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SHORT COMMUNICATION

Empagliflozin in women with type 2 diabetes and cardiovascular disease – an analysis of EMPA-REG OUTCOME®

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Abstract

Aims/hypothesis The global epidemic of type 2 diabetes affects women and men equally; however, the relative impact on the cardiovascular (CV) system appears greater for women than men when compared with peers without diabetes. Furthermore, women are often under-represented in CV outcome trials, resulting in less certainty about the impact of CV prevention therapies across the sexes. The EMPA-REG OUTCOME® trial, which included 28.5% women, found that empagliflozin, given in addition to standard of care, reduced the risk of CV death by 38%, heart failure (HF) hospitalisation by 35% and a composite endpoint for incident or worsening nephropathy by 39%. Here we report a secondary analysis of the trial to determine the relative effects of empagliflozin in women vs men.

Methods The population studied were individuals with type 2 diabetes (HbA_{1c} 53–86 mmol/mol [7–10%] and eGFR >30 ml min^{-1} [1.73 m]$^{-2}$), with established atherosclerotic CV disease. Individuals were randomised to receive empagliflozin 10 mg or 25 mg, or placebo once daily in addition to standard of care, and followed. The trial continued until ≥691 individuals had experienced an adjudicated event included in the primary outcome. All CV outcome events, including HF hospitalisations and deaths were prospectively adjudicated by blinded clinical events committees.

Results At baseline, the demographic profile of the 2004 women (age ± standard deviation 63.6 ± 8.8 years) compared with the 5016 men (age 63.0 ± 8.6 years) in the trial was largely similar, with the exception that LDL-cholesterol was numerically higher in women (2.5 ± 1.0 vs 2.1 ± 0.9 mmol/l), consistent with lower rates of lipid-lowering therapies (75.4% vs 83.2%). Women were also less likely to have smoked (31.5% vs 69.9%). The annualised incidence rate for women in the placebo group was numerically lower than in men for CV death (1.58% vs 2.19%), numerically higher for HF hospitalisation (1.75% vs 1.33%) and similar for renal events (7.22% vs 7.75%). We did not detect any effect modification by sex within the statistical power restrictions of the analysis for CV death, HF hospitalisation and incident or worsening nephropathy (interaction p values 0.32, 0.20 and 0.85, respectively). Compared with placebo, empagliflozin increased the rates of genital infections in both women (2.5% vs 10.0%) and men (1.5% vs 2.6%).

Conclusions/interpretation CV death, HF hospitalisation and incident or worsening nephropathy rate reductions induced by empagliflozin were not different between women and men.

Keywords Cardiovascular disease · Heart failure · Mortality · SGLT2 inhibition · Type 2 diabetes · Women

Odd Erik Johansen and David Fitchett are joint senior authors.

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Research in context

What is already known about this subject?

- The global epidemic of type 2 diabetes affects women and men equally; however, the relative cardiovascular impact is greater for women
- The EMPA-REG OUTCOME® trial that included 28.5% women found that empagliflozin, given in addition to standard care, reduced the risk of cardiovascular (CV) death by 38%, heart failure (HF) hospitalisation by 35% and a composite endpoint for incident or worsening nephropathy by 39%, while increasing the rates of genital infections two- to threefold

What is the key question?

- Are there differing effects of empagliflozin between women and men who participated in EMPA-REG OUTCOME®?

What are the new findings?

- The annualised incidence rate for women vs men in the placebo group was numerically lower for CV death (1.58% vs 2.19%), numerically higher for HF hospitalisation (1.75% vs 1.33%) and similar for renal events (7.22% vs 7.75%)
- Effects of empagliflozin on reducing clinical outcome events were not different between the sexes

How might this impact on clinical practice in the foreseeable future?

- In-depth analysis provides reassurance on the use of empagliflozin in both men and women. Consequently, clinicians should consider the reductions in risk of CV death, HF hospitalisation and incident or worsening nephropathy by empagliflozin when choosing therapies for their patients

Abbreviations

ACEi	ACE inhibitor
ARB	Angiotensin receptor blocker
CV	Cardiovascular
DBP	Diastolic blood pressure
HF	Heart failure
MDRD	Modification of diet in renal disease
SBP	Systolic blood pressure

Introduction

The global epidemic of type 2 diabetes is expected to affect 642 million individuals by 2040 and impacts women and men equally [1]. It has been postulated that when women develop diabetes, they lose their generally protective effect against cardiovascular (CV) complications. Thus, the relative risk for CV complications is greater in women with diabetes than men when compared with peers without diabetes. This observation may relate to differences in CV risk factors in men and women, influence of sex hormones on CV risk, or sex disparities in the management of diabetes and/or CV risk factors [2]. Moreover and disappointingly, women typically only constitute 25–40% of the study populations in major CV outcome trials [3–5]. Thus, there may be less certainty about efficacy and safety of CV preventive strategies in women with diabetes. The EMPA-REG OUTCOME® trial, which included 28.5% women, found that empagliflozin, given in addition to standard of care, reduced the risk of CV death by 38% (HR 0.62 [95% CI 0.49, 0.77]; $p < 0.001$), heart failure (HF) hospitalisation by 35% (HR 0.68 [0.57, 0.82]; $p < 0.001$) and a composite endpoint for incident or worsening nephropathy by 39% (HR 0.61 [0.53, 0.70]; $p < 0.001$) vs placebo [5–7]. As a result of this trial, approval for a CV death prevention indication in individuals with type 2 diabetes and established CV disease was granted by the US Food and Drug Administration and other regulatory authorities. Here we report a secondary prespecified analysis [5] of the trial to determine the relative effects of empagliflozin in women vs men.

Methods

Description of the trial design (NCT01131676) and methodology used has previously been reported [5–7]. In brief, the population studied was individuals with type 2 diabetes (HbA_{1c} 53–86 mmol/mol [7–10%] and eGFR >30 ml min^{-1} [1.73 $m]^{-2}$) who had established atherosclerotic CV disease. Individuals were randomised to receive empagliflozin 10 mg or 25 mg, or placebo once daily in addition to standard of care. Throughout the trial, investigators were encouraged to treat CV risk factors (including dyslipidaemia and hypertension) to achieve the best available standard of care according to local guidelines. All CV outcome events were

Table 1 Baseline characteristics by sex in EMPA-REG OUTCOME

	Women	Men
Total study population ($N = 7020$)	2004 (28.5)	5016 (71.5)
Age, years	63.6 ± 8.8	63.0 ± 8.6
BMI, kg/m^2	31.2 ± 5.7	30.4 ± 5.1
Weight, kg	77.9 ± 17.0	89.7 ± 18.6
Waist circumference, cm	102.1 ± 14.0	105.9 ± 13.5
Type 2 diabetes characteristics		
HbA$_{1c}$, mmol/mol	65.5 ± 9.7	64.4 ± 9.0
HbA$_{1c}$, %	8.1 ± 0.9	8.0 ± 0.8
>10 years since diabetes diagnosis, %	57.8	56.9
Glucose-lowering agents, %		
No treatment	1.8	1.8
1 treatment	31.1	28.8
2 treatments	50.3	47.8
≥3 treatments	14.6	18.4
Any metformin	73.5	74.2
Any sulfonylurea	41.0	43.5
Any insulin	51.0	47.1
Any glitazone	2.8	4.8
Any DPP4 inhibitor	8.2	12.6
Any GLP-1 receptor agonist	2.4	2.9
CV history and risk factors, %		
Smoking		
Never	68.5	30.1
Current	9.2	14.9
Coronary artery disease[a]	62.8	80.7
History of myocardial infarction	36.7	50.6
Coronary artery bypass grafting	16.7	28.0
History of stroke	31.6	20.0
Peripheral arterial disease	22.6	20.1
Heart failure	10.5	9.9
eGFR[b], ml min^{-1} [1.73 m]$^{-2}$	72.7 ± 22.2	74.6 ± 21.1
eGFR <60 ml min^{-1} [1.73 m]$^{-2}$, %	29.2	24.6
Systolic BP, mmHg	136.0 ± 17.6	135.2 ± 16.8
Diastolic BP, mmHg	76.0 ± 10.0	76.9 ± 9.8
LDL-cholesterol, mmol/l	2.5 ± 1.0	2.1 ± 0.9
Albuminuria, %		
Normoalbuminuria	64.0	57.6
Microalbuminuria	26.1	29.7
Macroalbuminuria	9.2	11.7
Missing	0.7	1.0
CV pharmacotherapy, %		
Any BP lowering agent	94.3	95.2
0 BP-lowering agent	5.7	4.8
1 BP-lowering agent	19.0	18.2
2 BP-lowering agents	29.9	32.4
3 BP-lowering agents	27.9	25.5
≥4 BP-lowering agents	17.5	19.1
ACEi/ARB	79.7	81.1
Diuretic agents	47.6	41.5
Beta blockers	58.9	67.3
Digitalis	2.1	3.1
Lipid-lowering therapies	75.4	83.2
Any statins	71.1	79.3
Any fibrate	7.7	9.5
Platelet inhibitors	80.9	87.7
Any ASA	77.5	84.7
Any clopidogrel	10.6	10.6

Data are given as *n* (%) or mean ± SD, as shown

[a] Coronary artery disease defined as any of the components of history of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease, single vessel coronary artery disease

[b] eGFR estimated using MDRD formula

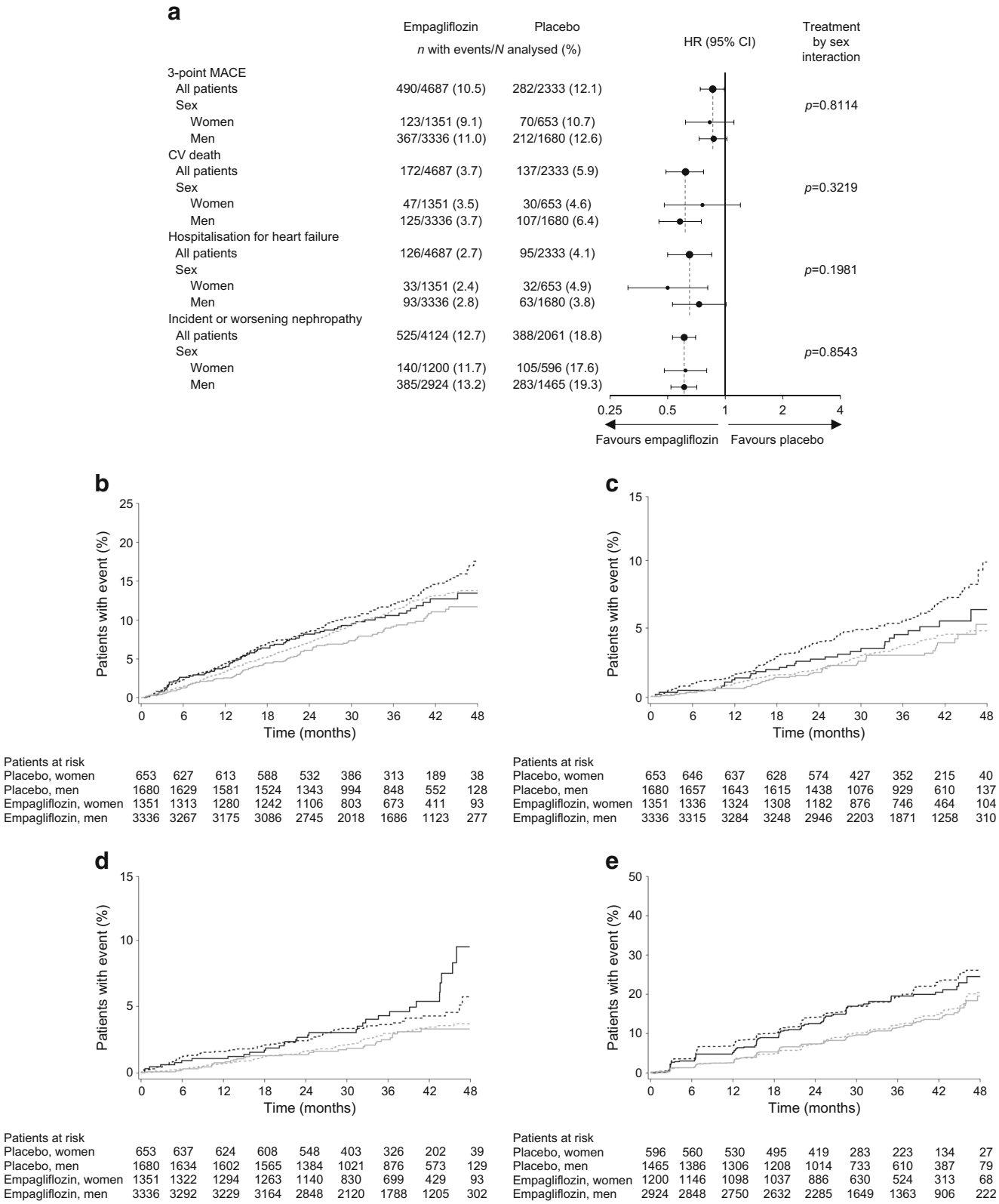
ASA, acetylsalicylic acid; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1

prospectively adjudicated by independent and blinded clinical events committees. For the renal outcomes analysed, serum creatinine and urinary albumin in spot urine samples obtained during regular study visits were measured in central laboratories with the use of standardised procedures. We used the modification of diet in renal disease (MDRD) formula to estimate the eGFR. Safety was assessed on the basis of adverse events that occurred during treatment or within 7 days after the last dose of study drug, and collected as previously reported [5–7].

Cox proportional hazards models were used to assess between-group differences in the risk of an outcome after adjustment for study group, age, sex, baseline BMI, HbA$_{1c}$, eGFR and region. We present overall HR according to sex and the interaction *p* value considering the interaction of treatment × sex for CV death, HF hospitalisation and the predefined composite renal outcome. Kaplan–Meier plots are presented to display events over time; adverse events are expressed as proportions. Post hoc power considerations were derived using ADDPLAN (version 6.1.1, 2014, ICON, www.iconplc.com/innovation/addplan). All study participants gave informed consent prior to enrolment, and the investigations were approved by ethics committees or institutional review boards.

Results

The profile at baseline (Table 1, electronic supplementary material [ESM] Table 1) was largely similar between the 2004 women in the trial (age [mean±SD], 63.6 ± 8.8 years;



BMI 31.2 ± 5.7 kg/m^2; systolic/diastolic blood pressure [SBP/DBP] 136.0 ± 17.6/76.0 ± 10.0 mmHg; eGFR 72.7 ± 22.2 ml min^{-1} [1.73 m]$^{-2}$; 64% normoalbuminuria), and the 5016 men (age 63.0 ± 8.6; BMI 30.4 ± 5.1; SBP/DBP 135.2 ± 16.8/76.9 ± 9.8; eGFR 74.6 ± 21.1; 57.6% normoalbuminuria). The geographic representation in the trial was also similar between the sexes (women: 41.0% Europe; 17.8% North America; 18.9% Latin

◀ **Fig. 1** (**a**) Forest plot of 3-point Major Adverse Cardiovascular Events (MACE [composite of CV death, nonfatal myocardial infarction or nonfatal stroke]), CV death, HF hospitalisation and nephropathy by sex, and interaction *p* values. Values were determined by Cox regression analysis in patients treated with ≥1 dose of study drug. (**b**–**e**) Kaplan–Meier estimates in patients treated with ≥1 dose of study drug. Solid grey line, women in the empagliflozin group; dashed grey line, men in the empagliflozin group; solid black line, women in the placebo group; dashed black line, men in the placebo group. (**b**) 3-point MACE over time in women and men with empagliflozin vs placebo. HR (95% CI): women, 0.83 (0.62, 1.11); men, 0.87 (0.73, 1.02). $p = 0.8114$ for treatment by sex interaction. (**c**) CV death over time in women and men with empagliflozin vs placebo. HR (95% CI): women, 0.76 (0.48, 1.20); men, 0.58 (0.45, 0.75). $p = 0.3219$ for treatment by sex interaction. (**d**) HF hospitalisation over time in women and men with empagliflozin vs placebo. HR (95% CI): women, 0.50 (0.31, 0.81); men, 0.73 (0.53, 1.01). $p = 0.1981$ for treatment by sex interaction. (**e**) Occurrence of worsening of nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of renal-replacement therapy, or death from renal disease) over time in women and men with empagliflozin vs placebo). HR (95% CI): women, 0.62 (0.48, 0.80); men, 0.61 (0.52, 0.71). $p = 0.8543$ for treatment by sex interaction

America;18.1% Asia; 4.2% South Africa vs men: 41.1% Europe; 20.7% North America; 14.0% Latin America;19.6% Asia; 4.5% South Africa). In addition, type 2 diabetes disease characteristics were also largely similar: HbA_{1c} 65.5 ± 9.7 mmol/mol (8.1% ± 0.9%) vs 64.4 ± 9.0 mmol/mol (8.0% ± 0.8%); type 2 diabetes duration > 10 years: 57.8% vs 56.9%; and any use of metformin (73.5% vs 74.2%), sulfonylurea (41.0% vs 43.5%) or insulin (51.0% vs 47.1%).

LDL-cholesterol was, however, numerically higher in women (2.5 ± 1.0 vs 2.1 ± 0.9 mmol/l), likely reflecting lower rates of lipid-lowering therapies (75.4% vs 83.2%), in particular statin use (71.1% vs 79.3%). Women also had lower prevalent use of anti-platelet therapies (80.9% vs 87.7%) and were less likely to have smoked (31.5% vs 69.9%). Use of antihypertensive drugs were similar (75.3% vs 77.0% used ≥ two antihypertensive agents), including use of angiotensin converting enzyme inhibitors (ACEis) / angiotensin receptor blockers (ARBs) (79.7% vs 81.1%), but slightly more women used diuretics (47.6% vs 41.5%) and slightly fewer women used beta blockers (58.9% vs 67.3%). Throughout the trial (ESM Table 2), a higher percentage of patients in the placebo group, for both men and women, received additional antihypertensive therapies (women: 49.8% [placebo] vs 42.9% [empagliflozin]; men: 51.5% vs 45.2%) and acetylsalicylic acid, with the latter occurring numerically more frequent in women (women: 21.7% vs 17.7%; men: 18.6% vs 18.0%), whereas new introduction of statin therapy was similar (women: 25.7% vs 24.9%; men: 25.8% vs 24.2%).

Prior coronary artery disease was less common in women (62.8% vs 80.7%), but women had a more frequent history of stroke (31.6% vs 20.0%). History of HF was similar (10.5% vs 9.9%).

Effects of empagliflozin on reducing BP, HbA_{1c}, weight and waist circumference were of similar magnitude regardless of sex (data not shown). The annualised incidence rate for women in the placebo group was numerically lower than that in men for CV death (1.58% vs 2.19%), numerically higher for HF hospitalisation (1.75% vs 1.33%), and similar for renal events (7.22% vs 7.75%). Empagliflozin reduced the primary composite endpoint (CV death, non-fatal stroke, non-fatal myocardial infarction) relatively by 14% (Fig. 1a,b) by a similar degree, irrespective of sex (interaction *p* value 0.8114). We did not detect any effect modification by sex within the statistical power restrictions of the analysis for CV death, HF hospitalisation and incident or worsening nephropathy (Fig. 1a, c–e; interaction *p* values 0.32, 0.20 and 0.85, respectively). Separation of the incidence curves for these events were generally early and risk reduction with empagliflozin vs placebo persisted for the trial's duration (Fig. 1b–e). Post hoc power considerations are provided in ESM Table 3.

Empagliflozin was well tolerated by women, with no remarkable difference between empagliflozin and placebo for most adverse events assessed, including urinary tract infections. Genital infections, which were more common in women than in men in both treatment groups, were increased with empagliflozin treatment. In women this was observed in 2.5% in the placebo group and 10.0% in the empagliflozin group while in men, 1.5% and 2.6%, respectively, consistent with the known safety profile of sodium–glucose co-transporter-2 (SGLT2) inhibition. Nevertheless, discontinuation of the study drug due to this adverse event was infrequent. For every 1000 women treated with empagliflozin for 3.1 years, there occurred 12 fewer CV deaths, 27 fewer hospitalised HFs and 83 fewer incident or worsening nephropathy events, with 101 more genital infections, in comparison with placebo.

Discussion

Women with type 2 diabetes and established CV disease who were enrolled in the EMPA-REG OUTCOME® trial experienced high CV and renal event rates, in particular hospitalisation for HF that occurred numerically more frequently than in men, emphasising the high impact of diabetes on complications in this group. The numerically higher event rate for HF hospitalisation in women than in men is interesting in light of a similar between-sexes a priori 5 year estimated HF risk using the Health ABC HF risk score [8], bearing in mind the limitation that our trial was not powered to address sex differences. This observation could be related both to underlying factors specific to women [2] or, as suggested by others [9], because evidence-based HF therapies are used less often by women. In EMPA-REG

OUTCOME®, use of glucose-lowering medications, ACEis/ARBs and overall antihypertensive therapy use (albeit characterised by somewhat more diuretic and somewhat less beta-blocker use), was similar in men and women. However, both women and men allocated to placebo had a higher proportion of new prescriptions of such drugs during the trial than those allocated to empagliflozin. Women did have lower use of lipid-lowering and anti-platelet therapies, but neither of these have been associated with HF outcomes. Also, as fewer women than men were current or former smokers, a habit usually associated with increased HF risk [10], our observation could lend support to the hypothesis of female-specific factors playing a role. Empagliflozin was generally well tolerated, with a higher frequency of genital infections in both sexes, more so both in relative and absolute terms in women. This is congruent with results from previous reports on the use of empagliflozin, which has increased the risk of yeast vaginitis in earlier trials involving women with type 2 diabetes at lower CV risk [11].

In conclusion, CV death, HF hospitalisation and incident or worsening nephropathy rate reductions induced by empagliflozin were not different between women and men.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Contribution statement All authors fulfil the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, are fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version. Representatives of Boehringer Ingelheim (UH, JTG, OEJ) were involved in the study design, collection, analysis and interpretation of data; writing the report and the decision to submit the report for publication. BZ is the guarantor of this work.

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