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Meta-Analysis

Sodium-Glucose Cotransporter-2 Inhibition Benefits in Cardiorenal Risk in Men and Women

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Abstract

Introduction: In addition to their antihyperglycemic action, sodium-glucose cotransporter-2 (SGLT2) inhibitors are used in patients with type 2 diabetes due to their cardioprotective effects. Meta-analyses of large clinical trials have reported mixed results when examining sex differences in their cardioprotective effects. For example, some studies reported that, compared to women, men had a greater reduction in cardiovascular risk with SGLT2 inhibition. Taking advantage of several recently completed large-scale randomized controlled clinical trials, we tested the hypothesis that women have an attenuated response in primary cardiorenal outcomes to SGLT2 inhibition compared to men.

Methods: We performed a systematic search using PubMed and the Cochrane Library to find completed large-scale, prospective, randomized controlled Phase III clinical trials with primary outcomes testing cardiovascular or renal benefit. Studies had to include at least 1000 participants and report data about sex differences in their primary cardiovascular or renal outcomes.

Results: The present meta-analysis confirmed that SGLT2 inhibition decreased adverse cardiorenal outcomes in a pooled sex analysis using 13 large-scale clinical trials. SGLT2 inhibition exhibited similar reduction in hazard ratios for both men (0.79, 95% CI, 0.73-0.85) and women (0.78, 95% CI, 0.72-0.84) for adverse cardiorenal outcomes.

Conclusion: In contrast to previous findings, our updated meta-analysis suggests that women and men experience similar cardiorenal benefit in response to SGLT2 inhibition. These findings strongly suggest that SGLT2 inhibition therapy should be considered in patients with high risk for cardiovascular disease irrespective of the patient sex.

Key Words: sodium-glucose cotransporter-2, sex differences, cardiorenal risk, meta-analysis

Cardiac and renal disease, especially those complicated by type 2 diabetes mellitus (T2DM), are leading causes of death in men and women [1]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are an antihyperglycemic agent used in patients with T2DM due to their ability to increase urinary glucose excretion. The landmark study EMPA-REG, using the SGLT2 inhibitor empagliflozin, was the first study that showed cardiovascular benefit by an antidiabetic medication in patients with T2DM [2]. Additionally, EMPA-REG also demonstrated renal-protective effects as one of its secondary endpoints [3]. Several similar studies, such as DECLARE-TIMI 58 [4], CANVAS [5], and CREDENCE [6], further showed this cardiovascular benefit in patients with T2DM while also demonstrating renal protection with the SGLT2 inhibitors dapagliflozin and canagliflozin. However, these protective effects were present with very minimal improvements in glycemic status [2, 5, 6], which suggest that the cardiorenal benefit of SGLT2 inhibitors are independent of their effect on blood glucose [6]. Therefore, it has been hypothesized that SGLT2 inhibitors could also confer cardiorenal benefit to patients with heart failure (HF) or chronic kidney disease (CKD) independent of their glycemic status. Indeed, with recent trials such as EMPEROR-Reduced [7], EMPEROR-Preserved [8], EMPA-Kidney [9], DAPA-HF [10], and DAPA-CKD [11], SGLT2 inhibition was shown to benefit patients with HF or CKD even in the absence of T2DM.

There is ongoing debate about the mechanism(s) by which SGLT2 inhibitors confer cardiorenal benefit [12]. The effect of SGLT2 inhibitors on blood glucose are modest [2, 5, 6], so it has been proposed that this protection is independent of their effects on blood glucose [6]. There are numerous hypotheses for how SGLT2 inhibitions protect the kidneys as SGLT2 is abundantly expressed in the proximal tubule of the nephron [12, 13]. Many of these hypotheses rely on SGLT2 inhibitors preventing hyperreabsorption in the proximal tubule, which allows for increased sodium delivery to the macula densa [12]. This can lead to a reversible reduction in the single nephron glomerular filtration rate (GFR), which may lessen the physical stress on glomeruli and ultimately preserve them [12]. This has been borne out in human studies, where there is an initial drop in GFR with SGLT2 inhibition,

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which is followed by an ultimate preservation in GFR [3, 6, 11]. Meanwhile, to explain the cardiac benefit of SGLT2 inhibitors, some studies have shown potential off-target binding to sodium-hydrogen exchanger 1 (NHE1) [14] as well as glucose transporter-1 (GLUT1) [15] and glucose transporter-4 (GLUT4) [15] in the heart. SGLT2 inhibitors could prevent calcium overloading during myocardial ischemia through inhibition of NHE1 [14], while SGLT2 inhibitors targeting GLUT1 and GLUT4 favor fatty acid oxidation instead of glycolysis for energy generation in cardiomyocytes [15]. The mechanisms for how SGLT2 inhibitors confer their cardiorenal benefit are still under investigation, so it still remains unknown how sex may or may not affect the efficacy of SGLT2 inhibitors.

A 2020 meta-analysis by Singh et al raised the question of whether the beneficial effects of SGLT2 inhibition were equivalent between men and women [16]. Using EMPA-REG, DECLARE-TIMI 58, and CANVAS, they found that men had a significant reduction in major adverse cardiac outcomes while women did not [16]. Their result was replicated in another meta-analysis by Mishriky et al [17]. In contrast, Rådholm et al [18] reported significant cardiovascular benefit in women with the addition of the CREDENCE trial. However, this study was followed by another meta-analysis by Patoulias et al [19] no longer showing significant cardiovascular benefit in women with SGLT2 inhibition following the completion of the VERTIS-CV trial. Biological sex and sex hormones influence the expression of renal SGLT2 [20, 21], which may suggest a sex difference in response to SGLT2 inhibitors. As there have been several large-scale clinical trials recently completed, we wanted to test the hypothesis that women had an attenuated response in primary cardiorenal outcomes to SGLT2 inhibition compared to men.

Methods

We performed a systematic search using PubMed and the Cochrane Library to find completed large-scale, prospective, randomized controlled Phase III clinical trials with primary outcomes testing cardiovascular or renal protection. The full text of eligible articles was independently reviewed by 2 authors for inclusion and data extraction. Studies had to include at least 1000 participants and report data about sex differences in their primary cardiovascular or renal outcomes. Our search phrase was "((sodium-glucose cotransporter-2) OR (sodium-glucose co-transporter-2)) AND ((Cardiovascular) OR (Renal))". On PubMed, with "Clinical Trial" selected as the article type, we had 360 results from inception to November 7, 2022. On the Cochrane Library, specifying to the website to use our search phrase on full abstract bodies, we had 719 trials appear from inception to November 7, 2022. We found 13eligible clinical trials including: EMPA-REG [2], EMPEROR-Reduced [7], EMPEROR-Preserved [8], CANVAS [5], CREDENCE [6], DECLARE-TIMI 58 [4], DAPA-HF [10], DAPA-CKD [11], VERTIS-CV [22], SOLOIST-WHF [23], SCORED [24], DELIVER [25], and EMPA-Kidney [9]. While EMPEROR-Reduced, EMPEROR-Preserved, EMPA-Kidney, DAPA-HF, DAPA-CKD, and DELIVER did not require patients to have T2DM for enrollment, approximately half of their patients had T2DM, and there were no differences in subgroup analyses between diabetic and nondiabetic patients for their primary endpoint [7, 8, 10, 11]. Therefore, these 6 studies were also included in this meta-analysis to further increase the statistical power. Two independent reviewers assessed the quality of the included randomized controlled trials with the Revised Cochrane risk of bias tool for randomized trials (RoB 2) [26] used for primary cardiorenal outcomes. A brief characterization of the 13 clinical trials analyzed can be found in Table 1.

Statistical Analysis

Meta-analytic techniques consistent with PRISMA guidelines were used, including forest plots depicting hazard ratios for the primary outcomes in the included trials. The pooled estimate was constructed using random-effects models with restricted maximum likelihood; τ^2, I^2, and Q statistics were used to assess heterogeneity. The analysis was then stratified into sex-specific subgroups, and a meta-regression was performed with sex as a fixed effect to determine if sex differences were indeed present. Funnel plots were constructed to assess publication bias, of which none was noted. Egger's test was used to assess the potential for bias arising from small study effects. All analyses were performed with Stata v17.1 (StataCorp LLC, College Station, TX). Two sensitivity analyses were performed to evaluate heterogeneity. As many previous meta-analyses examined specifically the cardiovascular benefit instead of the cardiorenal benefit, we performed another analysis excluding the trials that included renal outcomes in their primary composite endpoint (CREDENCE, DAPA-CKD, and EMPA-Kidney). In our second sensitivity analysis, we excluded the SOLOIST-WHF and SCORED trials as sotogliflozin has a much lower selectivity for SGLT2 vs SGLT1 compared to other SGLT2 inhibitors [24].

Results

Thirteen studies [2, 4-11, 22-25] were identified that met inclusion criteria, with a total number of participants in this meta-analysis being greater than 90 000. Risk of bias was considered low across all 13 included trials, and we did not detect publication bias. The EMPULSE trial [27] was excluded from our analysis due to having fewer than 1000 participants. As seen in Fig. 1, SGLT2 inhibition decreased cardiorenal risk across the 13 trials, with a composite hazard ratio (HR) of 0.78 (95% CI, 0.73-0.84). When analyzed by sex (Fig. 2A and 2B), we did not observe any difference in response between men and women, with both men (HR 0.79, 95% CI, 0.73-0.85) and women (HR 0.78 95% CI, 0.72-0.84) having an equivalent reduction in cardiorenal risk ($P = 0.673$).

As many previous meta-analyses examined specifically the cardiovascular benefit instead of the cardiorenal benefit, we performed a sensitivity analysis excluding the trials that included renal outcomes in their primary composite endpoint (CREDENCE, DAPA-CKD, and EMPA-Kidney). We similarly found notable cardiovascular benefit with SGLT2 inhibition in our pooled analysis (Fig. 3) with an HR of 0.82 (95% CI, 0.77-0.88). When analyzed by sex (Fig. 4A and 4B), we did not observe any difference in response between men and women, with both men (HR 0.83, 95% CI, 0.77-0.89) and women (HR 0.81, 95% CI, 0.75-0.87) having an equivalent reduction in cardiovascular risk ($P = 0.601$). Furthermore, we performed a second sensitivity analysis of selective SGLT2 inhibitors excluding the SOLOIST-WHF and SCORED trials. We found cardiorenal benefit with selective SGLT2 inhibition in our pooled analysis (Fig. 5) with an HR of 0.79 (95% CI, 0.73-0.86). When analyzed by sex (Fig. 6A and 6B), we still

Table 1. Characteristics of sodium-glucose cotransporter-2 clinical trials analyzed

Drug	Trial	Population	Primary outcome	Number of participants
Empagliflozin	EMPA-REG	T2DM at high CV risk	Composite of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke	7020 *M* = 5016 *F* = 2004
	EMPEROR-Reduced	HF with reduced ejection fraction (at least Class II)	Composite of death from CV causes or hospitalization for worsening HF	3730 *M* = 2837 *F* = 893
	EMPEROR-Preserved	HF with preserved ejection fraction (at least Class II)	Composite of death from CV causes or hospitalization for worsening HF	5988 *M* = 3312 *F* = 2676
	EMPA-Kidney	CKD	Composite of death from CV or renal causes, sustained decrease in estimated GFR of at least 40%, and onset of end-stage kidney disease	6609 *M* = 4417 *F* = 2192
Dapagliflozin	DECLARE-TIMI 58	T2DM at high cardiovascular risk	Composite of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke	17 160 *M* = 10 738 *F* = 6422
	DAPA-HF	HF with reduced ejection fraction (at least Class II)	Composite of death from CV causes or hospitalization for worsening HF	4744 *M* = 3635 *F* = 1109
	DAPA-CKD	CKD	Composite of death from CV or renal causes, sustained decline in estimated GFR of at least 50%, and onset end-stage kidney disease	4304 *M* = 2879 *F* = 1425
	DELIVER	HF with ejection fraction of greater than 40%	Composite of death from CV causes or unplanned hospitalization/urgent visits for HF	6263 *M* = 3516 *F* = 2747
Canagliflozin	CANVAS	T2DM at high cardiovascular risk	Composite of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke	10 100 *M* = 6509 *F* = 3633
	CREDENCE	T2DM with CKD	Composite of death from CV or renal causes, doubling of serum creatinine, and onset of end-stage kidney disease	4401 *M* = 2907 *F* = 1494
Ertugliflozin	VERTIS-CV	T2DM with established atherosclerotic cardiovascular disease	Composite of death from CV causes, nonfatal myocardial infarction, and nonfatal stroke	8238 *M* = 5764 *F* = 2474
Sotagliflozin	SOLOIST-WHF	T2DM recently hospitalized with worsening HF (either reduced or preserved ejection fraction)	Composite of death from CV causes or hospitalization/urgent visits for worsening HF	1222 *M* = 810 *F* = 412
	SCORED	T2DM with both CKD and additional cardiovascular risk	Composite of death from CV causes or hospitalization/urgent visits for worsening HF	10 584 *M* = 5830 *F* = 4754

Abbreviations: T2DM, type 2 diabetes mellitus; CV, cardiovascular; HF, heart failure; CKD, chronic kidney disease; GFR, glomerular filtration rate.

did not observe any difference in response between men and women, with both men (HR 0.80, 95% CI, 0.74-0.87) and women (HR 0.77, 95% CI, 0.71-0.84) having an equivalent reduction in cardiorenal risk ($P = 0.512$).

Discussion

Assessing sex differences in response to therapy is vital to providing optimal care to patients. This is especially important in providing care for cardiovascular disease as sex differences have been reported in therapeutic response to other cardioprotective medications. For example, in a nonprespecified post hoc analysis of TOPCAT [28], there was a significant interaction between the mineralocorticoid receptor antagonist spironolactone and sex, with spironolactone reducing all-cause mortality in women with HF with preserved ejection fraction but not in men. Likewise, in a prespecified analysis of the PARAGON-HF trial [29], there was a significant interaction between the neprilysin inhibitor sacubitril and sex, with sacubitril lowering the risk of HF hospitalization or cardiovascular in women but not in men. However, our updated meta-analysis suggests that men and women experience a similar cardiorenal benefit with SGLT2 inhibitors. As previous meta-analyses specifically examined cardiovascular benefit instead of cardiorenal benefit, we performed a sensitivity analysis for strictly cardiovascular benefit and similarly found that both men and women experience equal cardiovascular benefit. This is in contrast to previous meta-analyses that did not demonstrate protection by SGLT2 inhibitors in women [16, 17, 19]. One potential reason for this discrepancy is that the Singh and Singh [16] 2020 meta-analysis was only able to analyze EMPA-REG, DECLARE-TIMI 58, and CANVAS. In that meta-analysis, there was a tendency to decrease cardiovascular risk in both men and women, though only men had a statistically significant reduction [16]. While this result could have been because of a biological difference, it is likely that this result was due to women being underrepresented. As there are many more large-scale clinical trial data available since the meta-analyses of Singh and Singh [16], Mishriky et al [17], and Patoulias et al [19], we were able to

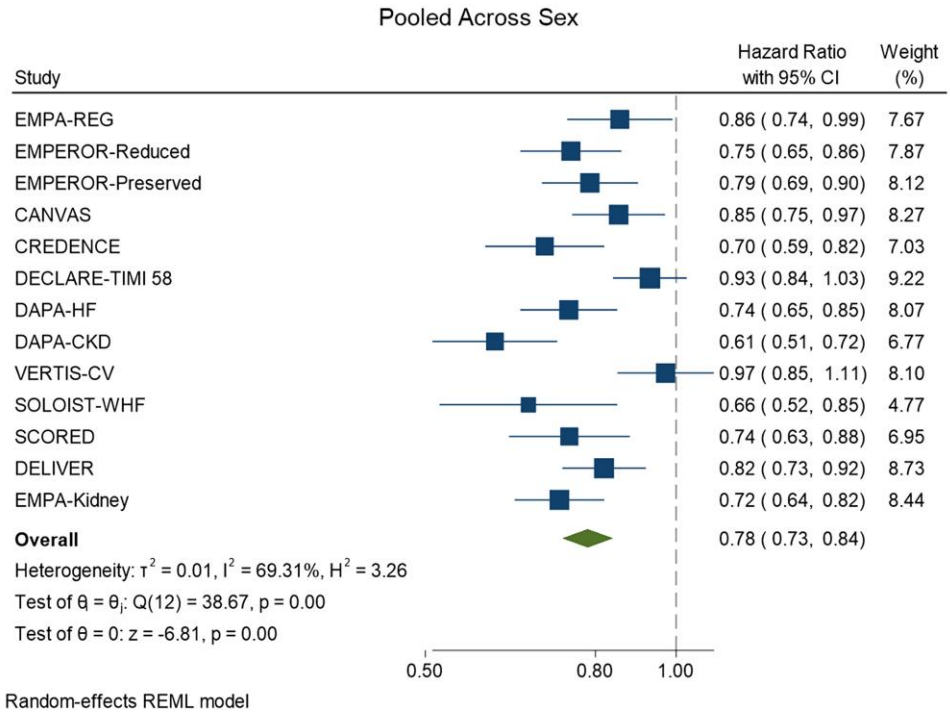

Figure 1. Effect of sodium-glucose cotransporter-2 inhibitors compared to control on the risk for the primary composite cardiorenal endpoint in pooled men and women.

more than double the number of participants from the previous meta-analyses [16] by including more recent clinical trials.

Sex differences have been described for several cardiovascular risk factors, cardiovascular diseases, and medications targeting those risk factors. For example, the prevalence of T2DM is higher in men than in women [30, 31]. Additionally, HF often presents differently in men vs women. Men are predisposed to get HF with reduced ejection fraction while women are predisposed to get HF with preserved ejection fraction [32]. This is due to a combination of factors such as differences in traditional cardiovascular risk factors, different etiologies of HF (such as peripartum cardiomyopathy), and the predominance of coronary macrovascular disease in men vs coronary microvascular disease in women [32]. Concerning kidney disease, there is an increased prevalence of CKD in women than in men from Western societies [33]. Generally, though, men experience more rapid progression to end-stage renal disease compared to women [33]. Furthermore, in a diabetic kidney disease cohort where men and women had equivalent estimated GFR (a marker of kidney function), men had significantly higher daily albuminuria (a marker of kidney damage) than women [34]. As expected, the mechanisms for sex differences in kidney injury are multifactorial and include the prominent role that sex steroids have

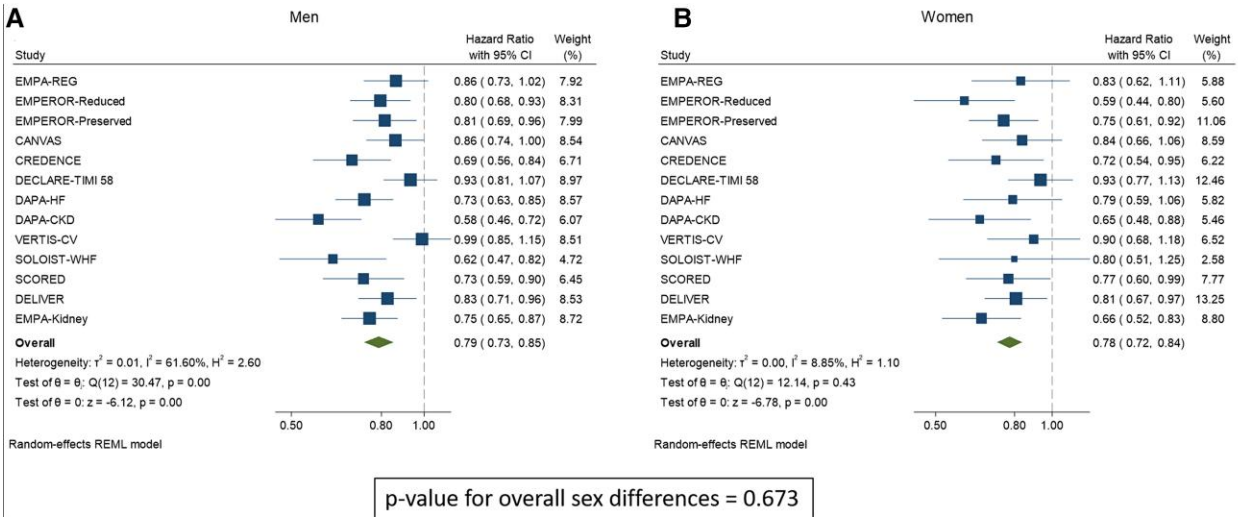

Figure 2. Effect of sodium-glucose cotransporter-2 inhibitors compared to control on the risk for the primary composite cardiorenal endpoint in men (A) and women (B).

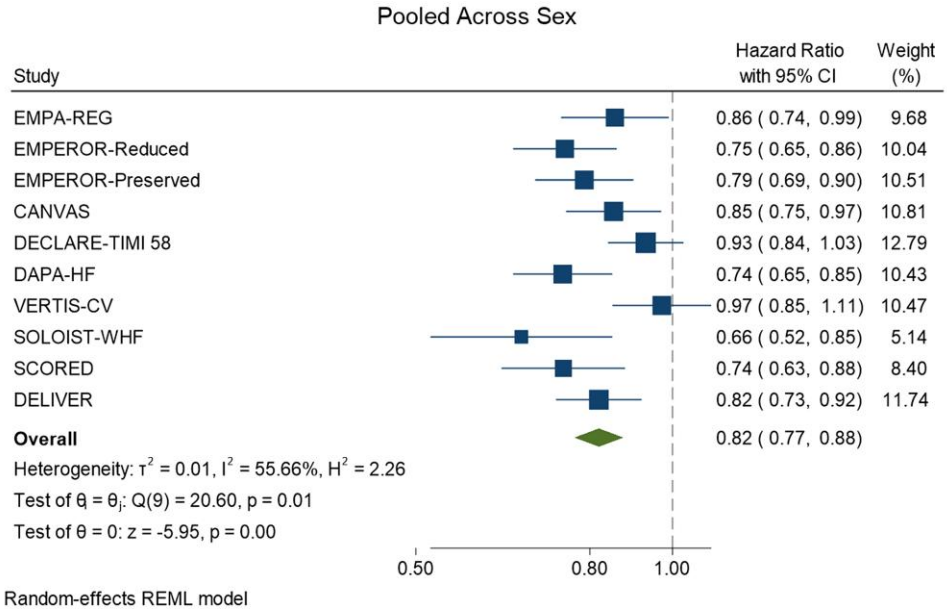

Figure 3. Effect of sodium-glucose cotransporter-2 inhibitors compared to control on the risk for the primary composite cardiovascular endpoint in pooled men and women.

on kidney function and damage, sex differences in the renin-angiotensin system, and lifestyle differences between men and women [33, 35, 36]. There is also a sex difference in fat expansion, where premenopausal women preferentially expand their subcutaneous white adipose tissue while men are more likely to expand their visceral white adipose tissue at younger ages [37]. This is an important distinction as visceral white adipose tissue is more associated with adverse cardiovascular events than subcutaneous white adipose tissue [38]. Furthermore, drugs often have different pharmacokinetics in women compared to men, which may be partially explained by differing volume of distribution and sex-specific expression of cytochrome P450 enzymes [39].

Exploring sex differences becomes more complicated when taking into account the differential role of androgens in both males and females. In males, independently of body mass index and waist to hip ratio, low total testosterone was predictive of the development of T2DM [40]. Meanwhile, in females, androgen excess is positively associated with T2DM as seen in polycystic ovary syndrome (PCOS) [41-43]. Likewise, circulating androgens in males were inversely correlated to plasma triglycerides even in males without T2DM [44] while dyslipidemia is highly prevalent in females with PCOS [41]. In regards to adiposity, hypoandrogenemia is associated with increased fat mass in males while hyperandrogenemia is associated with increased fat mass in females [45]. The relationship between blood pressure, androgens, and sex is more complicated. Low testosterone in men is associated with increased blood pressure [46]; however, male athletes taking anabolic steroids also have increased blood pressure [47]. To our knowledge, only high levels of androgens have been associated with hypertension in females, such as observed in females with PCOS [41-43]. While in this meta-analysis SGLT2 inhibitors do not demonstrate a

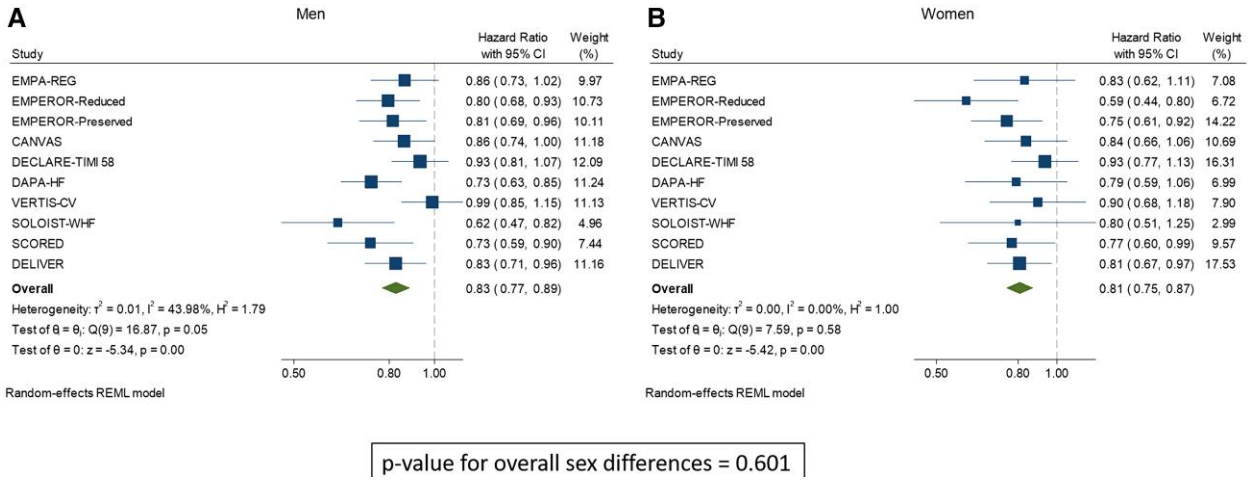

Figure 4. Effect of sodium-glucose cotransporter-2 inhibitors compared to control on the risk for the primary composite cardiovascular endpoint in men (A) and women (B).

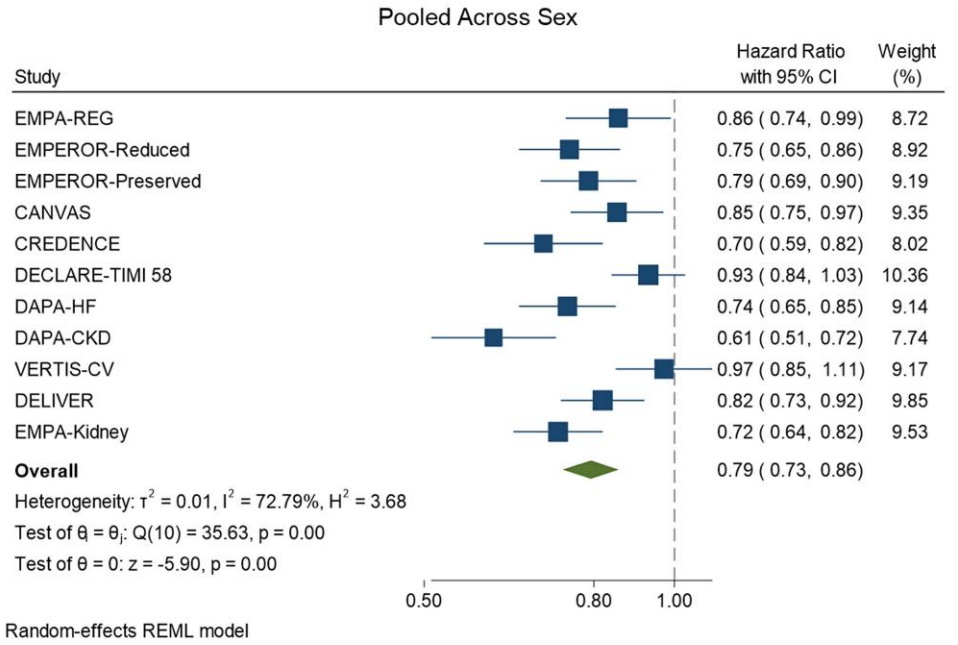

Figure 5. Effect of selective sodium-glucose cotransporter-2 inhibitors compared to control on the risk for the primary composite cardiorenal endpoint in pooled men and women.

sex difference in cardiorenal benefit, sex differences in future cardiovascular therapies should be carefully considered and fully explored.

Our study has several limitations. Some trials required patients to have T2DM while it was optional in others, which could have introduced more heterogeneity in our study. While this was done to get a broader sense of the effectiveness of SGLT2 inhibitors on cardiorenal outcomes, there may be sex differences that a more granular inspection of the data may detect although that is not possible with currently publicly reported data. However, while the data for men had high heterogeneity ($I^2 > 50\%$), the data for women had low heterogeneity ($I^2 < 10\%$). This difference in heterogeneity between men and women is likely due to the results of VERTIS-CV. As discussed earlier, SGLT2 inhibitors may bind to other targets, such as NHE1 [14], GLUT1 [15], and GLUT4 [15] in the heart. As off-target effects may be mediating cardiovascular benefit, slight differences in structures among SGLT2 inhibitors may explain in part the heterogeneity among SGLT2 inhibitors, as ertugliflozin in the VERTIS-CV trial [22] did not show cardiovascular benefit that other SGLT2 inhibitors in this meta-analysis demonstrated.

Our study has many strengths. A recent prespecified meta-analysis by Zannad et al [48] showed equivalent cardiovascular benefit with SGLT2 inhibitors between men and women, though only EMPEROR-Reduced and DAPA-HF trials were included in their analysis. In our study, we have a very broad overview using 13 high-quality, large-scale clinical trials, showing a similar cardiorenal benefit of SGLT2 inhibition in both men and women. Given the broadness of the trials we

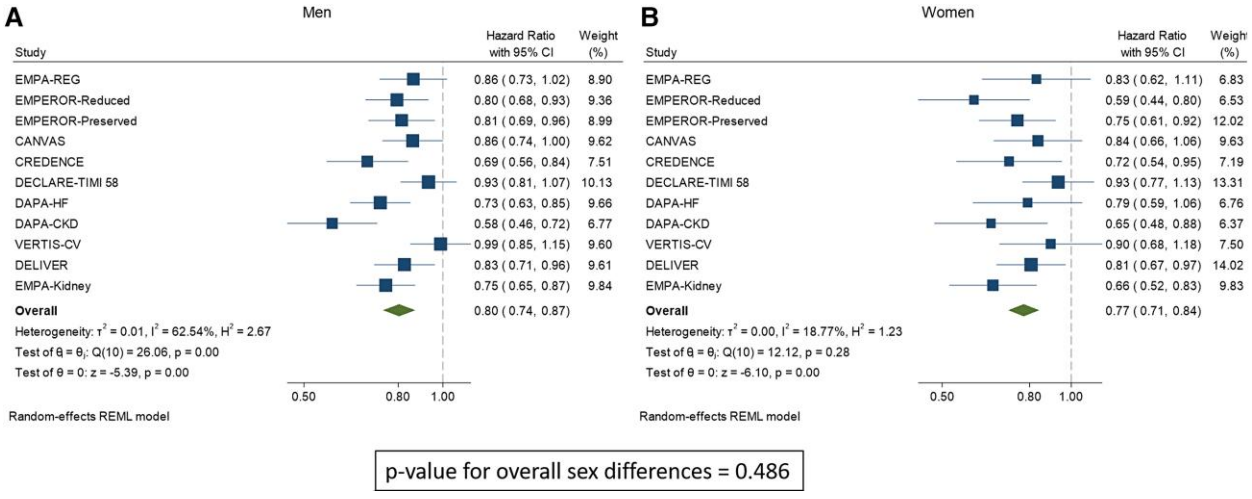

Figure 6. Effect of selective sodium-glucose cotransporter-2 inhibitors compared to control on the risk for the primary composite cardiorenal endpoint in men (A) and women (B).

included, with a mixture of patients with T2DM, HF, and CKD, our results are fairly generalizable. Thus, we provide robust data showing that women and men experience equivalent cardiorenal benefit from SGLT2 inhibition. Our findings are a reminder that SGLT2 inhibitors should be prescribed to patients irrespective of sex.

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Disclosures

The authors have nothing to disclose.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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