemiology and Biostatistics, Western University, London Ontario Canada

[5]Lawson Health Research Institute, London Ontario Canada

[6]Faculty of Medicine, University of New South Wales, Sydney, Australia

[7]Imperial College London, London, UK

[8]The George Institute for Global Health, University of Oxford, UK

[9]Department of Epidemiology, Johns Hopkins University, Baltimore MD, USA

Corresponding author:

Karin Rådholm, MD, PhD

Department for medical and health

s-581 83 Linköping

Phone: +46 (0)13-28 17 56

Karin.radholm@liu.se

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ABSTRACT

Aim
Sodium glucose cotransporter 2 (SGLT2) inhibitors prevent cardiovascular complications in type 2 diabetes. We aimed to study whether they have similar effects in women and men.

Methods
We summarised the effects of SGLT2 compared to placebo on vascular and safety outcomes by sex. We included patients with type 2 diabetes enrolled in the EMPA-REG OUTCOME, CANVAS Program, DECLARE TIMI-58 and CREDENCE trials.

Results
There were no sex differences in the risk ratios, SGLT2 versus control, for vascular efficacy outcomes or death (all p interaction ≥ 0.12) with clear protection against major adverse cardiovascular events, heart failure, vascular death and total mortality. SGLT2 inhibitor treatment was also associated with comparable relative risks in women and men for the safety outcomes of amputation, fracture, genital infection and urinary tract infection (all p interaction ≥ 0.17).

Conclusion
SGLT2 inhibition provided comparable protection against vascular risks and death, and similar risks of serious adverse events, for women and men.

INTRODUCTION

Treatment of type 2 diabetes with sodium glucose cotransporter 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 the limited power of analyses done to explore potential differences in responses to treatments between sexes (4). SGLT2 expression in rat models shows a sex difference such that a 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).

OBJECTIVES

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 underrepresented 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.

METHODS

This is 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 or over whereas men were recruited if aged 55 years or older.

Individual participant data for canagliflozin were extracted directly from the CANVAS and CREDENCE databases. Pubmed and clinicaltrials.gov were searched for all published articles from the EMPA-REG OUTCOME trial and DECLARE TIMI-58 trial, which were screened by one author (KR) for results reported by sex. Data were extracted by the same investigator (KR). 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 cardiovascular events (MACE), comprised of cardiovascular (CV) death, non-fatal acute myocardial infarction and non-fatal stroke; CV death; hospitalisation for heart failure; hospitalisation 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 (HR) and 95% confidence intervals (CI) 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.

Hazard ratios (and 95% confidence intervals) were sought for each outcome. Where only event numbers were available relative risks and 95% confidence intervals were calculated with the number of patients randomised used as the denominator and the number of events as the numerator. This occurred for the outcomes hospitalisation 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. Hazard ratios 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 hazard ratios 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 (i.e. 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. Due to multiple testing, results were considered significant when p < 0.01.

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

RESULTS

There were fewer women than men in all four trials: the CANVAS Program (35.8%), the CREDENCE trial (33.9%), the EMPA REG OUTCOME trial (28.8%) and 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 inhibitor therapy was clearly beneficial for all efficacy outcomes except MI and stroke (Figure 1; Supplement figure 1). There were no detectable sex differences for the effects of SGLT2 inhibition on any efficacy outcome (all p interaction ≥0.12), with a risk ratio for MACE of 0.86 (95% confidence interval (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 for genital tract infection (women 3.68; 2.71 to 5.00 versus men 4.62; 3.73 to 5.73, p for interaction = 0.23), and amputation (1.30; 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 which showed significant between-trial heterogenity in either sex was fracture in women (Q test p = 0.004).

DISCUSSION

In this pooled analysis of the EMPA REG OUTCOME trial, the CANVAS Program, the DECLARE-TIMI 58 trial and the CREDENCE trial we showed that use of SGLT2 inhibitor 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 programs, 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 programs 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 hazard ratios 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 prior 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 in the known risks of SGLT2 inhibition.
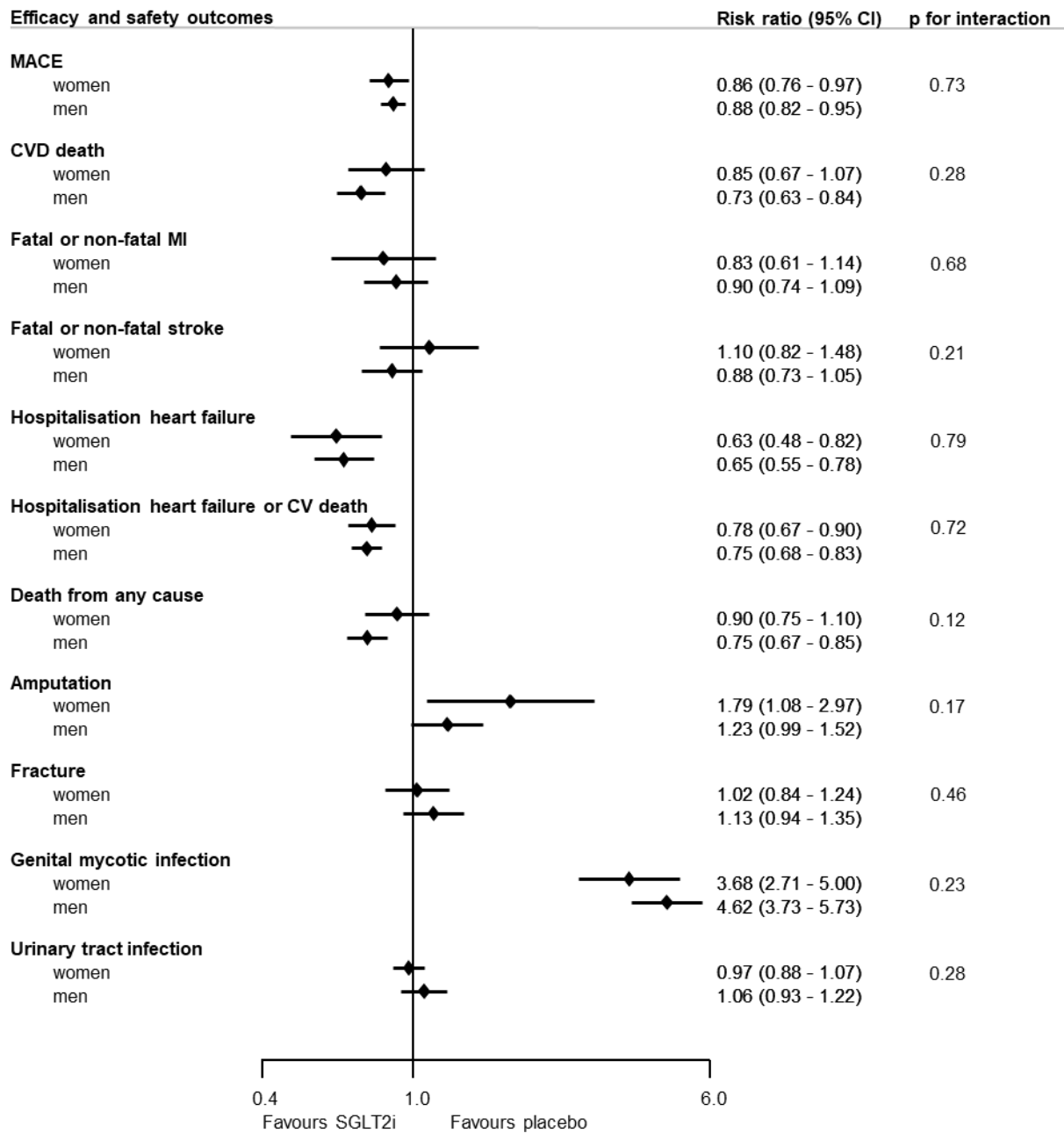
AUTHOR CONTRIBUTIONS

MW and BN conceived of the project. KR and ZZ did the statistical calculations. KR wrote the first draft. All authors have read and approved the final draft.

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Figure 1. Risk ratios and 95% confidence intervals for efficacy and safety outcomes by sex and overall, for participants with SGLT2 inhibitor (SGT2i) treatment versus placebo.

Efficacy and safety outcomes	Risk ratio (95% CI)	p for interaction
MACE		
women	0.86 (0.76 - 0.97)	0.73
men	0.88 (0.82 - 0.95)	
CVD death		
women	0.85 (0.67 - 1.07)	0.28
men	0.73 (0.63 - 0.84)	
Fatal or non-fatal MI		
women	0.83 (0.61 - 1.14)	0.68
men	0.90 (0.74 - 1.09)	
Fatal or non-fatal stroke		
women	1.10 (0.82 - 1.48)	0.21
men	0.88 (0.73 - 1.05)	
Hospitalisation heart failure		
women	0.63 (0.48 - 0.82)	0.79
men	0.65 (0.55 - 0.78)	
Hospitalisation heart failure or CV death		
women	0.78 (0.67 - 0.90)	0.72
men	0.75 (0.68 - 0.83)	
Death from any cause		
women	0.90 (0.75 - 1.10)	0.12
men	0.75 (0.67 - 0.85)	
Amputation		
women	1.79 (1.08 - 2.97)	0.17
men	1.23 (0.99 - 1.52)	
Fracture		
women	1.02 (0.84 - 1.24)	0.46
men	1.13 (0.94 - 1.35)	
Genital mycotic infection		
women	3.68 (2.71 - 5.00)	0.23
men	4.62 (3.73 - 5.73)	
Urinary tract infection		
women	0.97 (0.88 - 1.07)	0.28
men	1.06 (0.93 - 1.22)	

0.4   1.0   6.0
Favours SGLT2i   Favours placebo

SGLT2i: sodium glucose cotransporter 2 inhibitors