10.1161/CIRCULATIONAHA.122.062832

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

Running title: *Lam et al.; Sex differences in DAPA-HF and DELIVER*

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*** This work was presented as an abstract at AHA Scientific Sessions, November 5-7, 2022.

****This manuscript was sent to Eileen Hsich, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Abstract:

Background:
Sodium-glucose cotransporter-2 (SGLT2) 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 SGLT2 inhibitors remains unclear. Our analyses aim to assess the impact of sex on the efficacy and safety of dapagliflozin

Methods:
In a pre-specified patient-level pooled analysis of DAPA-HF and DELIVER, clinical outcomes were compared by sex (including the composite of cardiovascular [CV] death or worsening HF events; CV death; all-cause death, total events (first and recurrent HF hospitalization and CV death), and Kansas City Cardiomyopathy Questionnaire [KCCQ] scores) across the spectrum of left ventricular ejection fraction (EF).

Results:
Of a total of 11,007 randomized patients, 3856 (35%) were women. Women with HF were older, had 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 to men. At baseline, women had higher EF but worse KCCQ scores than men. After adjusting for baseline differences, women were less likely than men to experience CV death (adjusted hazard ratio [aHR] 0.69, 95% CI 0.60-0.79), all-cause death (aHR 0.69, 95% 0.62-0.78), HF hospitalizations (aHR 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 endpoint in both men and women similarly (p-interaction = 0.77) with no sex-related differences in secondary outcomes (all p-interactions > 0.35) or safety events. The benefit of dapagliflozin was observed across the entire EF spectrum and was not modified by sex (p-interaction > 0.40). There were no sex-related differences in serious adverse events, adverse events, or drug discontinuation due 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: Sodium-glucose Cotransporter-2 Inhibitors; Sex Differences; Dapagliflozin; Heart Failure

Non-standard Abbreviations and Acronyms:

AE = adverse event

AFF = atrial fibrillation or flutter;

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;

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;

HHF = heart failure hospitalization;

NT-proBNP = N-terminal pro-B-type natriuretic peptide;

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.

Clinical Perspectives

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 co-transporter-2 inhibitors, suggesting a class effect.
- There are no treatment-related differences in serious adverse events or adverse events in women versus 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.

Introduction

Sex is known to impact 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 [ARNI]) across a wider HF ejection fraction (EF) range compared to men.[2] This was particularly evident in the PARAGON-HF (Prospective comparison of angiotensin receptor–neprilysin inhibitor with angiotensin receptor blocker global outcomes in heart failure with preserved ejection fraction) trial, where sex was an independent effect modifier of the treatment response to ARNI, 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, since normal female hearts have a higher EF compared to their male counterparts,[5] using the same EF cutoff (e.g. 40%) may have included women with more adverse LV remodeling who then benefited more from neurohormonal modulators.

However, whether these considerations also apply to the sodium-glucose cotransporter-2 (SGLT2) inhibitors remain unclear. In a pre-specified subgroup analysis of EMPEROR-Preserved (Empagliflozin Outcomes Trial in Heart Failure and a Preserved Ejection Fraction), women and men derived similar reduction in cardiovascular (CV) death or HF hospitalization and had similar improvement in quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire clinical summary scores (KCCQ-CSS).[6] Likewise, in a pre-specified subgroup analysis of DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, dapagliflozin reduced the risk of worsening HF, CV 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-Preserved trials, 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 assess the impact 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] Briefly, DAPA-HF was a randomized, placebo-controlled trial enrolling ambulatory patients with New York Heart Association (NYHA) Class II-IV heart failure and ejection fraction ≤40% and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP).[9] The median follow-up was 18.2 months. DELIVER was a randomized, placebo-controlled trial in ambulatory or hospitalized patients ≥40 years of age, with chronic NYHA class II-IV heart failure, LVEF > 40%, structural heart disease (left atrial enlargement or left ventricular 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 takes responsibility for their integrity and the data analysis. Data underlying the findings described in this article may be obtained following AstraZeneca's data

sharing policy described

at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

Outcomes

The primary outcome in DAPA-HF was a composite of worsening HF or CV death. Worsening HF was defined as hospitalization or urgent visit resulting in intravenous therapy. Secondary outcomes included HF hospitalization and CV death, total HF hospitalizations and CV death, changes in KCCQ total symptom score (TSS) at 8 months; a renal composite endpoint (worsening renal function, end-stage renal disease, or renal death), and all-cause death. DELIVER had the same primary endpoint of worsening HF or CV death.[10, 11] Secondary outcomes included total number of worsening HF and CV death, change in KCCQ-TSS total symptom score (TSS), CV death, and all-cause death.

In the pooled analysis, the primary outcome was a composite of worsening HF or CV death. Secondary outcomes included CV death, all-cause death, HF hospitalization, urgent HF visits, HF hospitalization or urgent HF visit, and total events (first and recurrent HF hospitalization and CV death). Death from unknown causes were included in CV death. Total heart failure 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-TSS, clinical summary score (CSS), and overall summary score (OSS), were also assessed.

Key safety endpoints included any serious adverse events (SAEs), adverse events (AEs) 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 using Student's t-test and reported as mean ± standard deviation. Categorical variables were compared using the chi-square test and 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 vs. DELIVER). In Model 1, we adjusted for age and region, and stratified by trial. In Model 2, in addition to 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 mellitus, and atrial fibrillation) were included. Treatment effect for time-to-event outcomes were analyzed using Kaplan-Meier estimates and Cox proportional hazards models, stratified by diabetes status and trials. Total events were analyzed using Lin-Wei-Yang-Ying (LWYY) model. To assess the impact 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 week 32. Baseline KCCQ scores were included in the linear regression model to account for baseline differences. The impact 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 non-linear association between ejection fraction 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 via a joint test of the sex-treatment and sex-EF-treatment interaction terms.

Results

Baseline Characteristics

Of a total of 11007 randomized patients, 3856 (35%) were women (Table 1). Women with HF were older, had 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 to men. Women had higher LVEF and lower natriuretic peptides; however, after adjusting for LVEF, women had 4.3% (95% confidence interval [CI] 1.0% - 7.8%) higher natriuretic peptides compared to men. Women were more likely to have baseline NYHA class III or IV heart failure and lower KCCQ scores compared to men. At baseline, >75% of men and women were on ACEIs (angiotensin-converting enzyme inhibitors) or ARBs (angiotensin receptor antagonists), >95% were on diuretics (including mineralocorticoid receptor antagonists [MRAs]), and >85% were on beta-blockers (Table 1). Baseline characteristics in women and men were also compared by EF subgroups (Supplemental Table S1).

Outcomes by Sex

Overall, women had better outcomes compared to men (Table 2 and Figure 1) regardless of treatment arm. Over a median follow-up of 22 months, the primary outcome (composite of CV

death and worsening HF) occurred in 613 (8.4 per 100 person-year) women and 1397 (11.6 per 100 person-year) men -- a lower risk in women that was significant even after adjusting for baseline sex differences (adjusted hazard ratio [aHR] of 0.78; 95% CI 0.70-0.87, p<0.001, Table 2 Model 2). Women also had an unadjusted 27-30% lower risk of CV death and all-cause death (31% after multivariable adjustment, Table 2 Model 2), and 18-31% lower risk of HF hospitalization, urgent HF visits, and total events (first and recurrent HF hospitalization and CV death), compared to men after multivariable adjustment (Table 2 Model 2). In a sensitivity analysis, we used trial-specific definitions (deaths from unknown causes included as CV death in DAPA-HF; death from unknown causes excluded from CV death in DELIVER) and found similar results (Supplemental Table S2).

Impact of Sex on Treatment Effect of Dapagliflozin

Dapagliflozin reduced the incidence of primary outcome events in both women and men, with hazard ratio (HR) of 0.80 in women (95% CI 0.68-0.94, p=0.006) and HR of 0.78 in men (95% CI 0.70-0.86, p<0.001, Figure 1; p-interaction = 0.77). There was no effect modification by sex for any other endpoints (Figure 2). In a sensitivity analysis, we used trial-specific definitions of CV death and found similar results (Supplemental Table S3).

Total events (first and recurrent HF hospitalization and CV death) were also assessed in the pooled cohorts. Dapagliflozin was associated with a reduction in total events in both women (RR 0.77, 95% CI 0.64-0.93, p=0.006) and men (RR 0.76, 95% CI 0.67-0.86, p<0.001, Figure 1; p-interaction 0.89).

Women and men both reported improvement in their health status. Among those who reported KCCQ scores, men had a 2.4 points improvement in total symptom score from week 0 to week 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-interaction > 0.40 for all three KCCQ scores, Table 3).

Treatment Effect of Dapagliflozin across LVEF

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

Impact of Sex on Safety of Dapagliflozin

Men were more likely to experience any serious adverse events (SAE) (42.5% in men vs. 40.2% in women, p=0.018, Table 4). However, women were more likely to have adverse events (AE) leading to study drug discontinuation (6.1% in women vs 5.0% in men, p=0.020), and women were more likely to have drug discontinuation due to any reason (14.7% in women vs. 11.6% in men, p<0.001, Table 4). There were 4 (0.1%) vs. 1 (<0.1%) cases of diabetic ketoacidosis, and 13 (0.3%) vs. 8 (0.1%) major hypoglycemic events, in women vs. men respectively. There was no differential increased risk of adverse events in the dapagliflozin group in either men or women (all p-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 CV death or a worsening HF event, its components

(CV death, HF hospitalization or urgent HF visit), all-cause death, and total events (first and recurrent HF hospitalization and CV 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 two 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 been previously 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 to men with HF.[12] 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 inflammation 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 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 underlying reasons are not fully understood.[3, 6, 7, 13, 14] Overall, women had better outcomes compared to men in our pooled cohort, regardless of treatment assignment, and both before and after adjusting for baseline differences in clinical characteristics. This is consistent with prior epidemiological and clinical studies, such as those reported in 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).[13,15-17]

Our finding of a consistent treatment effect of dapagliflozin in women and men is consistent with similar analyses of the empagliflozin treatment effect,[8] although standing in contrast to observations in HF trials involving neurohormonal modulators (Supplemental Table S4). Sex was a significant effect modifier in two 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-interaction = 0.02).[18] In PARAGON-HF, sacubitril/valsartan reduced the primary outcome (composite of total heart failure hospitalizations and cardiovascular death) to a greater extent in women, with a rate ratio (RR) of 0.73 (95% CI 0.59-0.90), compared to men (RR 1.03, 95% CI 0.84-1.25, p-interaction = 0.017). Yet women derived less improvement in KCCQ-CSS than men in PARAGON-HF, while women and men had similar improvement in NYHA class. In contrast, in EMPEROR-Preserved, women and men derived similar reduction in CV 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 CV death in women and men. Our current results, now looking at the full spectrum of EF in a combined analysis of over 11,000 patients with HF, indicate that sex is not a modifier of the treatment effect of dapagliflozin, whether looking at "hard" clinical endpoints 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 attenuated treatment effect at higher EFs in HF trials of both neurohormonal modulators and empagliflozin. [2-4, 19, 20] One plausible explanation is that patients with lower EF may have greater activation of the neurohormonal axis, and thus medications such as MRAs and ARNI have a greater effect at the lower end of EF spectrum.[21] Since women have a higher normal EF, women may have a greater extent of adverse LV remodeling at any given EF compared to men, and thus derive more benefits from neurohormonal modulation.[5] While these prior observations have led to calls for sex-specific cut-offs in the determination of EF thresholds for treatment in HF,[22, 23] 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. While there is some evidence of favorable LV remodeling with SGLT2 inhibitors,[24-27] 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. [24, 28-31] The previously reported attenuation of empagliflozin treatment effect at EF ≥65% is likely a chance finding, given the lack of significant heterogeneity by pre-specified 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 (e.g. benefit in the EF>72.5% subgroup despite 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 two 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 CV death) contributed to the benefit of dapagliflozin, whereas in DELIVER, the composite primary endpoint was largely driven by HF hospitalization. Nevertheless, we saw no heterogeneity by sex in the combined analysis despite a higher proportion of women in DELIVER. Third, while sex differences in genital infections would be of relevance given the known higher risk in women than men,[32] 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.

In conclusion, 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 CV death or worsening HF and secondary outcomes including improvement in health status. Dapagliflozin was safe and well-tolerated in both sexes.

Acknowledgements

This manuscript is dedicated to the memory of Lauren Gilstrap, MD, a DELIVER investigator, colleague, co-author, and friend.

Sources of Funding

AstraZeneca was the sponsor and funder of the DAPA-HF and DELIVER trials.

Dr. Wang is supported by a T32 postdoctoral training grant from the National Heart, Lung, and Blood Institute (T32 HL094301), and by the Scott Schoen and Nancy Adams First.In.Women Cardiovascular Fellowship, Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital

Dr. Pabon is supported by John S. LaDue Memorial Fellowship at Harvard Medical School, and by the Scott Schoen and Nancy Adams First.In.Women Cardiovascular Fellowship, Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital.

Dr. Shah is supported by research grants from the National Institutes of Health (U54 HL160273, R01 HL140731, R01 HL149423)

Dr. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore.

Dr. McMurray is supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217

Disclosures

Dr. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen

Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai.

Dr. Zieroth received research grant support, served on advisory boards for, or speaker engagements with Abbott, Akcea AstraZeneca, Amgen, Alnylam, Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Servier and Vifor Pharma; and serves on a clinical trial committee or as a national lead for studies sponsored by AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis and Pfizer.

Dr. Inzucchi has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Merck, Pfizer, Bayer, Abbott, Lexicon, vTv Therapeutics and Esperion; and has delivered lectures sponsored by AstraZeneca and Boehringer Ingelheim.

Dr. Hegde receives fees paid to institution for consulting (core echo lab) from MyoKardia/Bristol Myers Squibb.

Dr. McMurray is supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217. He has received payments through Glasgow University from work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos Personal lecture fees: the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, Global Clinical Trial Partners (GCTP).

Dr. Kober receives speakers honorarium from AstraZeneca, Bayer, Boehringer, Novartis and Novo.

Dr. Hernandez has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic and Verily; and has served as a consultant or on the Advisory Board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Eidos, Intercept, Merck, and Novartis.

Dr. Shah is supported by research grants from the National Institutes of Health (U54 HL160273, R01 HL140731, R01 HL149423), Actelion, AstraZeneca, Corvia, Novartis, and Pfizer and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiora, Coridea, CVRx, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Eisai, Imara, Impulse Dynamics, GSK, Intellia, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Sardocor, Shifamed, Tenax, Tenaya, and United Therapeutics.

Dr. Solomon has received research grants from Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Cytokinetics, Eidos, GSK, Ionis, Lilly, MyoKardia, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros.

Dr. Vardeny reports having received research support from AstraZeneca, Bayer, and Cardurion.

Dr. Desai reported receiving grants from AstraZeneca, Abbott, Alnylam, Bayer, and Novartis; consulting fees from AstraZeneca, Abbott, Alnylam, Amgen, Bayer, Biofourmis, Cytokinetics,

GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Roche, Regeneron, Verily, Axon Therapeutics, Avidity, and New Amsterdam; and fees for data-safety monitoring board participant from Boston Scientific.

Dr. Jhund reported speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc. PSJ's employer the University of Glasgow has been remunerated for clincal trial work from AstraZeneca, Bayer AG, Novartis and NovoNordisk; Director Global Clinical Trial Partners (GCTP).

Dr. Claggett reported receiving consulting fees from Boehringer Ingelheim, Cardurion, Corvia, Cytokinetics, Intellia and Novartis outside of the submitted work.

Dr. Vaduganathan reported receiving grant support or advisory board fees from Amgen, AstraZeneca, American Regent, Baxter HealthCare, Bayer AG, Boehringer Ingelheim, Cytokinetics, Pharmacosmos, Relypsa, Novartis, Roche Diagnostics, Lexicon Pharmaceuticals, Galmed, Occlutech, Impulse Dynamics, Sanofi, and Tricog Health; speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics; and actively participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics outside the submitted work.

Dr. Katova receives consulting fees from AstraZeneca, Bayer Healthcare, and Novartis.

Dr. O'Meara receives research support from Canadian Heart Function Alliance – CIHR Team Grant (steering committee) and steering committee member for DAPA-ACT (TIMI group and AstraZeneca), NLI for DELIVER (AstraZeneca), steering committee member for HEART-FID (American Regent) and CARDINAL-HF (Cardurion). She receives consulting fees from

AstraZeneca, Boehringer Ingelheim, Bayer, Eli Lilly, Janssen and speaker fees from AstraZeneca, Boehringer Ingelheim, Bayer. She serves as a member of heart failure guidelines writing committee for Canadian Cardiovascular Society.

Dr. Langkilde is employed by and holds stock in AstraZeneca.

Dr. De Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche.

Dr. Martinez receives consulting fees from AstraZeneca.

Dr. Kosiborod receives consulting fees from Alnylam Pharmaceuticals, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, Esperion Therapeutics, Janssen Global Services, Lexicon Pharmaceuticals, Merck, Novo Nordisk, Pharmacosmos, Sanofi, Vifor Pharma; he also receives grant/contract or travel fees from AstraZeneca and Boehringer Ingelheim.

Dr. Sabatine reports research grant support through Brigham and Women's Hospital from Abbott; Amgen; Anthos Therapeutics; AstraZeneca; Daiichi-Sankyo; Eisai; Intarcia; Ionis; Merck; Novartis; Pfizer, and consulting Althera; Amgen; Anthos Therapeutics; AstraZeneca; Beren Therapeutics; Boehringer Ingelheim; Bristol-Myers Squibb; Fibrogen; Intarcia; Merck; Moderna; Novo Nordisk; Silence Therapeutics. Additionally, Dr. Sabatine is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from: ARCA Biopharma, Inc., Janssen Research and Development, LLC, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, and Zora Biosciences.

Dr. Pouleur is supported by a Clinician Researcher from the Belgian Fonds National de la Recherche Scientifique; has served as consultant/or on the Advisory Board Committee/or speaker engagements for AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, Vifor Pharma.

All others (Drs. Wang, Pabon, McGrath, Ponikowski) have no relevant disclosures.

Supplemental Materials

Table S1: Baseline characteristics in women and men across ejection fraction subgroups.

Table S2: Comparison of outcomes in women and men, with trial-specific definitions of cardiovascular death.

Table S3: Treatment effect of dapagliflozin in women and men, with trial-specific definitions of cardiovascular death.

Table S4: Select sex-related differences in clinical trials of modern heart failure therapy.

Figure S1: Treatment effect of dapagliflozin in women and men across the range of ejection fraction, with trial-specific definitions of cardiovascular death.

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Table 1. Baseline Characteristics in Women and Men.

	Women	Men	
	n=3856	n=7151	p-value
Age	71 ± 10	68 ± 11	<0.001
Region			<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			<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 (beats/min)	72 ± 12	71 ± 12	<0.001
Systolic Blood Pressure (mmHg)	127 ± 16	124 ± 16	<0.001
Diastolic Blood Pressure (mmHg)	74 ± 11	74 ± 10	0.71
Body Mass Index	29.9 ± 6.7	28.7 ± 5.7	<0.001
Clinical History			
Hypertension	3298 (85.5%)	5778 (80.8%)	<0.001
Type 2 Diabetes Mellitus	1619 (42.0%)	3170 (44.3%)	0.018
Prior Stroke	319 (8.3 %)	744 (10.4%)	<0.001
Prior MI	906 (23.5%)	2825 (39.5%)	<0.001
Atrial Fibrillation/Flutter	1383 (35.9%)	2389 (33.4%)	0.010
Prior HF Hospitalization	1615 (41.9%)	3175 (44.4%)	0.011
NYHA III/IV	1145 (29.7%)	1945 (27.2%)	0.005
KCCQ-TSS	66.9 ± 22.5	74.0 ± 21.5	<0.001
KCCQ-OSS	62.8 ± 20.7	69.6 ± 20.0	<0.001
KCCQ-CSS	64.3 ± 20.9	72.2 ± 20.2	<0.001
eGFR (mL/min/1.73m2)	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 (umol/L)	92 ± 26	110 ± 31	<0.001
Baseline treatment: no. (%)			
Diuretics including MRA	3721 (96.5%)	6835 (95.6%)	0.020
Loop diuretic	2954 (76.6%)	5682 (79.5%)	<0.001
Non-loop diuretic excluding MRA	810 (21.0%)	1045 (14.6%)	<0.001
ACEi	1416 (36.7%)	3540 (49.5%)	<0.001
ARB	1541 (40.0%)	2038 (28.5%)	<0.001
ACEi or ARB	2947 (76.4%)	5548 (77.6%)	0.17
ARNI	189 (4.9 %)	620 (8.7 %)	<0.001
Beta-blocker	3317 (86.0%)	6418 (89.7%)	<0.001

MRA	1913 (49.6%)	4124 (57.7%)	<0.001
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

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

Table 2. Comparison of Outcomes in Women and Men.

	Event Number [Event Rate; per 100 py]		**HR or RR (reference = male) & 95 CI**		
Variable	Women (N=3856)	Men (N=7151)	Unadjusted*	Adjusted - Model 1†	Adjusted - Model 2‡
Primary Endpoint	613 [8.4]	1397 [11.6]	0.79 (0.72, 0.87); p<0.001	0.79 (0.71, 0.87); p<0.001	0.78 (0.70, 0.87); p<0.001
CV death	371 [4.1]	815 [6.3]	0.70 (0.61, 0.80); p<0.001	0.66 (0.58, 0.76); p<0.001	0.69 (0.60, 0.79); p<0.001
All-cause death	489 [6.3]	1139 [8.8]	0.73 (0.65, 0.81); p<0.001	0.68 (0.61, 0.75); p<0.001	0.69 (0.62, 0.78); p<0.001
HF hospitalization	414 [5.6]	882 [7.3]	0.84 (0.74, 0.94); p=0.003	0.84 (0.75, 0.95); p=0.006	0.82 (0.72, 0.94); p=0.004
Urgent HF visit	60 [0.8]	111 [0.9]	0.79 (0.58, 1.09); p=0.15	0.81 (0.59, 1.12); p=0.20	0.69 (0.49, 0.98); p=0.040
HHF or urgent visit	449 [6.1]	937 [7.8]	0.84 (0.75, 0.94); p=0.003	0.85 (0.76, 0.95); p=0.005	0.82 (0.72, 0.93); p=0.002
Total events (first and recurrent HHF and CV death)	955 [12.3]	2201 [17.1]	0.77 (0.71, 0.83); p<0.001	0.76 (0.70, 0.82); p<0.001	0.77 (0.71, 0.84); p<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 [log], estimated glomerular filtration rate, NYHA class, LVEF, previous HF hospitalization, myocardial infarction, diabetes mellitus, and atrial fibrillation, region; stratified by trial.

CI = confidence interval; CV = cardiovascular; HF = heart failure; HHF = heart failure hospitalization; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; py = person-year; RR = rate ratio.

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

Variable	Women	Men	P-interaction
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

* $p<0.001$ for changes from week 0 to week 32

† $p<0.005$ for changes from week 0 to week 32

Table 4. Safety of Dapagliflozin in Women and Men.

	Women			Men			
	All	Dapa	Placebo	All	Dapa	Placebo	P-interaction
	n=3856	n=1928	n=1928	n=7151	n=3576	n=3575	
Any SAE	1547 (40.2%)	761 (39.6%)	786 (40.8%)	3034 (42.5%)	1446 (40.5%)	1588 (44.5%)	0.16
Any AE 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 AE 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 due to 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 AE 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

AE = adverse events; Dapa = dapagliflozin; SAE = serious adverse events.

Figure Legends

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.

Figure 3: Treatment Effect of Dapagliflozin in Women and Men across Left Ventricular Ejection Fraction.

Men – blue; women – red.

CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; p-int = p-interaction for sex-by-treatment-by-ejection fraction.