



Sex Differences in Characteristics, Outcomes, and Treatment Response With Dapagliflozin Across the Range of Ejection Fraction in Patients With Heart Failure: Insights From DAPA-HF and DELIVER

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BACKGROUND: Sodium-glucose cotransporter-2 inhibitors have emerged as a key pharmacotherapy in heart failure (HF) with both reduced and preserved ejection fraction. The benefit of other HF therapies may be modified by sex, but whether sex modifies the treatment effect and safety profile of sodium-glucose cotransporter-2 inhibitors remains unclear. Our analyses aim to assess the effect of sex on the efficacy and safety of dapagliflozin.

METHODS: In a prespecified patient-level pooled analysis of DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), clinical outcomes were compared by sex (including the composite of cardiovascular death or worsening HF events, cardiovascular death, all-cause death, total events [first and recurrent HF hospitalization and cardiovascular death], and Kansas City Cardiomyopathy Questionnaire scores) across the spectrum of left ventricular ejection fraction.

RESULTS: Of a total of 11 007 randomized patients, 3856 (35%) were women. Women with HF were older and had higher body mass index but were less likely to have a history of diabetes and myocardial infarction or stroke and more likely to have hypertension and atrial fibrillation compared with men. At baseline, women had higher ejection fraction but worse Kansas City Cardiomyopathy Questionnaire scores than men did. After adjustment for baseline differences, women were less likely than men to experience cardiovascular death (adjusted hazard ratio, 0.69 [95% CI, 0.60–0.79]), all-cause death (adjusted hazard ratio, 0.69 [95% CI, 0.62–0.78]), HF hospitalizations (adjusted hazard ratio, 0.82 [95% CI, 0.72–0.94]), and total events (adjusted rate ratio, 0.77 [95% CI, 0.71–0.84]). Dapagliflozin reduced the primary end point in both men and women similarly ($P_{\text{interaction}}=0.77$) with no sex-related differences in secondary outcomes (all $P_{\text{interaction}}>0.35$) or safety events. The benefit of dapagliflozin was observed across the entire ejection fraction spectrum and was not modified by sex ($P_{\text{interaction}}>0.40$). There were no sex-related differences in serious adverse events, adverse events, or drug discontinuation attributable to adverse events.

CONCLUSIONS: In DAPA-HF and DELIVER, the response to dapagliflozin was similar between men and women. Sex did not modify the treatment effect of dapagliflozin across the range of ejection fraction.

Key Words: dapagliflozin ■ heart failure ■ sex characteristics ■ sodium-glucose transporter 2 inhibitors

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Clinical Perspective

What Is New?

- Dapagliflozin has recently been shown to reduce worsening heart failure and cardiovascular death across the range of ejection fraction.
- In a pooled analysis of DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), women and men derived similar benefits from dapagliflozin for both the primary outcome of worsening heart failure or cardiovascular death and secondary outcomes, including improvement in health status.
- Dapagliflozin was safe and well tolerated in both sexes.

What Are the Clinical Implications?

- Across the full spectrum of ejection fraction in heart failure, women and men derived similar benefits from dapagliflozin compared with placebo.
- Our findings are consistent with other sodium-glucose cotransporter-2 inhibitors, suggesting a class effect.
- There are no treatment-related differences in serious adverse events or adverse events in women compared with men. However, detailed safety events such as genital and urinary tract infections were limited in DELIVER given the well-established safety profile of dapagliflozin in prior studies.

Sex is known to affect almost every facet of heart failure (HF), from risk factors to clinical presentation, treatment response, and prognosis.¹ Sex differences in response to HF pharmacotherapies have recently been highlighted wherein women appear to benefit from neurohormonal modulators (namely angiotensin receptor blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors) across a wider HF ejection fraction (EF) range compared with men.² This was particularly evident in the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction), in which sex was an independent effect modifier of the treatment response to angiotensin receptor-neprilysin inhibitors, along with left ventricular (LV) EF.^{3,4} Women and those with lower EF derived more benefit than men and those with higher EF in PARAGON-HF. The exact mechanism for this difference is unclear. However, because normal female hearts have a higher EF compared with their male counterparts,⁵ using the same EF cutoff (eg, 40%) may have included women with more adverse LV remodeling who then benefited more from neurohormonal modulators.

Nonstandard Abbreviations and Acronyms

CHARM	Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DELIVER	Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure
EF	ejection fraction
EMPEROR-Preserved	Empagliflozin Outcomes Trial in Heart Failure and a Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcomes Trial in Heart Failure and a Reduced Ejection Fraction
HF	heart failure
I-PRESERVE	Irbesartan in Heart Failure With Preserved Ejection Fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	left ventricular
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PARAGON-HF	Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction
SGLT2	sodium-glucose cotransporter 2
TOPCAT	Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function

However, whether these considerations also apply to the sodium-glucose cotransporter-2 (SGLT2) inhibitors remains unclear. In a prespecified subgroup analysis of EMPEROR-Preserved (Empagliflozin Outcomes Trial in Heart Failure and a Preserved Ejection Fraction), women and men derived a similar reduction in cardiovascular death or HF hospitalization and had similar improvement in quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary

score.⁶ Likewise, in a prespecified subgroup analysis of DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), dapagliflozin reduced the risk of worsening HF, cardiovascular death, and all-cause death regardless of sex, with similar improvements in quality of life.⁷ In a pooled analysis across EMPEROR-Reduced (Empagliflozin Outcomes Trial in Heart Failure and a Reduced Ejection Fraction) and EMPEROR-Pre-served, there appeared to be attenuation of benefit with empagliflozin at higher EFs (at and beyond 65%) that was present in both women and men.⁸

In this analysis, we aim to expand the existing data and to assess the effect of sex on the efficacy and safety of dapagliflozin across a full EF spectrum in HF.

METHODS

Study Design and Patient Population

The study designs of DAPA-HF and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) have been described.^{9,10} In brief, DAPA-HF was a randomized, placebo-controlled trial enrolling ambulatory patients with New York Heart Association (NYHA) class II to IV HF and EF \leq 40% and elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide).⁹ The median follow-up was 18.2 months. DELIVER was a randomized, placebo-controlled trial in ambulatory or hospitalized patients \geq 40 years of age with chronic NYHA class II to IV HF, LVEF $>$ 40%, structural heart disease (left atrial enlargement or LV hypertrophy), and elevation in natriuretic peptides.¹⁰ In both trials, patients were randomized to receive dapagliflozin 10 mg daily or placebo, in addition to other recommended therapies. The trial protocols for DAPA-HF and DELIVER were approved by institutional review boards at each trial center, and trial participants gave informed consent.

The corresponding authors had full access to all the trial data and take responsibility for their integrity and the data analysis. Data underlying the findings described in this article may be obtained by following AstraZeneca's data-sharing policy.¹¹

Outcomes

The primary outcome in DAPA-HF was a composite of worsening HF or cardiovascular death. Worsening HF was defined as hospitalization or urgent visit resulting in intravenous therapy. Secondary outcomes included HF hospitalization and cardiovascular death, total HF hospitalizations and cardiovascular death, changes in KCCQ total symptom score at 8 months, a renal composite end point (worsening renal function, end-stage renal disease, or renal death), and all-cause death. DELIVER had the same primary end point of worsening HF or cardiovascular death.^{10,12} Secondary outcomes included total number with worsening HF and cardiovascular death, change in KCCQ total symptom score, cardiovascular death, and all-cause death.

In the pooled analysis, the primary outcome was a composite of worsening HF or cardiovascular death. Secondary outcomes included cardiovascular death, all-cause death, HF hospitalization, urgent HF visits, HF hospitalization or urgent HF visit, and total events (first and recurrent HF

hospitalization and cardiovascular death). Death resulting from unknown causes was included in cardiovascular death. Total HF events were defined as first and recurrent HF hospitalizations in both DAPA-HF and DELIVER.^{9,10} Changes in patient-reported health status, as measured by KCCQ total symptom score, clinical summary score, and overall summary score, were also assessed.

Key safety end points included any serious adverse events, adverse events leading to drug discontinuation or dose interruption, diabetic ketoacidosis, hypoglycemia, and amputation.

Statistical Analysis

Descriptive statistics, including baseline characteristics and safety events, were compared between women and men. Continuous variables were compared with the Student *t* test and are reported as mean \pm SD. Categorical variables were compared with the χ^2 test and are reported as percentages. Linear regression analysis was performed to adjust NT-proBNP levels for baseline LVEF.

We used Cox models to compare outcomes in women and men. We constructed 3 models. In the unadjusted model, analysis was stratified by trial (DAPA-HF versus DELIVER). In model 1, we adjusted for age and region and stratified by trial. In model 2, besides the covariates in model 1, additional covariates (heart rate, systolic blood pressure, body mass index, smoking status, log values of NT-proBNP, estimated glomerular filtration rate, NYHA class, LVEF, previous HF hospitalization, myocardial infarction, diabetes, and atrial fibrillation) were included. Treatment effects for time-to-event outcomes were analyzed with Kaplan-Meier estimates and Cox proportional hazards models stratified by diabetes status and trials. Total events were analyzed with the Lin-Wei-Yang-Ying model. To assess the effect of sex on the treatment effect of dapagliflozin, we included a sex-by-treatment interaction term in the Cox proportional hazards models stratified by trial. The proportional hazards assumption was not met for the primary analysis in DELIVER. However, application of an alternative approach (that does not require this assumption) produced similar results.¹⁰

Linear regression was used to compare changes in KCCQ scores from week 0 to 32. Baseline KCCQ scores were included in the linear regression model to account for baseline differences. The effect of sex on changes in KCCQ scores was tested by including a sex-by-treatment interaction term in the linear regression model stratified by trial.

To test for sex-related differences in the potentially nonlinear association between EF and the treatment effect of dapagliflozin, we used Poisson regression to estimate the incidence rate of time-to-event outcomes as a function of EF using restricted cubic splines with 3 knots for each sex/treatment groups. We subsequently used those rates to estimate sex-specific treatment effect rate ratios and finally tested for effect modification with a joint test of the sex-treatment and sex-EF-treatment interaction terms.

RESULTS

Baseline Characteristics

Of a total of 11 007 randomized patients, 3856 (35%) were women (Table 1). Women with HF were older and had

Table 1. Baseline Characteristics in Women and Men

Variable	Women (n=3856)	Men (n=7151)	P value
Age, y	71±10	68±11	<0.001
Region, n (%)			<0.001
Europe and Saudi Arabia	1877 (48.7)	3282 (45.9)	
North America	492 (12.8)	1036 (14.5)	
South America	804 (20.9)	1194 (16.7)	
Asia/Pacific	683 (17.7)	1639 (22.9)	
Race/ethnicity, n (%)			<0.001
White	2772 (71.9)	5000 (69.9)	
Asian	710 (18.4)	1680 (23.5)	
Black or African American	154 (4.0)	231 (3.2)	
American Indian or Alaska Native	96 (2.5)	97 (1.4)	
Native Hawaiian or other Pacific Islander	0 (0.0)	2 (0.0)	
Other	124 (3.2)	141 (2.0)	
LVEF, %	49±14	42±13	<0.001
Pulse, bpm	72±12	71±12	<0.001
Systolic blood pressure, mm Hg	127±16	124±16	<0.001
Diastolic blood pressure, mm Hg	74±11	74±10	0.71
Body mass index, kg/m ²	29.9±6.7	28.7±5.7	<0.001
Clinical history			
Hypertension, n (%)	3298 (85.5)	5778 (80.8)	<0.001
Type 2 diabetes, n (%)	1619 (42.0)	3170 (44.3)	0.018
Prior stroke, n (%)	319 (8.3)	744 (10.4)	<0.001
Prior MI, n (%)	906 (23.5)	2825 (39.5)	<0.001
AFF, n (%)	1383 (35.9)	2389 (33.4)	0.010
Prior HF hospitalization, n (%)	1615 (41.9)	3175 (44.4)	0.011
NYHA III/IV score	1145 (29.7)	1945 (27.2)	0.005
KCCQ-TSS score	66.9±22.5	74.0±21.5	<0.001
KCCQ-OSS score	62.8±20.7	69.6±20.0	<0.001
KCCQ-CSS score	64.3±20.9	72.2±20.2	<0.001
eGFR, mL·min ⁻¹ ·1.73 m ⁻²	59.7±19.0	64.9±19.4	<0.001
NT-proBNP, ng/L	1127 (661, 2015)	1207 (722, 2180)	<0.001
NT-proBNP in AFF, ng/L	1542 (1045, 2354)	1549 (1026, 2578)	0.21
NT-proBNP when no AFF, ng/L	875 (531, 1692)	1013 (588, 1912)	<0.001
HbA1c, %	6.6±1.5	6.5±1.3	0.25
Creatinine, μmol/L	92±26	110±31	<0.001
Baseline treatment, n (%)			
Diuretics including MRA	3721 (96.5)	6835 (95.6)	0.020
Loop diuretic	2954 (76.6)	5682 (79.5)	<0.001
Nonloop diuretic excluding MRA	810 (21.0)	1045 (14.6)	<0.001
ACE inhibitor	1416 (36.7)	3540 (49.5)	<0.001
ARB	1541 (40.0)	2038 (28.5)	<0.001
ACE inhibitor or ARB	2947 (76.4)	5548 (77.6)	0.17
ARNI	189 (4.9)	620 (8.7)	<0.001
β-Blocker	3317 (86.0)	6418 (89.7)	<0.001
MRA	1913 (49.6)	4124 (57.7)	<0.001

(Continued)

Table 1. Continued

Variable	Women (n=3856)	Men (n=7151)	P value
Statin	2351 (61.0)	4864 (68.0)	<0.001
Antiplatelet	1558 (40.4)	3664 (51.2)	<0.001
Anticoagulant	1884 (48.9)	3467 (48.5)	0.71
CRT-D or ICD	206 (5.3)	915 (12.8)	<0.001

ACE indicates angiotensin-converting enzyme; AFF, atrial fibrillation or flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; bpm, beats per minute; CRT-D, cardiac resynchronization therapy-defibrillator; CSS, clinical summary score; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; and TSS, total symptom score.

higher body mass index but were less likely to have a history of diabetes and myocardial infarction/stroke and more likely to have hypertension and atrial fibrillation compared with men. Women had higher LVEF and lower natriuretic peptides; however, after adjustment for LVEF, women had 4.3% (95% CI, 1.0%–7.8%) higher natriuretic peptides compared with men. Women were more likely to have baseline NYHA class III or IV HF and lower KCCQ scores compared with men. At baseline, >75% of men and women were on angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, >95% were on diuretics (including mineralocorticoid receptor antagonists), and >85% were on β -blockers (Table 1). Baseline characteristics in women and men were also compared by EF subgroups (Table S1).

Outcomes by Sex

Overall, women had better outcomes compared with men (Table 2 and Figure 1) regardless of treatment arm. Over a median follow-up of 22 months, the primary outcome (composite of cardiovascular death and worsening HF) occurred in 613 women (8.4 per 100 person-years) and 1397 men (11.6 per 100 person-year), a lower risk in women that was significant even after adjustment for baseline sex differences (adjusted hazard ratio, 0.78 [95% CI, 0.70–0.87]; $P<0.001$; Table 2, model 2). Women also had an unadjusted 27% to 30% lower risk of cardiovascular death and all-cause death (31% after multivariable adjustment; Table 2, model 2) and 18% to 31% lower risk of HF hospitalization, urgent HF visits, and total events (first and recurrent HF hospitalization and cardiovascular death) compared with men after multivariable adjustment (Table 2, model 2). In a sensitivity analysis, we used trial-specific definitions (deaths resulting from unknown causes included as cardiovascular death in DAPA-HF; death resulting from unknown causes excluded from cardiovascular death in DELIVER) and found similar results (Table S2).

Effect of Sex on Treatment Effect of Dapagliflozin

Dapagliflozin reduced the incidence of primary outcome events in both women and men, with a hazard ratio of

0.80 in women (95% CI, 0.68–0.94; $P=0.006$) and 0.78 in men (95% CI, 0.70–0.86; $P<0.001$; $P_{\text{interaction}}=0.77$; Figure 1). There was no effect modification by sex for any other end points (Figure 2). In a sensitivity analysis, we used trial-specific definitions of cardiovascular death and found similar results (Table S3).

Total events (first and recurrent HF hospitalization and cardiovascular death) were also assessed in the pooled cohorts. Dapagliflozin was associated with a reduction in total events in both women (rate ratio, 0.77 [95% CI, 0.64–0.93]; $P=0.006$) and men (rate ratio, 0.76 [95% CI, 0.67–0.86]; $P<0.001$; $P_{\text{interaction}}=0.89$; Figure 1).

Both women and men reported improvement in their health status. Among those who reported KCCQ scores, men had a 2.4-point improvement in total symptom score from week 0 to 32 ($P<0.001$). Women had a similar magnitude of improvement (Table 3). Sex was not found to modify the effect of dapagliflozin on KCCQ scores ($P_{\text{interaction}}>0.40$ for all 3 KCCQ scores; Table 3).

Treatment Effect of Dapagliflozin Across LVEF

Dapagliflozin had a similar effect on the primary composite outcome, worsening HF events or cardiovascular death, in men and women across the EF spectrum (Figure 3). There was no evidence of heterogeneity of treatment effect by EF or sex (for treatment-by-sex-by-EF interaction, $P>0.35$ for all 3 outcomes; Figure 3). Using trial-specific definitions of cardiovascular death yielded similar results (Figure S1).

Effect of Sex on Safety of Dapagliflozin

Men were more likely to experience any serious adverse events (42.5% in men versus 40.2% in women; $P=0.018$; Table 4). However, women were more likely to have adverse events leading to study drug discontinuation (6.1% in women versus 5.0% in men; $P=0.020$), and women were more likely to have drug discontinuation for any reason (14.7% in women versus 11.6% in men; $P<0.001$; Table 4). There were 4 cases (0.1%) versus 1 case (<0.1%) of diabetic ketoacidosis and 13 (0.3%) versus 8 (0.1%) major hypoglycemic events in women

Table 2. Comparison of Outcomes in Women and Men

Variable	Event no. (event rate per 100 person-y)		Hazard ratio or relative risk; reference: male (95% CI); P value		
	Women (n=3856)	Men (n=7151)	Unadjusted*	Adjusted, model 1†	Adjusted, model 2‡
Primary end point	613 (8.4)	1397 (11.6)	0.79 (0.72, 0.87); <0.001	0.79 (0.71, 0.87); <0.001	0.78 (0.70, 0.87); <0.001
Cardiovascular death	371 (4.1)	815 (6.3)	0.70 (0.61, 0.80); <0.001	0.66 (0.58, 0.76); <0.001	0.69 (0.60, 0.79); <0.001
All-cause death	489 (6.3)	1139 (8.8)	0.73 (0.65, 0.81); <0.001	0.68 (0.61, 0.75); <0.001	0.69 (0.62, 0.78); <0.001
Heart failure hospitalization	414 (5.6)	882 (7.3)	0.84 (0.74, 0.94); 0.003	0.84 (0.75, 0.95); 0.006	0.82 (0.72, 0.94); 0.004
Urgent heart failure visit	60 (0.8)	111 (0.9)	0.79 (0.58, 1.09); 0.15	0.81 (0.59, 1.12); 0.20	0.69 (0.49, 0.98); 0.040
Heart failure hospitalization or urgent visit	449 (6.1)	937 (7.8)	0.84 (0.75, 0.94); 0.003	0.85 (0.76, 0.95); 0.005	0.82 (0.72, 0.93); 0.002
Total events (first and recurrent heart failure hospitalization and cardiovascular death)	955 (12.3)	2201 (17.1)	0.77 (0.71, 0.83); <0.001	0.76 (0.70, 0.82); <0.001	0.77 (0.71, 0.84); <0.001

*Stratified by trial.

†Adjusted for age and region; stratified by trial.

‡Adjusted for age, heart rate, systolic blood pressure, body mass index, smoking status, NT-proBNP (N-terminal pro-B-type natriuretic peptide) [log], estimated glomerular filtration rate, New York Heart Association class, left ventricular ejection fraction, previous HHF, myocardial infarction, diabetes, atrial fibrillation, and region; stratified by trial.

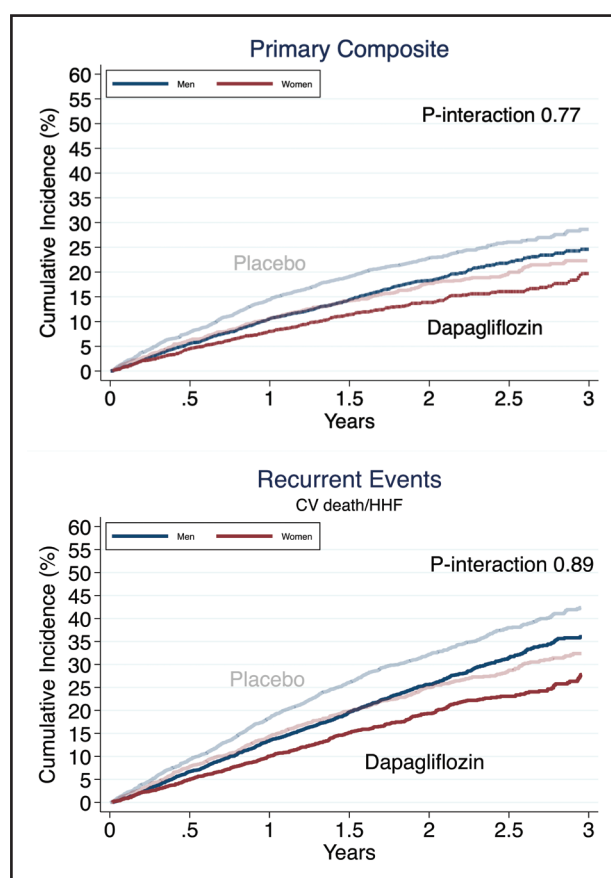
versus men, respectively. There was no differential increased risk of adverse events in the dapagliflozin group in either men or women (all $P_{\text{interaction}} > 0.10$).

DISCUSSION

In this patient-level pooled meta-analysis of DAPA-HF and DELIVER, women generally had better outcomes than men with HF, despite being older and more symptomatic. Nevertheless, both women and men derived similar benefits from dapagliflozin; specifically, dapagliflozin reduced the primary composite outcome of cardiovascular death or a worsening HF event, its components (cardiovascular death, HF hospitalization, or urgent HF visit), all-cause death, and total events (first and recurrent HF hospitalization and cardiovascular death), as well as improved KCCQ scores, similarly in men and women. The safety profile of dapagliflozin compared with placebo was also similar in men and women in these 2 trials. In contrast to prior HF studies using neurohormonal modulators, there was no evidence of treatment heterogeneity by EF in either sex for dapagliflozin.

The sex differences in baseline demographics and outcomes of this pooled analysis reflect what has previously been reported in HF studies. Consistent with prior epidemiological studies, women tended to be older with more age-related comorbidities such as hypertension and atrial fibrillation and were less likely to have prior myocardial infarction or stroke compared with men with HF.¹³ Such observations have been attributed to a predisposition to macrovascular coronary artery disease and myocardial infarction in men, whereas in women, coronary microvascular dysfunction and endothelial inflam-

mation may play a key role in the predominance of HF with preserved EF, as well as potentially explain the predisposition of women to other cardiomyopathies such as

**Figure 1. Cumulative incidence for the outcomes in DAPA-HF and DELIVER trials in women and men.**

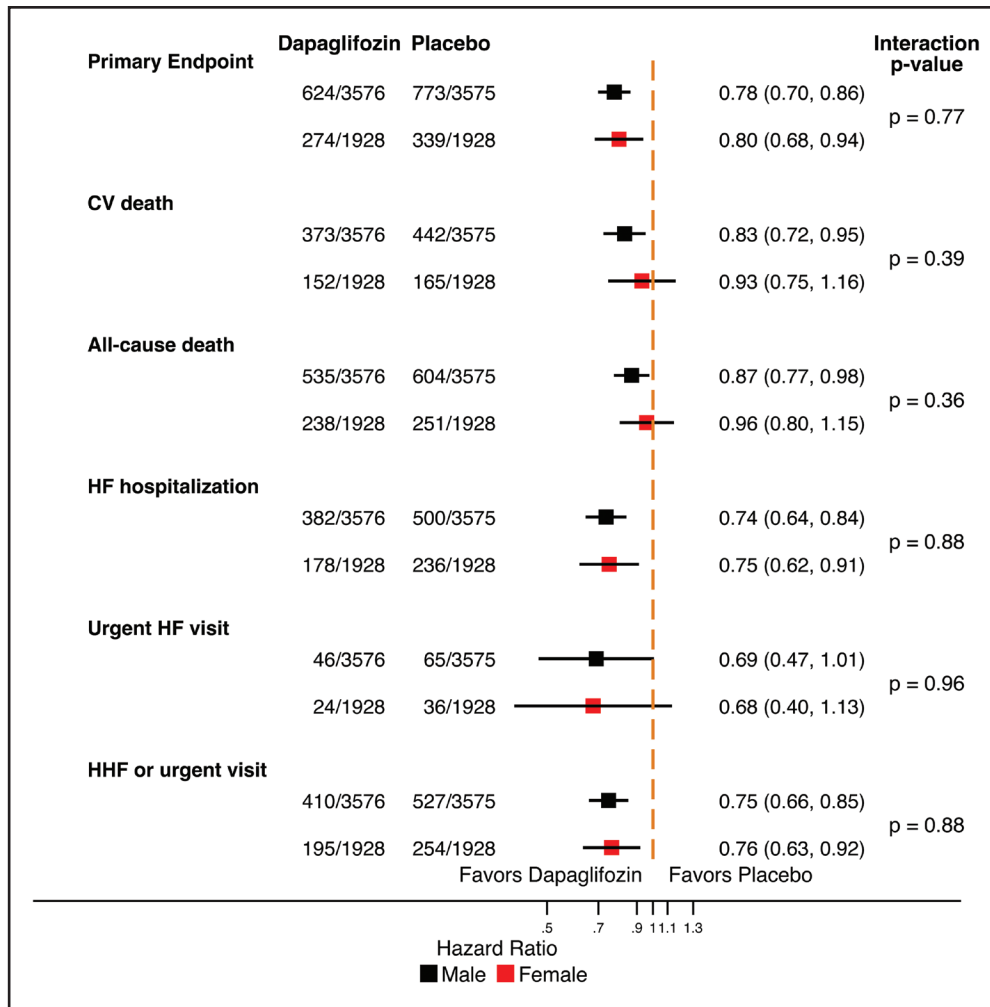


Figure 2. Treatment effect of dapagliflozin in women and men.

CV indicates cardiovascular; HF, heart failure; and HHF, hospitalization for heart failure.

takotsubo, peripartum, and breast cancer radiotherapy-induced cardiomyopathy.¹ Despite a higher EF, women had worse baseline functional status (as measured by NYHA class) and worse patient-reported health status (as measured by KCCQ scores), an observation also consistent with prior clinical trials, although the underlying reasons are not fully understood.^{3,6,7,14,15} Overall, women had better outcomes compared with men in our pooled cohort, regardless of treatment assignment and both before and after adjustment for baseline differences in clinical characteristics. This is consistent with prior epidemiological and clinical studies such as those reported in the Rochester Epidemiology Project (Olmsted County, Minnesota), Framingham Heart Study, and analyses from CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) and I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction).^{14,16–18}

Our finding of a consistent treatment effect of dapagliflozin in women and men is consistent with similar analyses of the empagliflozin treatment effect⁸ but

stands in contrast to observations in HF trials involving neurohormonal modulators (Table S4). Sex was a significant effect modifier in 2 trials. In TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function), among patients from the Americas, spironolactone was associated with a 34% reduction of all-cause mortality in women but not in men ($P_{\text{interaction}}=0.02$).¹⁹ In PARAGON-HF, sacubitril/valsartan reduced the primary outcome (composite of total HF hospitalizations and cardiovascular death) to a greater extent in women, with a rate ratio of 0.73 (95% CI, 0.59–0.90),

Table 3. Changes in Quality of Life From Week 0 to 32

Variable	Women	Men	$P_{\text{interaction}}$ value
Total symptom score	2.4 (0.8, 4.0)*	2.4 (1.2, 3.7)†	0.96
Clinical summary score	2.5 (1.0, 3.9)†	2.2 (1.1, 3.4)†	0.82
Overall summary score	2.5 (1.1, 3.9)†	1.8 (0.7, 3.0)*	0.45

* $P<0.005$ for changes from week 0 to 32.

† $P<0.001$ for changes from week 0 to 32.

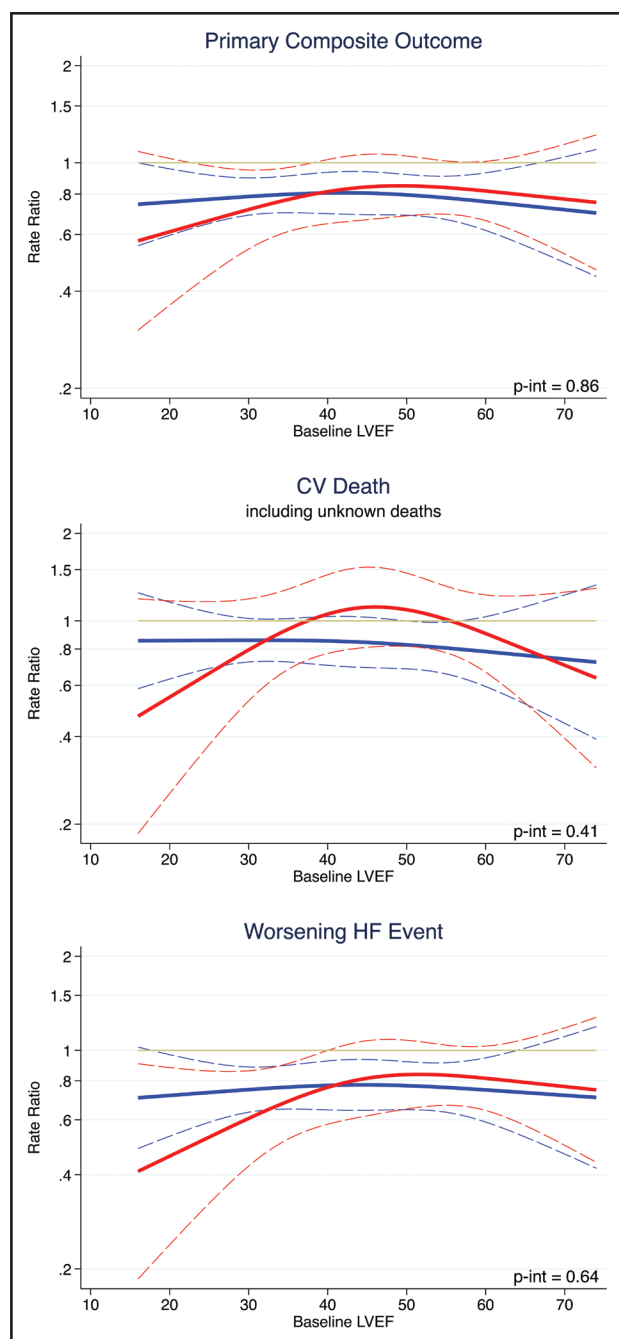


Figure 3. Treatment effect of dapagliflozin in women (red) and men (blue) across left ventricular ejection fraction.

CV indicates cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction; and p-int, *P* for interaction for sex by treatment by ejection fraction.

compared with men (rate ratio, 1.03 [95% CI, 0.84–1.25]; $P_{\text{interaction}}=0.017$). However, women derived less improvement in KCCQ clinical summary score than men in PARAGON-HF, whereas women and men had similar improvement in NYHA class. In contrast, in EMPEROR-Preserved, women and men derived a similar reduction in cardiovascular death or HF hospitalization and had similar improvement in KCCQ scores. Similarly, in DAPA-HF, dapagliflozin resulted in a similar reduction of worsening

HF events or cardiovascular death in women and men. Our current results, now looking at the full spectrum of EF in a combined analysis of >11 000 patients with HF, indicate that sex is not a modifier of the treatment effect of dapagliflozin, whether we are looking at hard clinical end points or patient-reported health status. Given the consistency with the EMPEROR trials, this likely applies to the evidence-based SGLT2 inhibitors in HF as a class, suggesting that sex-specific indications are not needed for this class of therapies in HF.

The lack of treatment heterogeneity across the full range of EF in our pooled analysis stands in contrast to prior observations of the attenuated treatment effect at higher EFs in HF trials of both neurohormonal modulators and empagliflozin.^{2–4,20,21} One plausible explanation is that patients with lower EF may have greater activation of the neurohormonal axis; thus, medications such as mineralocorticoid receptor antagonists and angiotensin receptor-neprilysin inhibitors have a greater effect at the lower end of the EF spectrum.²² Because women have a higher normal EF, women may have a greater extent of adverse LV remodeling at any given EF compared with men and thus derive more benefits from neurohormonal modulation.⁵ Although these prior observations have led to calls for sex-specific cutoffs in the determination of EF thresholds for treatment in HF,^{23,24} the current results indicate that this may not be the case for therapies that are equally effective across the entire EF spectrum of HF such as the evidence-based SGLT2 inhibitors. The mechanism of action of SGLT2 inhibitors in HF, although incompletely understood, is clearly distinct from that of neurohormonal modulators that focus on reverse LV remodeling. Although there is some evidence of favorable LV remodeling with SGLT2 inhibitors,^{25–28} there have been conflicting reports, and results for both LV volume reduction and natriuretic peptide lowering (as an indicator of reduction in LV wall stress) are less convincing than for the neurohormonal modulators.^{25,29–32} The previously reported attenuation of the empagliflozin treatment effect at EF $\geq 65\%$ is likely a chance finding given the lack of significant heterogeneity by prespecified EF subgroups or continuous EF in the primary analyses of EMPEROR-Preserved and pooled EMPEROR trials, respectively, as well as the variability of results with different post hoc EF cut points in the EMPEROR trials (eg, benefit in the EF >72.5% subgroup despite a lack of benefit in the 62.5%–67.5% and 67.5%–72.5% subgroups).⁸

The results of this analysis must be interpreted within the confines of the study design. First, DAPA-HF and DELIVER were 2 large randomized trials with strict inclusion and exclusion criteria, and the generalizability of these findings should consider these criteria. Second, only 35% of the patients were women, which reflects the lower rates of HF with reduced EF in women. In DAPA-HF, both components of the primary end point (worsening HF or cardiovascular death) contributed to the

Table 4. Safety of Dapagliflozin in Women and Men

	Women, n (%)			Men, n (%)			<i>P</i> _{interaction} value
	All (n=3856)	Dapagliflozin (n=1928)	Placebo (n=1928)	All (n=7151)	Dapagliflozin (n=3576)	Placebo (n=3575)	
Any serious adverse event	1547 (40.2)	761 (39.6)	786 (40.8)	3034 (42.5)	1446 (40.5)	1588 (44.5)	0.16
Any adverse event leading to drug discontinuation	233 (6.1)	122 (6.3)	111 (5.8)	357 (5.0)	171 (4.8)	186 (5.2)	0.27
Any adverse event leading to dose interruption	553 (14.4)	263 (13.7)	290 (15.0)	1010 (14.1)	457 (12.8)	553 (15.5)	0.33
Discontinuation for any reason	568 (14.7)	294 (15.3)	274 (14.2)	825 (11.6)	399 (11.2)	426 (11.9)	0.17
Any definite or probable diabetic ketoacidosis	4 (0.1)	4 (0.2)	0 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	...
Any major hypoglycemic event	13 (0.3)	6 (0.3)	7 (0.4)	8 (0.1)	4 (0.1)	4 (0.1)	0.87
Any amputation	20 (0.5)	7 (0.4)	13 (0.7)	49 (0.7)	25 (0.7)	24 (0.7)	0.23
Any adverse event that potentially placed a patient at risk for lower-limb amputation	162 (4.2)	77 (4.0)	85 (4.4)	287 (4.0)	144 (4.0)	143 (4.0)	0.58

benefit of dapagliflozin, whereas in DELIVER, the composite primary end point was driven largely by HF hospitalization. Nevertheless, we saw no heterogeneity by sex in the combined analysis despite a higher proportion of women in DELIVER. Third, although sex differences in genital infections would be of relevance given the known higher risk in women than men,³³ only data on serious adverse events, adverse events that led to discontinuation of dapagliflozin or placebo, and select other adverse events were collected in DELIVER given the extensive data on the safety of dapagliflozin from prior studies.

Conclusions

Across the full spectrum of EF in HF, women and men derived similar benefits from dapagliflozin compared with placebo for both the primary outcome of cardiovascular death or worsening HF and secondary outcomes, including improvement in health status. Dapagliflozin was safe and well tolerated in both sexes.

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Supplemental Material

Tables S1–S4

Figure S1

REFERENCES

- Lam CSP, Arnett C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859–3868c. doi: 10.1093/eurheartj/ehz835
- Dewan P, Jackson A, Lam CSP, Pfeffer MA, Zannad F, Pitt B, Solomon SD, McMurray JJV. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail*. 2020;22:898–901. doi: 10.1002/ehf.1776
- McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, Lefkowitz MP, Maggioni AP, Martinez F, Packer M, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation*. 2020;141:338–351. doi: 10.1161/CIRCULATIONAHA.119.044491
- Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, Rouleau J, Pfeffer MA, Desai A, Lund LH, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141:352–361. doi: 10.1161/CIRCULATIONAHA.119.044586
- St Pierre SR, Peirlinck M, Kuhl E. Sex matters: a comprehensive comparison of female and male hearts. *Front Physiol*. 2022;13:831179. doi: 10.3389/fphys.2022.831179
- Butler J, Filippatos G, Jamal Siddiqi T, Pedro Ferreira J, Brueckmann M, Bocchi E, Böhm M, Chopra VK, Giannetti N, Iwata T, et al. Effects of empagliflozin in women and men with heart failure and preserved ejection fraction. *Circulation*. 2022;146:1046–1055. doi: 10.1161/CIRCULATIONAHA.122.059755
- Butt JH, Docherty KF, Petrie MC, Schou M, Kosiborod MN, O'Meara E, Katova T, Ljungman CEA, Diez M, Oggunniyi MO, et al. Efficacy and safety of dapagliflozin in men and women with heart failure with reduced ejection fraction: a prespecified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial. *JAMA Cardiol*. 2021;6:678–689. doi: 10.1001/jamacardio.2021.0379
- Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, Brueckmann M, Pocock SJ, Zannad F, Anker SD. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J*. 2022;43:416–426. doi: 10.1093/eurheartj/ehab798
- McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Böhölváček J, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
- Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–1098. doi: 10.1056/NEJMoa2206286
- AstraZeneca. Disclosure commitment. Accessed January 18, 2023. <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.
- Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Lindholm D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail*. 2021;23:1217–1225. doi: 10.1002/ehf.2249
- Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14:591–602. doi: 10.1038/nrcardio.2017.65
- Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, McKelvie RS, McMurray JJ, Zile MR, Massie BM, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail*. 2012;5:571–578. doi: 10.1161/circheartfailure.112.970061
- Dewan P, Rorth R, Raparelli V, Campbell RT, Shen L, Jhund PS, Petrie MC, Anand IS, Carson PE, Desai AS, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12:e006539. doi: 10.1161/CIRCHEARTFAILURE.119.006539

16. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Piña IL, Granger CB, Ostergren J, Michelson EL, Solomon SD, Pocock S, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;115:3111–3120. doi: 10.1161/CIRCULATIONAHA.106.673442
17. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344–350. doi: 10.1001/jama.292.3.344
18. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham study. *J Am Coll Cardiol*. 1993;22(suppl A):6A–13A. doi: 10.1016/0735-1097(93)90455-a
19. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT trial. *JACC Heart Fail*. 2019;7:228–238. doi: 10.1016/j.jchf.2019.01.003
20. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37:455–462. doi: 10.1093/eurheartj/ehv464
21. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail*. 2018;20:1230–1239. doi: 10.1002/ehf.1149
22. Benedict CR, Weiner DH, Johnstone DE, Bourassa MG, Ghali JK, Nicklas J, Kirilin P, Greenberg B, Quinones MA, Yusuf S. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry. *J Am Coll Cardiol*. 1993;22(suppl A):146A–153A. doi: 10.1016/0735-1097(93)90480-o
23. Lam CSP, Voors AA, Piotr P, McMurray JJV, Solomon SD. Time to rename the middle child of heart failure: heart failure with mildly reduced ejection fraction. *Eur Heart J*. 2020;41:2353–2355. doi: 10.1093/eurheartj/ehaa158
24. Lam CSP, Solomon SD. Classification of heart failure according to ejection fraction: JACC review topic of the week. *J Am Coll Cardiol*. 2021;77:3217–3225. doi: 10.1016/j.jacc.2021.04.070
25. Lan NSR, Fegan PG, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. *ESC Heart Fail*. 2019;6:927–935. doi: 10.1002/ehf2.12505
26. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation*. 2021;143:516–525. doi: 10.1161/CIRCULATIONAHA.120.052186
27. Omar M, Jensen J, Ali M, Frederiksen PH, Kistorp C, Videbæk L, Poulsen MK, Tuxen CD, Möller S, Gustafsson F, et al. Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: a substudy of the EMPHIRE HF randomized clinical trial. *JAMA Cardiol*. 2021;6:836–840. doi: 10.1001/jamacardio.2020.6827
28. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, Macaluso F, Sartori S, Roque M, Sabatel-Perez F, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;77:243–255. doi: 10.1016/j.jacc.2020.11.008
29. Verma S, Garg A, Yan AT, Gupta AK, Al-Omran M, Sabongui A, Teoh H, Mazer CD, Connelly KA. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care*. 2016;39:e212–e213. doi: 10.2337/dc16-1312
30. Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2018;17:73. doi: 10.1186/s12933-018-0717-9
31. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol*. 2018;17:132. doi: 10.1186/s12933-018-0775-z
32. Cohen ND, Gutman SJ, Briganti EM, Taylor AJ. Effects of empagliflozin treatment on cardiac function and structure in patients with type 2 diabetes: a cardiac magnetic resonance study. *Intern Med J*. 2019;49:1006–1010. doi: 10.1111/imj.14260
33. McGovern AP, Hogg M, Shields BM, Sattar NA, Holman RR, Pearson ER, Hattersley AT, Jones AG, Dennis JM. Risk factors for genital infections in people initiating SGLT2 inhibitors and their impact on discontinuation. *BMJ Open Diabetes Res Care*. 2020;8:e001238. doi: 10.1136/bmjdr-2020-001238