Diabetologia (2021) 64:1226–1234
https://doi.org/10.1007/s00125-021-05399-2

ARTICLE

The efficacy and safety of dapagliflozin in women and men with type 2 diabetes mellitus

Michelle L. O'Donoghue[1] · Eri T. Kato[2] · Ofri Mosenzon[3] · Sabina A. Murphy[1] · Avivit Cahn[3] · Marisol Herrera[4] · Tsvetalina Tankova[5] · Alena Šmahelová[6] · Piera Merlini[7] · Ingrid Gause-Nilsson[8] · Anna Maria Langkilde[8] · Darren K. McGuire[9] · John P. H. Wilding[10] · Larry A. Leiter[11] · Deepak L. Bhatt[1,12] · Itamar Raz[3] · Marc S. Sabatine[1] · Stephen D. Wiviott[1]

Received: 22 October 2020 / Accepted: 9 December 2020 / Published online: 20 February 2021

Abstract

Aims/hypothesis Women remain underrepresented in clinical trials and those with type 2 diabetes mellitus are at high risk for cardiovascular (CV) events. The sodium–glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduces the risk of CV death or heart failure hospitalisations in individuals with type 2 diabetes. Here, we performed a pre-specified analysis to examine whether sex modifies these effects.

Methods The DECLARE-TIMI 58 trial randomised 17,160 patients with type 2 diabetes with or at risk for atherosclerotic disease to dapagliflozin or placebo (median follow-up 4.2 years). The dual efficacy outcomes were CV death or heart failure hospitalisations, and major adverse cardiovascular events (MACE; CV death, myocardial infarction or ischaemic stroke). The renal-specific composite outcome was a sustained ≥40% drop in eGFR to <60 ml min^{-1} [1.73 m]$^{-2}$, new end-stage renal disease or renal death. Cox models were run separately by sex with treatment-by-sex interaction testing for each outcome.

Results At baseline, women (n = 6422, 37.4%) had higher HbA_{1c}, longer type 2 diabetes duration, and were on fewer glucose-lowering medications. There was no evidence of modification of the effect of dapagliflozin by sex for (1) CV death or heart failure hospitalisations: women (3.8% vs 4.5%; HR 0.84, 95% CI 0.66, 1.07) and men (5.3% vs 6.4%; HR 0.83, 95% CI 0.71, 0.96; $p_{interaction}$ = 0.90); (2) MACE: women (6.3% vs 6.8%; HR 0.93, 95% CI 0.77, 1.12) and men (10.0% vs 10.7%; HR 0.93, 95% CI 0.83, 1.05; $p_{interaction}$ = 0.99); or (3) renal-specific composite: women (1.4% vs 2.8%; HR 0.50, 95% CI 0.35, 0.70) and men (1.5% vs 2.5%; HR 0.55, 95% CI 0.42, 0.73; $p_{interaction}$ = 0.64). The overall safety profile of dapagliflozin was similar for women and men.

Conclusions/interpretation Dapagliflozin offers comparable CV and renal benefits and a comparable safety profile in women and men.

Funding AstraZeneca.

Trial registration clinicaltrials.gov NCT01730534.

✉ Michelle L. O'Donoghue
modonoghue@bwh.harvard.edu

[1] TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

[2] Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

[3] Diabetes Unit, Hadassah Hebrew University Hospital, Jerusalem, Israel

[4] Torre Medica Providencia, Guadalajara, Mexico

[5] Department of Endocrinology, Medical University, Sofia, Bulgaria

[6] Faculty Hospital Hradec Kralove, Hradec Kralove, Czech Republic

[7] 2nd Division of Cardiology, Ca' Granda Niguarda Hospital, Milan, Italy

[8] BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[9] Division of Cardiology, University of Texas Southwestern Medical Center, and Parkland Health and Hospital System, Dallas, TX, USA

[10] Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK

[11] Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, ON, Canada

[12] Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

Research in context

What is already known about this subject?

- The sodium–glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduces the risk of cardiovascular death or heart failure hospitalisation in type 2 diabetes mellitus

What is the key question?

- Is the efficacy and safety of dapagliflozin comparable in women and men?

What are the new findings?

- Dapagliflozin had similar effects on the relative risk of cardiovascular death or heart failure hospitalisation, as well as major adverse cardiovascular events, in both women and men
- Dapagliflozin reduced renal-specific events by 45–50% in both women and men
- The overall safety profile of dapagliflozin was similar for women and men

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

- These findings provide important reassurance that dapagliflozin offers comparable efficacy and safety in both women and men

Keywords Cardiovascular outcomes · Clinical trials · SGLT2 inhibitors · Women

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CV	Cardiovascular
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase-4
ESRD	End-stage renal disease
GLP1-RA	Glucagon-like peptide 1 receptor agonists
HF	Heart failure
HHF	Heart failure hospitalisation
LSM	Least-squares mean
MACE	Major adverse cardiovascular events
SAE	Serious adverse events
SGLT2	Sodium–glucose cotransporter 2

Introduction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular (CV) events, including CV death or heart failure (HF), in patients with type 2 diabetes mellitus [1], and in patients with HF with reduced ejection fraction independent of type 2 diabetes status [2, 3]. However, since women remain underrepresented across clinical trials, it is important to define the efficacy and safety of SGLT2 inhibitors by participant sex. Supporting these concerns, sex disparities already exist in the management and treatment of CV risk factors in women with type 2 diabetes [4]. In the presence of a similar burden of risk factors, women are less likely than men to be treated with LDL-C-lowering therapies or to achieve adequate BP or glycaemic control [4]. As such, in a pre-specified analysis, we assessed in a large population with robust female representation ($n = 6422$, 37.4%) whether sex modifies the efficacy and safety of the SGLT2 inhibitor dapagliflozin in individuals with type 2 diabetes with or at increased risk of atherosclerotic disease in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial [5].

Methods

Study population and procedures The design and results of the DECLARE-TIMI 58 trial have been reported previously [5, 6]. In brief, DECLARE-TIMI 58 was a Phase III, multinational, double-blind, placebo-controlled trial that randomised 17,160 patients with type 2 diabetes with or at risk for atherosclerotic disease to dapagliflozin vs placebo. Eligible patients were 40 years or older with type 2 diabetes, had a creatinine clearance ≥60 ml/min and either multiple risk factors for atherosclerotic CV disease (ASCVD) or established ASCVD, coronary artery disease, cerebrovascular disease or peripheral artery disease. Eligible participants with multiple risk factors were men ≥55 years of age or women ≥60 years of age with at least one additional traditional ASCVD risk

factor including hypertension, dyslipidaemia or current tobacco use. Following a single-blind placebo run-in period, patients who remained eligible were randomised in a double-blind fashion to dapagliflozin 10 mg/day vs matching placebo and followed up for a median of 4.2 years.

Outcomes The dual efficacy outcomes were the composites of (1) CV death or HF hospitalisation (HHF) and (2) major adverse cardiovascular events (MACE; CV death, myocardial infarction or ischaemic stroke). The pre-specified cardiorenal outcome was the composite of a decrease of ≥40% in eGFR to <60 ml min^{-1} [1.73 m]$^{-2}$, end-stage renal disease (ESRD) or CV or renal death. The pre-specified renal-specific outcome was the composite of a ≥40% drop in eGFR to <60 ml min^{-1} [1.73 m]$^{-2}$, new ESRD or renal death. Safety events collected were adverse events leading to drug discontinuation, adverse events of special interest or serious adverse events (SAEs). An independent and blinded clinical events committee adjudicated all CV outcomes analysed.

Statistical analysis Baseline characteristics are presented as medians (IQRs) for continuous variables and frequencies for categorical variables. Baseline characteristics were compared with the Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables.

Mixed models for repeated measures in HbA_{1c}, weight, systolic BP and diastolic BP were analysed to produce least-squares mean (LSM) estimates and 95% CIs by treatment and sex subgroup. Efficacy analyses were conducted with Cox proportional hazards models that included a treatment arm, two randomisation stratification factors (presence of established atherosclerotic disease and baseline haematuria) and run separately by participant sex as captured on the electronic case-report form. Effect modification was assessed by including interaction terms in the models. All efficacy analyses were conducted in the intention-to-treat study population and event rates are reported as Kaplan–Meier estimates at 4 years. Safety analyses were performed using the on-treatment analysis set, as previously described, except for amputation, fracture and malignancy outcomes, which included all events after first dose in all patients who were randomised and received at least one dose of the study drug [5, 7]. All tests were two-sided with a p value <0.05 considered to be significant. The TIMI study group conducted all analyses. Analyses were performed using Stata/SE version 16.1 (Stata, College Station, Texas) or SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 17,160 patients enrolled in the DECLARE-TIMI 58 trial, 6422 (37.4%) were women. The baseline characteristics of the study population by participant sex are summarised in Table 1. Women were treated with fewer non-insulin glucose-

Table 1 Baseline characteristics for women and men in DECLARE-TIMI 58

Variable	Men (N =10,738)	Women (N =6422)	p value
Age (years), median (IQR)	63 (58–68)	65 (61–69)	<0.01
White (%)	81.5	76.3	<0.01
BMI (kg/m^2), median (IQR)	31 (28–35)	32 (28–36)	<0.01
Current tobacco (%)	16.9	10.6	<0.01
Region (%)			<0.01
North America	34.5	27.4	
Europe	43.9	45.3	
Latin America	9.2	13.9	
Asia Pacific	12.3	13.4	
Established CVD (%)	46.8	30.3	<0.01
Prior myocardial infarction (%)	25.5	13.2	<0.01
HbA_{1c} (mmol/mol), median (IQR)	63.9 (56.3–74.9)	65.0 (57.4–76.0)	<0.01
HbA_{1c} (%), median (IQR)	8.0 (7.3–9.0)	8.1 (7.4–9.1)	<0.01
eGFR (CKD-EPI) (ml min^{-1} [1.73 m]$^{-2}$), median (IQR)	88 (75–97)	89 (75–96)	0.91
UACR (mg/g), median (IQR)	14 (6–53)	12 (7–32)	<0.01
LDL-C (mmol/l), median (IQR)	2.0 (1.5–2.6)	2.3 (1.8–3.0)	<0.01
LV ejection fraction (%) (n=4088), median (IQR)	56 (49–62)	60 (55–65)	<0.01
Duration of type 2 diabetes (years), median (IQR)	10 (6–16)	11 (6–17)	<0.01

Abbreviations: UACR, urinary albumin/creatinine ratio; LV, left ventricular

lowering medications than men were (Table 2), and these findings were largely consistent across regions (electronic supplementary material [ESM] Table 1) and by age and/or qualifying disease status (ESM Table 2). The use of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RA) was significantly lower in women than men ($p < 0.001$). Background use of insulin and sulfonylureas did not differ by sex (Table 2). Crude rates of study drug discontinuation were similar in both women and men (23.6% vs 22.8%, $p = 0.23$), including both the active (21.3% vs 21.0%, $p = 0.72$) and placebo arms (25.8% vs 24.6%, $p = 0.21$).

Effect of dapagliflozin on CV risk factors Participants randomised to dapagliflozin had a lower HbA_{1c} at month 12 than participants randomised to placebo did; this was true for both women (LSM absolute difference −0.49%, 95% CI −0.55, −0.43; or −3.59 mmol/mol, 95% CI −4.30, −2.87) and men (LSM absolute difference −0.55%, 95% CI −0.59, −0.51; or −3.81 mmol/mol, 95% CI −4.36, −3.25) ($p_{interaction} = 0.07$). Similarly, patients treated with dapagliflozin had a lower body weight at 12 months than placebo-treated patients did regardless of sex (women: 12-month LSM absolute difference −1.7 kg, 95% CI −1.9, −1.6; men: 12-month LSM absolute difference −1.8 kg, 95% CI −2.0, −1.7; $p_{interaction} = 0.64$]. At 12 months, patients treated with dapagliflozin had lower systolic BP than placebo-treated patients; this was true for both women (−2.7 mmHg, 95% CI −3.4, −2.0) and men (−3.0 mmHg, 95% CI −3.5, −2.5) ($p_{interaction} = 0.52$); similarly, the difference in diastolic BP between treatment groups was −0.8 mmHg (95% CI −1.2, −0.4) in women and −0.9 mmHg (95% CI −1.2, −0.6) in men ($p_{interaction} = 0.87$).

Efficacy outcomes In the placebo arm, the crude incidence of CV death/HHF was 4.5% in women and 6.4% in men, and the incidence of MACE was 6.8% in women and 10.7% in men. All-cause mortality at 4 years was 5.4% in women and 6.3% in men. The incidence of MACE remained lower in women than men for those patients with (13.3% vs 16.2%) or without established ASCVD (4.0% vs 6.2%). Similarly, the incidence of CV death/HHF was lower in women than men in those with (15.2% vs 22.3%) or without a prior HF (3.5% vs 4.6%).

Dapagliflozin reduced the risk of CV death/HHF in women (HR 0.84, 95% CI 0.66, 1.07) and in men (HR 0.83, 95% CI 0.71, 0.96; $p_{interaction} = 0.90$; Fig. 1). The effects of dapagliflozin on risk of MACE did not differ between women (HR 0.93, 95% CI 0.77, 1.12) and men (HR 0.93, 95% CI 0.83, 1.05; $p_{interaction} = 0.99$; Table 3). Effects of dapagliflozin on risk of myocardial infarction also did not differ by sex (women: HR 0.89, 95% CI 0.67, 1.17; men: HR 0.88, 95% CI 0.75, 1.03; $p_{interaction} = 0.99$).

The cardiorenal composite outcome was reduced by dapagliflozin in women (HR 0.68, 95% CI 0.54, 0.86) and in men (HR 0.81, 95% CI 0.68, 0.96; $p_{interaction} = 0.26$; Table 3). For the renal-specific composite outcome, dapagliflozin reduced events in women (HR 0.50, 95% CI 0.35, 0.70) and in men (HR 0.55, 95% CI 0.42, 0.73; $p_{interaction} = 0.64$; Fig. 2; ESM Fig. 1).

In patients with established ASCVD, the HR for dapagliflozin vs placebo for risk of MACE was 0.85 (95% CI 0.66, 1.09) in women and 0.91 (95% CI 0.79, 1.05) in men ($p_{interaction} = 0.63$).

In patients with prior HF, dapagliflozin reduced the risk of CV death/HHF in women (0.78, 95% CI 0.51, 1.20) and in men (HR 0.81, 95% CI 0.62, 1.05; $p_{interaction} = 0.89$). In patients with prior myocardial infarction, the HR for dapagliflozin vs placebo for risk of MACE was 0.71 (95% CI 0.50, 1.02) in women and 0.88 (95% CI 0.74, 1.06) in men ($p_{interaction} = 0.29$). Similarly, the HR for dapagliflozin vs placebo for risk of recurrent myocardial infarction in patients with prior myocardial infarction were 0.70 (95% CI 0.45, 1.10) in women and 0.80 (95% CI 0.63, 1.00) in men ($p_{interaction} = 0.65$).

Safety outcomes Treatment-emergent SAEs were less common in dapagliflozin-treated than placebo-treated women (29.3% vs 31.5%) and men (36.9% vs 39.0%; $p_{interaction} = 0.78$; Table 4). Urinary tract infections (SAEs or leading to drug discontinuation) were more frequent in women than men, but were not different in those randomised to

Table 2 Baseline use of glucose-lowering medication for women and men

Variable	Men (N =10,738)	Women (N =6422)	*p* value
Insulin (%)	41.0	40.7	0.71
Any non-insulin glucose-lowering medication (%)	89.7	88.7	0.028
≥3 glucose-lowering medications (%)	20.6	16.4	<0.001
Metformin (%)	82.8	80.6	<0.001
Sulfonylurea (%)	42.7	42.6	0.87
DPP4 inhibitor (%)	18.0	14.9	<0.001
GLP1 RA (%)	4.8	3.7	<0.001

Table 3 Efficacy of dapagliflozin vs placebo stratified by participant sex

Outcome	Dapagliflozin N=3171 women N=5411 men Event rate	Placebo N=3251 women N=5327 men Event rate	HR (95% CI)	$p_{interaction}$
CV death or HHF (%)				
Women	3.8	4.5	0.84 (0.66, 1.07)	0.90
Men	5.3	6.4	0.83 (0.71, 0.96)	
MACE (%)				
Women	6.3	6.8	0.93 (0.77, 1.12)	0.99
Men	10.0	10.7	0.93 (0.83, 1.05)	
CV death (%)				
Women	2.1	2.4	0.93 (0.67, 1.27)	0.69
Men	3.1	3.0	1.00 (0.81, 1.24)	
Myocardial infarction (%)				
Women	3.0	3.2	0.89 (0.67, 1.17)	0.99
Men	5.5	6.2	0.88 (0.75, 1.03)	
Stroke (%)				
Women	2.5	2.4	1.05 (0.77, 1.42)	0.48
Men	3.1	3.5	0.92 (0.75, 1.13)	
HHF (%)				
Women	2.1	2.5	0.81 (0.59, 1.12)	0.44
Men	2.7	3.9	0.70 (0.56, 0.86)	
Sustained decrease of ≥40% in eGFR to <60 ml min^{-1} [1.73 m]$^{-2}$, ESRD or renal or CV death (%)				
Women	3.5	5.1	0.68 (0.54, 0.86)	0.26
Men	4.6	5.4	0.81 (0.68, 0.96)	
Renal-specific composite outcome (%)				
Women	1.4	2.8	0.50 (0.35, 0.70)	0.64
Men	1.5	2.5	0.55 (0.42, 0.73)	

$p_{interaction}$ reflects the two-way interaction between treatment arm and sex in a Cox model

Event rates are Kaplan–Meier estimates at 4 years

MACE includes CV death, myocardial infarction or ischaemic stroke; Renal-specific outcome includes ≥40% drop in eGFR to < 60 ml min^{-1} [1.73m]$^{-2}$, new ESRD or renal death

dapagliflozin or placebo, irrespective of sex (women: 2.2% vs 2.1%; men: 1.0% vs 1.2%; $p_{interaction} = 0.30$); genital mycotic infections (SAEs or leading to drug discontinuation) were more common with dapagliflozin in both women (1.0% vs 0.1%) and men (0.8% vs 0.1%; $p_{interaction} = 0.93$). The incidence of diabetic ketoacidosis (DKA) with dapagliflozin vs placebo was 0.5% vs 0.2% in women and 0.2% vs 0.1% in men ($p_{interaction} = 0.56$). The incidence of amputation with dapagliflozin compared with placebo was not different between women (0.7% vs 0.6%) and men (1.9% vs 1.7%; $p_{interaction} = 0.87$; Table 4).

Discussion

In patients with type 2 diabetes with or at high risk for ASCVD, the SGLT2 inhibitor dapagliflozin demonstrated comparable efficacy and safety in both women and men. Specifically, dapagliflozin significantly reduced the risk of CV death or HHF by 16–17%, irrespective of sex. Dapagliflozin also significantly reduced the risk of renal events by 45–50% irrespective of sex.

The current analysis uncovered notable differences at baseline in the management of type 2 diabetes in women and men. Although women had slightly higher baseline HbA_{1c} and slightly longer duration of type 2 diabetes, women were less likely to be treated with non-insulin glucose-lowering medications including metformin, DPP-4 inhibitors and GLP-1 RAs. Although not previously well described for glucose-lowering medications in patients with type 2 diabetes, it is well established that women are less likely to be treated with evidence-based therapies across several disease states, including the management of CVD [8]. Although the reasons for these differences may be multifactorial and need to be elucidated, continued emphasis on the use of appropriate evidence-

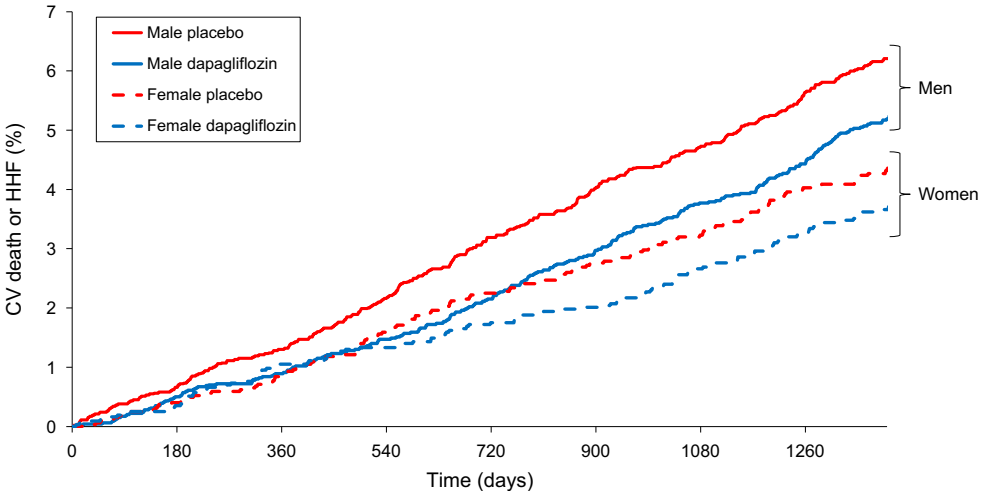

Fig. 1 The cumulative incidence of CV death or HHF in women and men by randomised treatment arm in DECLARE-TIMI 58. Dapagliflozin similarly reduced the risk of CV death/HHF in women (HR 0.84, 95% CI 0.66, 1.07) and in men (HR 0.83, 95% CI 0.71, 0.96; $p_{interaction}$=0.90)

based therapies in the setting of CV risk factors in both women and men is of the utmost importance. In the current analysis, it cannot be determined whether the relative underuse of non-insulin glucose-lowering medications in women was warranted, but this would be an important avenue for future research.

To date, the efficacy and safety of SGLT2 inhibitors has not been compared between women and men. In the EMPA-REG OUTCOME trial (n = 2004 women), empagliflozin demonstrated comparable benefit toward reducing CV events and slowing nephropathy irrespective of sex, but suggested a possible absolute excess in the risk of genital infections with empagliflozin in women (10.0% vs 2.5%) compared with men (2.6% vs 1.5%). Other safety outcomes were not specifically reported by sex [9]. In the CANVAS programme (n = 3633 women) [10] and CREDENCE trial (n = 1494 women) [11], canagliflozin similarly had comparable CV and renal protective effects by sex, but safety data by sex were not published. Prior to the completion of DECLARE-TIMI 58, a pooled analysis of Phase IIb/III data for dapagliflozin demonstrated that women were more likely than men to experience urinary tract or genital infections irrespective of treatment with dapagliflozin, but did not specifically address the relative risk of these events for women and men treated with the drug owing to relatively fewer events (n = 667 women and 3296 men treated with dapagliflozin in a 24-week pool) [12].

In the present analyses of DECLARE-TIMI 58 (n = 6422 women with a median follow-up of 4.2 years), dapagliflozin demonstrated similar CV efficacy and renal protection in both women and men. In DECLARE-TIMI 58, in patients with prior myocardial infarction, dapagliflozin significantly reduced the risk of recurrent myocardial infarction by 22% (95% CI 5, 27) in the overall trial with directionally similar effects in women (30% relative risk reduction) and men (20% relative risk reduction), thereby supporting the concept that the CV benefits of SGLT2 inhibition toward reducing atherosclerotic events may be enhanced in patients with established coronary disease [1]. Although dapagliflozin increased the risk of genital mycotic infections (SAEs or those leading to drug

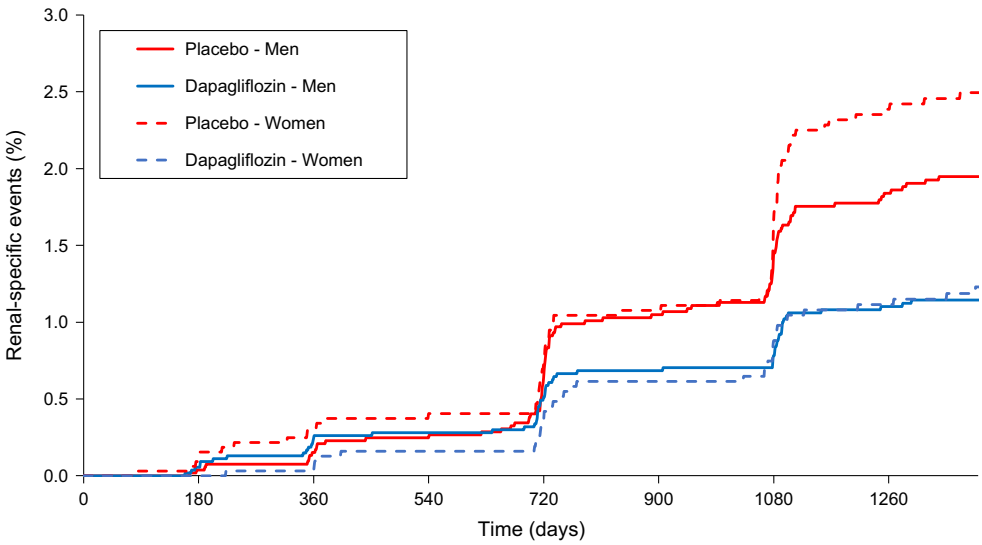

Fig. 2 The cumulative incidence of renal-specific events (a decrease of ≥40% in eGFR to <60 ml min^{-1} [1.73 m]^{2}, ESRD, or renal death) by participant sex and randomised treatment arm. Kaplan–Meier event rates at 4 years are displayed. Dapagliflozin reduced renal-specific events in women (HR 0.50, 95% CI 0.35, 0.70) and in men (HR 0.55, 95% CI 0.42, 0.73; $p_{interaction}$=0.64)

Table 4 The safety of dapagliflozin vs placebo stratified by participant sex

Outcome	Dapagliflozin N=3169 women N=5405 men Event rate	Placebo N=3246 women N=5323 men Event rate	HR (95% CI)	$p_{interaction}$
Treatment-emergent SAE (%)				
Women	29.3	31.5	0.90 (0.82, 0.98)	0.78
Men	36.9	39.0	0.91 (0.86, 0.97)	
Major hypoglycaemic event (%)				
Women	0.7	0.7	0.95 (0.54, 1.68)	0.16
Men	0.6	1.1	0.57 (0.38, 0.87)	
Diabetic ketoacidosis (%)				
Women	0.5	0.2	2.64 (1.03, 6.74)	0.56
Men	0.2	0.1	1.75 (0.65, 4.72)	
Urinary tract infection (%)				
Women	2.2	2.1	1.06 (0.76, 1.48)	0.30
Men	1.0	1.2	0.81 (0.57, 1.15)	
Genital infection (%)				
Women	1.0	0.1	8.09 (2.86, 22.9)	0.93
Men	0.8	0.1	8.60 (3.41, 21.7)	
Malignancy event (%)				
Women	4.1	4.7	0.85 (0.67, 1.08)	0.15
Men	6.5	6.2	1.04 (0.90, 1.21)	
Acute renal failure (%)				
Women	3.1	3.2	0.93 (0.70, 1.22)	0.07
Men	3.6	5.1	0.69 (0.57, 0.82)	
Symptoms of volume depletion (%)				
Women	1.7	1.8	0.88 (0.61, 1.27)	0.43
Men	3.0	2.8	1.05 (0.84, 1.31)	
Amputation (%)				
Women	0.7	0.6	1.13 (0.62, 2.04)	0.87
Men	1.9	1.7	1.07 (0.80, 1.41)	
Fracture (%)				
Women	7.2	6.6	1.09 (0.90, 1.31)	0.52
Men	4.3	4.2	1.00 (0.83, 1.20)	

Diabetic ketoacidosis and malignancy events were independently adjudicated. Diabetic ketoacidosis events reported are those adjudicated as definite or probable

$p_{interaction}$ reflects the two-way interaction between treatment arm and sex in a Cox model

Event rates are *n*/*N* in the on-treatment analysis set

discontinuation), the relative excess was similar in both women (1.0% vs 0.1%) and men (0.8% vs 0.1%), and urinary tract infections were not increased compared with placebo; however, individuals at highest risk of genitourinary infections may not have been enrolled in the trial. Although infrequent, a numerical excess in DKA cases was also observed with dapagliflozin vs placebo, as has been described with other SGLT2 inhibitors, in both women (0.5% vs 0.2%) and men (0.2% vs 0.1%). Symptoms of volume depletion and amputation risk were not increased with dapagliflozin in participants of either sex.

Limitations to the current analyses include that individual subgroups were underpowered for statistical significance; therefore, one cannot definitively exclude that a study with a larger population would detect differences in efficacy and safety by participant sex. Nonetheless, the DECLARE-TIMI 58 trial was the largest of the Phase III trials of an SGLT2 inhibitor in type 2 diabetes [10, 13, 14].

In summary, the use of and interest in SGLT2 inhibitors with regard to CV and kidney effects has continued to expand because randomised trials have demonstrated consistent CV and kidney benefit in patients with or without type 2 diabetes

in the presence of chronic kidney disease or HF with reduced left ventricular ejection fraction. Therefore, the current results provide important reassurance that the efficacy and safety of dapagliflozin are consistent in both women and men.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05399-2.

Data availability The data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Funding The DECLARE-TIMI 58 trial was sponsored by AstraZeneca. The study sponsor was not involved in writing the first draft of the report; had the ability to provide non-binding comments and could not impose any restrictions regarding the publication of the report.

Authors' relationships and activities MLOD has received grant funding via Brigham and Women's Hospital from AstraZeneca, Medimmune, Amgen, Janssen, GlaxoSmithKline, Intarcia and Novartis/Medicines Company; she has received consulting fees from Amgen, AstraZeneca/Medimmune, Novartis, Janssen and CRICO. ETK reports lecture fees from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, MSD KK, Tanabe-Mitsubishi Pharma and Ono Pharmaceutical and Bayer and a grant from Ono Pharmaceutical. SAM reports institutional research grants to the TIMI Study Group at Brigham and Women's Hospital from Abbott, Amgen, Anthos Therapeutics, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Takeda, The Medicines Company, Zora Biosciences. DLB discloses the following relationships: member of the advisory board for Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma and Regado Biosciences; member of the board of directors for: Boston VA Research Institute, Society of Cardiovascular Patient Care and TobeSoft; Chair for the American Heart Association quality oversight committee; member of the following data monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; received honoraria from: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); other: Clinical Cardiology (Deputy Editor), NCDR-ACTION registry steering committee (Chair), VA CART Research and Publications committee (Chair); received research funding from: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; received royalties from: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); site co-investigator at: Biotronik, Boston Scientific, CSI, St Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda. LAL reports grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Eli Lilly, grants and personal fees from Janssen, personal fees from Merck, grants and personal fees from Novo Nordisk, grants and personal fees from Sanofi, personal fees from Servier, and grants from GSK and Lexicon. DKM has received honoraria for clinical trial leadership from AstraZeneca, Boehringer Ingelheim, Eisai, Esperion, GlaxoSmithKline, Janssen, Lexicon, Merck Sharpe & Dohme Corp., Merck & Co., Inc., Novo Nordisk, Sanofi, Pfizer Inc., and has received consultancy fees from Afimmune, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Lilly, Merck & Co., Inc., Novo Nordisk, Metavant, and Sanofi. IGN and AML are AstraZeneca employees. TT is a member of an advisory board for and has received speaking fees from Boehringer Ingelheim, Astra Zeneca, Novo Nordisk, Eli Lilly, Sanofi, Servier and MSD. AC reports grants and personal fees from AstraZeneca and Novo Nordisk and personal fees from Abbott, Eli Lilly, Sanofi, Boehringer Ingelheim, Merck Sharp & Dohme, Medial Early-Sign and GlucoMe. MSS received research grant support through Brigham and Women's Hospital from: Amgen; Anthos Therapeutics, Inc.; AstraZeneca; Daiichi-Sankyo; Eisai; Intarcia; Medicines Company; MedImmune; Merck; Novartis; Pfizer and has undertaken consultancy for: Althera; Amgen; Anthos Therapeutics; AstraZeneca; Intarcia; Merck.

Contribution statement All authors contributed to the analysis and interpretation of data, provided critical revisions for important intellectual content and gave final approval of the version to be published. MLOD drafted the manuscript and takes full responsibility for the work as a whole, including the current study design, access to data and the decision to submit and publish the manuscript.

References

1. Zelniker TA, Wiviott SD, Raz I et al (2019) SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 393(10166):31–39. https://doi.org/10.1016/S0140-6736(18)32590-X
2. McMurray JJV, Solomon SD, Inzucchi SE et al (2019) Dapagliflozin in Patints with Heart Failure and Reduced Ejection Fraction. N Engl J Med 381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303
3. Packer M, Anker SD, Butler J et al (2020) Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 383:1413–1424. https://doi.org/10.1056/NEJMoa2022190
4. Gouni-Berthold I, Berthold HK, Mantzoros CS, Bohm M, Krone W (2008) Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. Diabetes Care 31(7):1389–1391. https://doi.org/10.2337/dc08-0194
5. Wiviott SD, Raz I, Bonaca MP et al (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 380(4):347–357. https://doi.org/10.1056/NEJMoa1812389

6. Wiviott SD, Raz I, Bonaca MP et al (2018) The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J 200:83–89. https://doi.org/10.1016/j.ahj.2018.01.012
7. Cahn A, Raz I, Bonaca M et al (2020) Safety of dapagliflozin in a broad population of patients with type 2 diabetes: Analyses from the DECLARE-TIMI 58 study. Diabetes Obes Metab 22(8):1357–1368. https://doi.org/10.1111/dom.14041
8. Sarma AA, Braunwald E, Cannon CP et al (2019) Outcomes of Women Compared With Men After Non-ST-Segment Elevation Acute Coronary Syndromes. J Am Coll Cardiol 74(24):3013–3022. https://doi.org/10.1016/j.jacc.2019.09.065
9. Zinman B, Inzucchi SE, Wanner C et al (2018) Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME(R). Diabetologia 61(7):1522–1527. https://doi.org/10.1007/s00125-018-4630-2
10. Neal B, Perkovic V, Mahaffey KW et al (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 377(7):644–657. https://doi.org/10.1056/NEJMoa1611925
11. Perkovic V, Jardine MJ, Neal B et al (2019) Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 380(24):2295–2306. https://doi.org/10.1056/NEJMoa1811744
12. Ptaszynska A, Johnsson KM, Parikh SJ, de Bruin TW, Apanovitch AM, List JF (2014) Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug Saf 37(10):815–829. https://doi.org/10.1007/s40264-014-0213-4
13. Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 373(22):2117–2128. https://doi.org/10.1056/NEJMoa1504720
14. Cannon CP, Pratley R, Dagogo-Jack S et al (2020) Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 383(15):1425–1435. https://doi.org/10.1056/NEJMoa2004967