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Effects of dapagliflozin in DAPA-HF according to background heart failure therapy

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Aims In the DAPA-HF trial, the SGLT2 inhibitor dapagliflozin reduced the risk of worsening heart failure (HF) and death in patients with HF and reduced ejection fraction. We examined whether this benefit was consistent in relation to background HF therapy.

Methods and results In this *post hoc* analysis, we examined the effect of study treatment in the following yes/no subgroups: diuretic, digoxin, mineralocorticoid receptor antagonist (MRA), sacubitril/valsartan, ivabradine, implanted cardioverter-defibrillating (ICD) device, and cardiac resynchronization therapy. We also examined the effect of study drug according to angiotensin-converting enzyme inhibitor/angiotensin receptor blocker dose, beta-blocker (BB) dose, and MRA (≥50% and <50% of target dose). We analysed the primary composite endpoint of cardiovascular death or a worsening HF event. Most randomized patients ($n = 4744$) were treated with a diuretic (84%), renin–angiotensin system (RAS) blocker (94%), and BB (96%); 52% of those taking a BB and 38% taking a RAS blocker were treated with ≥50% of the recommended dose. Overall, the dapagliflozin vs. placebo hazard ratio (HR) was 0.74 [95% confidence interval (CI) 0.65–0.85] for the primary composite endpoint ($P < 0.0001$). The effect of dapagliflozin was consistent across all subgroups examined: the HR ranged from 0.57 to 0.86 for primary endpoint, with no significant randomized treatment-by-subgroup interaction. For example, the HR in patients taking a RAS blocker, BB, and MRA at baseline was 0.72 (95% CI 0.61–0.86) compared with 0.77 (95% CI 0.63–0.94) in those not on all three of these treatments (*P*-interaction 0.64).

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Conclusion The benefit of dapagliflozin was consistent regardless of background therapy for HF.

Keywords Heart failure • SGLT2 inhibitor • Heart failure and reduced ejection fraction

Introduction

In the placebo-controlled Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial, the sodium–glucose cotransporter 2 inhibitor (SGLT2i) dapagliflozin reduced the risk of heart failure (HF) hospitalization and mortality, and improved symptoms, in 4744 patients with HF and reduced ejection fraction (HFrEF).[1,2] It is clearly important to know whether these effects were truly additive to the benefits obtained from other evidence-based treatments in HFrEF. Therefore, in this *post hoc* analysis, we examined outcomes in patients randomized to dapagliflozin, vs. placebo, according to background drug and device therapy. Because >90% of patients were receiving each of a renin–angiotensin system (RAS) blocker and beta-blocker (BB) at baseline, we examined the effect of dapagliflozin added to a higher or lower dose of these treatments. For other therapies, including a mineralocorticoid receptor antagonists (MRAs), digoxin and devices, we examined outcomes according to whether the treatment was taken at baseline or not. We also examined the effect of dapagliflozin in patients receiving combination therapy.

Methods

The design and results of DAPA-HF are published.[1,2] Briefly, DAPA-HF was a prospective, randomized, double-blind, placebo-controlled trial in patients with HFrEF, which evaluated the efficacy and safety of dapagliflozin 10 mg once daily, compared with matching placebo, added to standard care. Ethics committees at each of the 410 participating institutions (in 20 countries) approved the protocol, and all patients gave written informed consent.

Study patients

Men and women aged ≥18 years with HF were eligible if they were in New York Heart Association (NYHA) functional Class II–IV, had a left ventricular ejection fraction (LVEF) ≤40%, and, in the view of the investigator, were optimally treated with pharmacological and device therapy for HFrEF, according to local guidelines. The protocol advised that an angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) or sacubitril/valsartan and a BB, as well as an MRA, should be used at guideline-recommended doses, unless contraindicated or not tolerated.

Participants were also required to have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the previous 12 months). Patients with atrial fibrillation or atrial flutter were required to have an NT-proBNP level ≥900 pg/mL, irrespective of history of HF hospitalization. Key exclusion criteria included: symptoms of hypotension or systolic blood pressure <95 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (or rapidly declining renal function), Type 1 diabetes mellitus, and another condition likely to prevent patient participation in the trial or greatly limit life expectancy. A full list of exclusion criteria is provided in the design paper.[1]

Trial outcomes

The primary outcome was the composite of an episode of worsening HF or cardiovascular (CV) death, whichever occurred first. An episode of worsening HF was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for HF. Secondary endpoints included the composite of the occurrence of HF hospitalization or CV death. All-cause mortality was a prespecified secondary endpoint. For the purposes of this analysis, we examined the effect of dapagliflozin, compared to placebo, on the primary composite outcome and the individual component of CV death.

Background treatment subgroups

In this *post hoc* analysis, we compared the effect of dapagliflozin with placebo in subgroups of patients treated with other background pharmacological and device therapies. Subgroups were limited to those with >200 individuals to minimize the likelihood of a Type 1 error.[3,4] Therefore, the yes/no groups which were analysed, included diuretic, digitalis glycosides (hereafter referred to as digoxin), MRA, sacubitril/valsartan, ivabradine, defibrillating device [implantable cardioverter-defibrillator or cardiac resynchronization therapy plus defibrillator (CRT-D)] and CRT (CRT-P and CRT-D). Because so few patients not taking a BB or a RAS blocker, we analysed the effect of study drug according to BB and RAS blocker dose at baseline, defined as ≥50% target dose and <50% of target dose. We also examined the treatment effect in patients receiving ≥50 and <50% of target MRA dose. Target daily doses were taken from contemporary guidelines[5,6] and included: carvedilol 50 mg, bisoprolol 10 mg, metoprolol succinate 200 mg, metoprolol tartrate 200 mg, and nebivolol 10 mg; patients ($n = 85$) taking other β-blockers were classified as taking <50% target dose. Target daily doses for ACE inhibitors and ARB were captopril 150 mg, enalapril 40 mg, fosinopril 40 mg, lisinopril 35 mg, perindopril 16 mg, quinapril 40 mg, ramipril 10 mg, trandolapril 4 mg, candesartan 32 mg, losartan 150 mg, valsartan 320 mg, and irbesartan 300 mg; patients ($n = 315$) taking other ACE inhibitors/ARB were classified as taking <50% target dose. The target doses of MRA were defined as either eplerenone or spironolactone 50 mg daily. For the purposes of this analysis, MRAs were not classified as a diuretic and sacubitril/valsartan was not included in the analysis of dose of ACE inhibitor/ARB.

Statistical analysis

Baseline characteristics were compared between groups by using the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. The effect of dapagliflozin compared to placebo on each outcome was examined by means of hazard ratio (HR) and 95% confidence intervals (CIs) derived from Cox proportional-hazards models, stratified according to diabetes status and adjusted for a history of hospitalization for HF and treatment-group assignment. We analysed the effect of dapagliflozin compared to placebo on the proportion of patients (presented as an odds ratio) who reported a clinically significant (≥5 point) improvement or deterioration in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) at 8 months following

randomization using previously described methods.[7] Change in systolic blood pressure and serum creatinine was analysed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment and interaction of treatment, and visit with a random intercept and slope per patient). The least-squares mean differences between treatment groups are presented by subgroup with 95% CI. Prespecified adverse events of interest (volume depletion and renal adverse events) were analysed in patients who were randomized and received at least one dose of dapagliflozin or placebo. All analyses were performed using Stata version 16 (College Station, TX, USA) and SAS, version 9.4 (SAS institute). A *P*-value <0.05 was considered statistically significant.

Results

Most patients in DAPA-HF were treated with a diuretic (84%), RAS blocker (94%), and BB (96%). Of patients taking a RAS blocker ($n = 3952$), 1517 patients (38%) were treated with ≥50% of a guideline-recommended target dose. Of those taking a BB ($n = 4558$), 2349 patients (52%) were treated with ≥50% of the guideline-recommended dose of an evidence-based drug. Overall, 71% of patients were treated with an MRA, 19% with digoxin, 26% with a defibrillator, and 7% had a CRT device. The majority of patients (96%) were treated with at least two of an ACE inhibitor/ARB/ARNI, a BB and/or an MRA, with 3091 (65%) patients on all three of these classes of drugs (Supplementary material online, *Figure S1*).

Baseline characteristics according to background therapy

Table 1 shows the background characteristics in all randomized patients and by background therapy and *Table 2* shows the characteristics by combinations of background therapy. Compared with the overall DAPA-HF population, patients treated with digoxin had a lower LVEF, and, compared to other treatment subgroups, the worst NYHA functional class distribution, worst symptoms [as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS)], highest NT-proBNP level and greatest frequency of prior HF hospitalization and atrial fibrillation. Excepting atrial fibrillation, similar trends were seen for patients treated with diuretics and an MRA, although both the latter groups also had worse renal function than the overall DAPA-HF population (especially patients treated with diuretics). Patients receiving sacubitril/valsartan were more likely to have an implanted device (ICD and/or CRT), and a lower mean LVEF and median NT-proBNP level, than the overall population. Patients receiving ivabradine were less likely to be taking a BB or to have atrial fibrillation than the overall DAPA-HF population.

Patients receiving ≥50% of target RAS blocker dose had a higher systolic blood pressure and lower median NT-proBNP level and KCCQ-TSS than patients in the overall DAPA-HF population. Other than a lower KCCQ-TSS, there were no major differences between patients taking ≥50% of target dose BB than in the overall DAPA-HF population.

Among patients with a device, fewer were women (especially an ICD) and patients with a device were generally older than in the overall DAPA-HF population; they also had a worse KCCQ-TSS and lower LVEF. CRT patients had a higher median NT-proBNP level, worse renal function and were more likely to have been hospitalized for HF previously, compared to the overall population.

Effect of dapagliflozin according to background therapy

Supplementary material online, *Figure S2* shows the cumulative incidence of the primary endpoint in the major treatment subgroups of interest. The HRs for the effect of dapagliflozin, compared with placebo, for the primary composite outcome and CV death, according to background therapy are summarized in *Figures 1* and *2*, respectively. The benefit of dapagliflozin over placebo was consistent across all treatment subgroups, including diuretic, digoxin, MRA, sacubitril/valsartan, ivabradine, and devices (ICD or CRT), without any significant interaction between background therapy and the effect of randomized therapy on the primary composite outcome (*Figure 1*) or CV death (*Figure 2*).

We also examined the effect of dapagliflozin, compared with placebo, according to background ACE inhibitor/ARB, BB and MRA dose. The effect of dapagliflozin, vs. placebo, was the same in patients treated with ≥50% of target doses of these drugs, compared with those treated with a lower dose (*Figures 1* and *2*).

Effect of dapagliflozin according to combinations of treatment

Figures 2 and *3*, respectively, summarize the HRs for dapagliflozin, compared with placebo, for CV death and the primary composite outcome, according to various combinations of background therapy. The beneficial effect of dapagliflozin was consistent regardless of whether patients were treated with the combination of a RAS-blocker, BB and MRA, or were not on all three of these treatments at baseline. Neither the combination of an ICD and ≥50% of target dose of both an RAS blocker and BB, nor an MRA with ≥50% of target dose of both an RAS blocker and BB, modified the response to dapagliflozin (*Figures 2* and *3*). A small proportion of patients (7%) were on 'quadruple-therapy' at baseline with a combined angiotensin receptor neprilysin inhibitor (sacubitril/valsartan), a BB and an MRA; the benefit of dapagliflozin was consistent in this subgroup with no significant interaction when compared with participants not receiving 'quadruple-therapy'.

Effect of dapagliflozin on symptom frequency and severity according to background therapy

A significantly greater proportion of patients randomized to dapagliflozin compared to placebo self-reported a clinically significant improvement (≥5 point increase) in the KCCQ-TSS at 8 months following randomization and significantly fewer dapagliflozin patients reported a meaningful deterioration (≥5 point decrease) compared to placebo (*Table 3*). This effect was consistent across all subgroups of background therapy and combinations analysed.

Table 1 Baseline characteristics by background heart failure therapy

	All patients (*N* = 4744)	Diuretic (*N* = 4008)	MRA (*N* = 3370)	Digoxin (*N* = 887)	ARNI (*N* = 508)	Ivabradine (*N* = 228)	ACE/ARB ≥50% target dose (*N* = 1517)	Beta-blocker ≥50% target dose (*N* = 2349)	MRA ≥50% target dose (*N* = 2953)	ICD[a] (*N* = 1242)	CRT[b] (*N* = 354)
Age (years)	66.3 ± 10.9	66.2 ± 10.9	65.3 ± 11.0	64.9 ± 11.3	66.2 ± 11.0	61.1 ± 11.8	66.2 ± 10.7	66.1 ± 10.5	65.2 ± 10.9	66.7 ± 9.6	69.1 ± 9.3
Female sex, *n* (%)	1109 (23.4)	943 (23.5)	787 (23.4)	203 (22.9)	96 (18.9)	47 (20.6)	381 (25.1)	587 (25.0)	706 (23.9)	207 (16.7)	72 (20.3)
NYHA functional classification, *n* (%)											
II	3203 (67.5)	2615 (65.2)	2178 (64.6)	533 (60.1)	353 (69.5)	153 (67.1)	1050 (69.2)	1567 (66.7)	1907 (64.6)	842 (67.8)	227 (64.1)
III	1498 (31.6)	1356 (33.8)	1158 (34.4)	334 (37.7)	149 (29.3)	74 (32.5)	457 (30.1)	767 (32.7)	1029 (34.8)	395 (31.8)	126 (35.6)
IV	43 (0.9)	37 (0.9)	34 (1.0)	20 (2.3)	6 (1.2)	1 (0.4)	10 (0.7)	15 (0.6)	17 (0.6)	5 (0.4)	1 (0.3)
Median KCCQ-TSS (IQR)	77.1 (58.3–91.7)	76.0 (57.3–91.7)	77.1 (58.3–91.7)	75.0 (56.3–91.7)	77.6 (58.3–92.7)	79.2 (62.5–93.8)	75.0 (57.3–91.7)	75.0 (56.3–90.6)	76.0 (56.3–91.7)	77.1 (60.4–91.7)	77.1 (58.3–91.7)
Left ventricular ejection fraction (%)	31.1 ± 6.8	30.9 ± 6.9	30.7 ± 6.8	29.8 ± 7.1	28.4 ± 7.3	29.7 ± 7.1	31.7 ± 6.6	31.1 ± 6.9	30.7 ± 6.8	28.6 ± 7.0	29.2 ± 7.1
Median NT-proBNP (IQR) (pg/mL)	1437 (857–2650)	1526 (891–2815)	1437 (838–2689)	1680 (1055–3164)	1309 (836–2335)	1324 (747–2346)	1358 (821–2430)	1420 (852–2593)	1442 (836–2674)	1457 (892–2581)	1616 (983–3039)
Heart rate (b.p.m.)	71.5 ± 11.7	71.8 ± 11.6	71.5 ± 11.6	74.0 ± 12.4	70.0 ± 11.7	70.3 ± 10.1	71.0 ± 11.6	71.2 ± 11.5	71.6 ± 11.5	69.5 ± 10.5	69.5 ± 9.5
Systolic blood pressure (mmHg)	121.8 ± 16.3	121.5 ± 16.1	120.3 ± 15.7	119.6 ± 15.4	115.1 ± 16.2	121.4 ± 17.4	126.5 ± 17.1	122.5 ± 16.7	120.8 ± 15.7	118.7 ± 15.8	117.1 ± 15.4
Principal cause of heart failure, *n* (%)											
Ischaemic	2674 (56.4)	2250 (56.1)	1898 (56.3)	381 (43.0)	260 (51.2)	124 (54.4)	857 (56.5)	1305 (55.6)	1677 (56.8)	749 (60.3)	183 (51.7)
Non-ischaemic	1687 (35.6)	1440 (35.9)	1227 (36.4)	398 (44.9)	208 (40.9)	81 (35.5)	543 (35.8)	866 (36.9)	1075 (36.4)	416 (33.5)	146 (41.2)
Unknown	383 (8.1)	318 (7.9)	245 (7.3)	108 (12.2)	40 (7.9)	23 (10.1)	117 (7.7)	178 (7.6)	201 (6.8)	77 (6.2)	25 (7.1)
Medical history, *n* (%)											
Hospitalization for heart failure	2251 (47.4)	1980 (49.4)	1616 (48.0)	475 (53.6)	210 (41.3)	117 (51.3)	698 (46.0)	1095 (46.6)	1382 (46.8)	554 (44.6)	188 (53.1)
Atrial fibrillation	1818 (38.3)	1601 (39.9)	1239 (36.8)	542 (61.1)	208 (40.9)	24 (10.5)	562 (37.0)	989 (42.1)	1103 (37.4)	538 (43.3)	165 (46.6)
Diabetes mellitus[c]	1983 (41.8)	1740 (43.4)	1404 (41.7)	379 (42.7)	212 (41.7)	111 (48.7)	685 (45.2)	1057 (45.0)	1216 (41.2)	536 (43.2)	144 (40.7)
Estimated GFR											
Mean (mL/min/1.73 m^2)	65.8 ± 19.4	64.9 ± 19.4	67.1 ± 19.6	67.7 ± 19.9	64.1 ± 18.8	69.8 ± 21.0	66.3 ± 19.2	65.2 ± 19.2	67.1 ± 19.4	62.8 ± 18.2	59.4 ± 18.0
Rate <60 (mL/min/1.73 m^2), *n* (%)	1926 (40.6)	1710 (42.7)	1296 (38.5)	338 (38.1)	221 (43.5)	70 (30.7)	593 (39.1)	979 (41.7)	1117 (37.8)	568 (45.8)	186 (52.5)
Device therapy											
Implantable cardioverter-defibrillator[a]	1242 (26.2)	1075 (26.8)	889 (26.4)	238 (26.8)	263 (51.8)	62 (27.2)	353 (23.3)	706 (30.1)	782 (26.5)	1242 (100.0)	301 (85.0)

Continued

Table 1 *Continued*

	All patients (*N* = 4744)	Diuretic (*N* = 4008)	MRA (*N* = 3370)	Digoxin (*N* = 887)	ARNI (*N* = 508)	Ivabradine (*N* = 228)	ACE/ARB ≥50% target dose (*N* = 1517)	Beta-blocker ≥50% target dose (*N* = 2349)	MRA ≥50% target dose (*N* = 2953)	ICD[a] (*N* = 1242)	CRT[b] (*N* = 354)
Cardiac resynchronization therapy[b]	354 (7.5)	308 (7.7)	250 (7.4)	70 (7.9)	75 (14.8)	16 (7.0)	86 (5.7)	200 (8.5)	213 (7.2)	301 (24.2)	354 (100.0)
Heart failure medication											
Diuretic	4008 (84.5)	4008 (100.0)	2945 (87.4)	807 (91.0)	417 (82.1)	201 (88.2)	1301 (85.8)	1993 (84.8)	2604 (88.2)	1075 (86.6)	308 (87.0)
ACE inhibitor	2661 (56.1)	2273 (56.7)	1970 (58.5)	513 (57.8)	4 (0.8)	103 (45.2)	1047 (69.0)	1334 (56.8)	1772 (60.0)	647 (52.1)	166 (46.9)
ARB	1307 (27.6)	1089 (27.2)	894 (26.5)	223 (25.1)	15 (3.0)	70 (30.7)	479 (31.6)	627 (26.7)	766 (25.9)	260 (20.9)	86 (24.3)
ARNI	508 (10.7)	417 (10.4)	342 (10.1)	88 (9.9)	508 (100.0)	33 (14.5)	8 (0.5)	292 (12.4)	276 (9.3)	263 (21.2)	75 (21.2)
Beta-blocker	4558 (96.1)	3863 (96.4)	3259 (96.7)	841 (94.8)	485 (95.5)	196 (86.0)	1477 (97.4)	2349 (100.0)	2862 (96.9)	1219 (98.1)	344 (97.2)
Mineralocorticoid receptor antagonist	3370 (71.0)	2945 (73.5)	3370 (100.0)	682 (76.9)	342 (67.3)	184 (80.7)	1087 (71.7)	1700 (72.4)	2953 (100.0)	889 (71.6)	250 (70.6)
Digoxin	887 (18.7)	807 (20.1)	682 (20.2)	887 (100.0)	88 (17.3)	33 (14.5)	269 (17.7)	453 (19.3)	561 (19.0)	238 (19.2)	70 (19.8)

Data are presented as mean (SD) unless otherwise indicated. Percentages may not total 100 because of rounding.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score—range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or above is considered to reflect satisfactory health status.; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

[b]Cardiac-resynchronization therapy with or without a defibrillator.

[c]Nine hundred and ninety-three patients (41.8%) in the dapagliflozin group and 990 in the placebo group (41.8%) had a history of diabetes at baseline. An additional 82 patients in the dapagliflozin group and 74 in the placebo group had previously undiagnosed diabetes defined as a glycated haemoglobin level of 6.5% or greater (≥48 mmol/mol) measured in a central laboratory at both screening and randomization.

Table 2 **Baseline characteristics by combinations of background heart failure therapy**

	All patients (*N* = 4744)	ACEi/ARB + beta-blocker + MRA (*N* = 2765)	ACEi/ARB ≥50% target dose + beta-blocker ≥50% target dose (*N* = 975)	ACEi/ARB ≥50% target dose + beta-blocker ≥50% target dose + MRA (*N* = 711)	ACEi/ARB ≥50% target dose + beta-blocker ≥50% target dose + ICD (*N* = 244)	ARNI + beta-blocker + MRA (*N* = 332)
Age (years)	66.3 ± 10.9	65.0 ± 11.0	65.8 ± 10.6	65.1 ± 10.7	65.5 ± 9.4	65.3 ± 11.0
Female sex, *n* (%)	1109 (23.4)	666 (24.1)	258 (26.5)	181 (25.5)	37 (15.2)	64 (19.3)
NYHA functional classification, *n* (%)						
II	3203 (67.5)	1775 (64.2)	684 (70.2)	480 (67.5)	180 (73.8)	221 (66.6)
III	1498 (31.6)	962 (34.8)	285 (29.2)	227 (31.9)	63 (25.8)	108 (32.5)
IV	43 (0.9)	28 (1.0)	6 (0.6)	4 (0.6)	1 (0.4)	3 (0.9)
Median KCCQ-TSS (IQR)	77.1 (58.3–91.7)	76.0 (58.3–91.7)	75.0 (56.2–91.7)	72.9 (54.2–90.6)	76.0 (63.5–91.7)	78.1 (58.3–91.7)
Left ventricular ejection fraction (%)	31.1 ± 6.8	31.0 ± 6.6	31.5 ± 6.6	31.2 ± 6.7	28.9 ± 6.8	28.0 ± 7.3
Median NT–proBNP (IQR) (pg/mL)	1437 (857–2650)	1426 (834–2689)	1369 (831–2418)	1369 (822–2430)	1300 (848–2107)	1299 (828–2296)
Heart rate (b.p.m.)	71.5 ± 11.7	71.6 ± 11.6	71.1 ± 11.7	71.0 ± 11.5	68.3 ± 10.3	70.0 ± 11.5
Systolic blood pressure (mmHg)	121.8 ± 16.3	121.4 ± 15.3	126.1 ± 17.5	124.5 ± 17.3	123.3 ± 16.4	113.3 ± 15.7
Principal cause of heart failure, *n* (%)						
Ischaemic	2674 (56.4)	1580 (57.1)	541 (55.5)	404 (56.8)	150 (61.5)	168 (50.6)
Non–ischaemic	1687 (35.6)	992 (35.9)	360 (36.9)	263 (37.0)	79 (32.4)	142 (42.8)
Unknown	383 (8.1)	193 (7.0)	74 (7.6)	44 (6.2)	15 (6.1)	22 (6.6)
Medical history, *n* (%)						
Hospitalization for heart failure	2251 (47.4)	1326 (48.0)	457 (46.9)	345 (48.5)	119 (48.8)	143 (43.1)
Atrial fibrillation	1818 (38.3)	972 (35.2)	375 (38.5)	269 (37.8)	101 (41.4)	135 (40.7)
Diabetes mellitus[a]	1983 (41.8)	1148 (41.5)	472 (48.4)	348 (48.9)	118 (48.4)	139 (41.9)
Estimated GFR						
Mean (mL/min/1.73 m^2)	65.8 ± 19.4	67.7 ± 19.6	66.3 ± 19.1	67.6 ± 19.1	65.2 ± 18.2	65.0 ± 19.1
Rate of <60 (mL/min/1.73 m^2), *n* (%)	1926 (40.6)	1025 (37.1)	385 (39.6)	262 (36.8)	96 (39.5)	140 (42.2)
Device therapy						
Implantable cardioverter-defibrillator[b]	1242 (26.2)	653 (23.6)	244 (25.0)	181 (25.5)	244 (100.0)	176 (53.0)
Cardiac resynchronization therapy[c]	354 (7.5)	179 (6.5)	59 (6.1)	42 (5.9)	46 (18.9)	50 (15.1)
Heart failure medication						
Diuretic	4008 (84.5)	2428 (87.8)	831 (85.2)	620 (87.2)	208 (85.2)	277 (83.4)
ACE inhibitor	2661 (56.1)	1926 (69.7)	667 (68.4)	486 (68.4)	181 (74.2)	2 (0.6)
ARB	1307 (27.6)	848 (30.7)	310 (31.8)	227 (31.9)	64 (26.2)	4 (1.2)
ARNI	508 (10.7)	6 (0.2)	3 (0.3)	2 (0.3)	3 (1.2)	332 (100.0)
Beta-blocker	4558 (96.1)	2765 (100.0)	975 (100.0)	711 (100.0)	244 (100.0)	332 (100.0)
Mineralocorticoid receptor antagonist	3370 (71.0)	2765 (100.0)	711 (72.9)	711 (100.0)	181 (74.2)	332 (100.0)
Digoxin	887 (18.7)	550 (19.9)	175 (17.9)	133 (18.7)	41 (16.8)	63 (19.0)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score—range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or above is considered to reflect satisfactory health status.; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a]Nine hundred and ninety-three patients (41.8%) in the dapagliflozin group and 990 in the placebo group (41.8%) had a history of diabetes at baseline. An additional 82 patients in the dapagliflozin group and 74 in the placebo group had previously undiagnosed diabetes defined as a glycated haemoglobin level of 6.5% or greater (≥48 mmol/mol) measured in a central laboratory at both screening and randomization.

[b]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

[c]Cardiac-resynchronization therapy with or without a defibrillator.

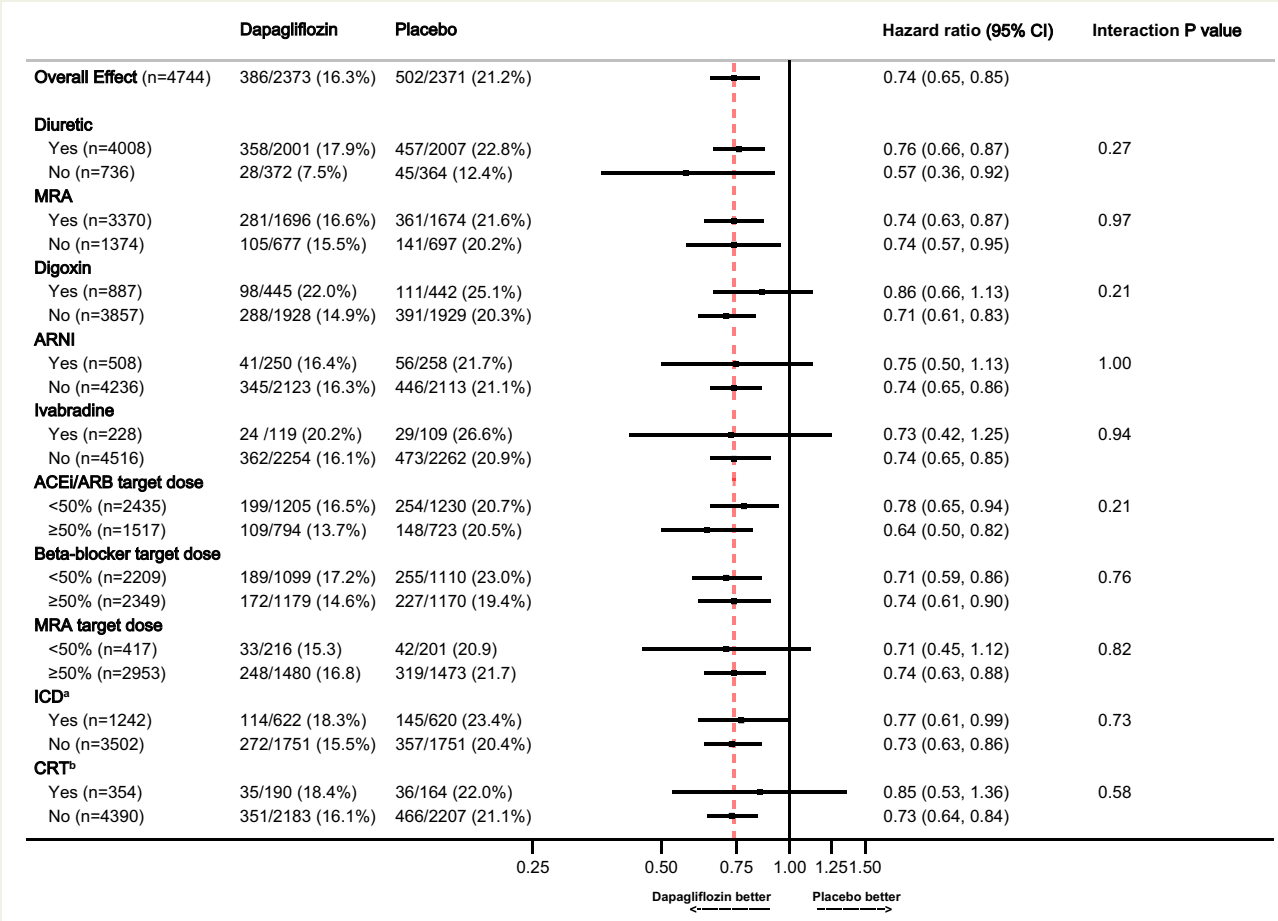

Figure 1 Effect of dapagliflozin compared to placebo on the primary composite outcome by background heart failure therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes. Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure, and treatment-group assignment as explanatory variables. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist. [a]ICD or cardiac resynchronization therapy with defibrillator. [b]Cardiac resynchronization therapy with or without a defibrillator.

Effect of dapagliflozin on change in systolic blood pressure and serum creatinine according to background therapy

Compared with placebo, dapagliflozin reduced blood pressure at 8 months following randomization with no significant treatment effect modification observed by individual background therapy or their combinations (*Table 3*). The small increase in serum creatinine observed with dapagliflozin compared to placebo at 8 months was similar among the subgroups analysed (*Table 3*).

Effect of dapagliflozin on volume depletion or renal adverse events according to background therapy

In patients treated with a diuretic, adverse events related to volume depletion occurred more frequently with dapagliflozin compared to placebo, with fewer events seen in those not on a diuretic and randomized to dapagliflozin (*Table 4*). A similar pattern was observed in those treated with ≥50% of target MRA dose, the combination of an RAS blocker, BB, and MRA, and combinations including ≥50% of both RAS blocker and BB target dose (*Table 4*). Renal adverse events were less common with dapagliflozin compared to placebo in those not on a diuretic at baseline with no difference in those treated with a diuretic (*Table 4*). Patients treated with ≥50% of target RAS blocker dose more frequently had a renal adverse event with dapagliflozin compared to placebo than those on <50% target dose with the same pattern in those on combinations of therapy that include ≥50% of target RAS blocker dose.

Discussion

When new treatments are shown to improve outcomes in HFrEF, a key question is whether the benefit is truly incremental, i.e. clearly

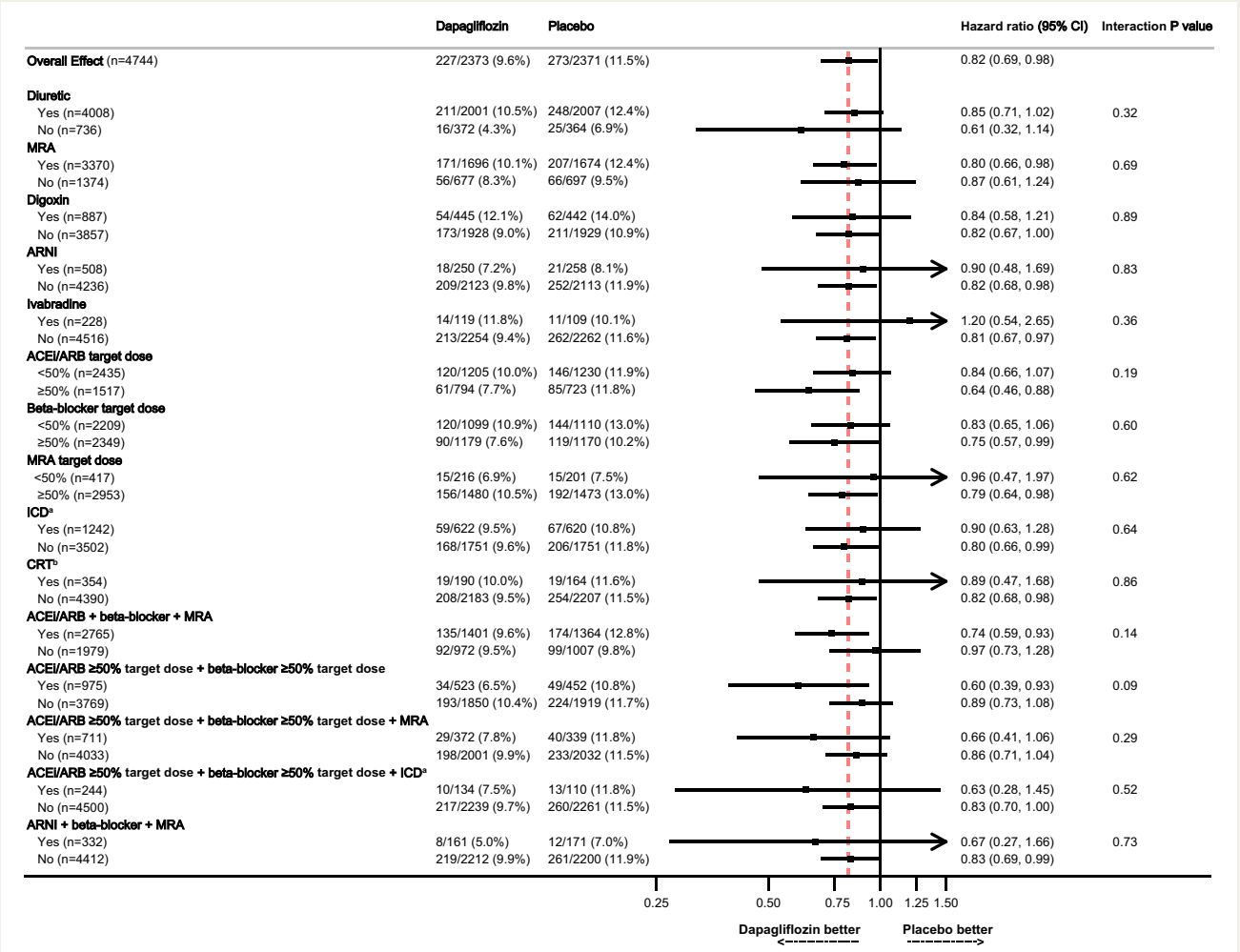

Figure 2 Effect of dapagliflozin compared to placebo on cardiovascular death by background heart failure therapy. Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure, and treatment-group assignment as explanatory variables. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist. [a]ICD or cardiac resynchronization therapy with defibrillator. [b]Cardiac resynchronization therapy with or without a defibrillator.

additive to the benefits of established treatments. There is no dispute that the three core pharmacological therapies for HFrEF are an RAS blocker (ACE inhibitor/ARB), BB and MRA, based on at least two randomized trials showing each of these treatments reduced mortality and hospitalization, and in the case of BBs and MRAs, even when these treatments were added to an RAS blocker (and in the case of an MRA, added to a BB also).[8–15] Over the past decade, three new pharmacological approaches have demonstrated additional benefit when added to these core therapies. The first was the sinus node inhibitor, ivabradine, followed by the neprilysin inhibitor sacubitril and most recently, the SGLT2 inhibitor, dapagliflozin.[2,16,17] In the present report, we have shown that dapagliflozin not only improves outcomes when added to the core combination of RAS blocker, BB and MRA but also had a consistent benefit whether background therapy included either ivabradine or sacubitril/valsartan or not. The demonstration that neither of these agents modified the response to dapagliflozin supports the view that SGLT2 inhibition acts in a mechanistically independent and complementary way to other therapies for HFrEF. Initially considered to be glucose-lowering medications for the management of Type 2 diabetes mellitus, the finding in DAPA-HF that the benefit of dapagliflozin occurred in patients both with, and without diabetes, suggests that this benefit is independent of any glucose-lowering effect.[2] Various theories as to the mechanisms of action behind the benefits of dapagliflozin have been proposed, including a diuretic effect, an increase in renal erythropoietin secretion, reduction in myocardial fibrosis, along with potential effects on the peripheral vasculature, ion transporters, adipokines, and sympathetic nervous system activity.[18]

We also attempted to address further questions that are often raised in discussions about the treatment of HFrEF.

One such question relates to dosing of background pharmacological therapy. The evidence-based target doses of certain RAS

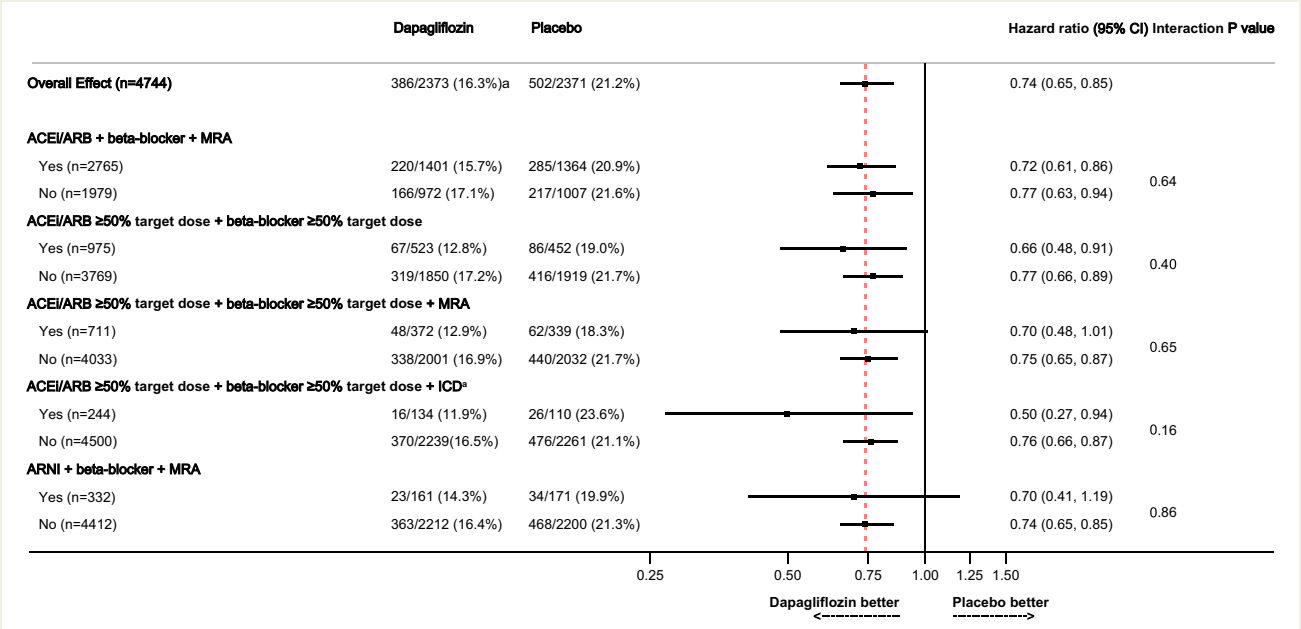

Figure 3 Effect of dapagliflozin compared to placebo on the primary composite outcome by combinations of background heart failure therapy. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist. [a]ICD or cardiac resynchronization therapy with defibrillator.

inhibitors and BBs are well defined and there is evidence of a dose-response for RAS inhibitors, at least in terms of reduction in HF hospitalization.[19,20] Yet registry studies repeatedly show that these evidence-based target doses are infrequently achieved in clinical practice and it is not always clear that this is because of intolerance of higher doses.[21,22] Consequently, it is possible that the incremental benefit of a new treatment might be less if the dosing of conventional treatments was optimized. To address this issue, we also examined the effectiveness of dapagliflozin according to background dose of both RAS blockers, BBs and MRAs, demonstrating consistent benefit irrespective of whether patients were taking higher (≥50% guideline target) or lower (<50%) doses of these drugs.

Device therapy also plays an important role in the management of HFrEF, but as with drug dosing, 'real world' studies show devices are underutilized in practice, with substantial geographical variation in rates of use, suggesting the influence of economic factors, among others, in explaining this variance.[23–25] We also examined the incremental efficacy of dapagliflozin in patients with an implanted defibrillating device and in those with CRT. Again, we found a consistent benefit in patients with either type of device, with no evidence that background device therapy modified the response to dapagliflozin.

Lastly, although its use is declining, digoxin was shown in a large randomized trial to reduce hospitalization rates when added to an ACE inhibitor in patients with HFrEF.[26] Therefore, we also examined the effect of adding dapagliflozin to digoxin and once more found a consistent benefit according to whether background therapy included digoxin or not.

As with all analyses like these, there are limitations. Most of these subgroups were not pre-specified. Despite requiring each subgroup to include >200 patients, such analyses are inherently underpowered. We had too few patients treated with the combination of hydralazine and isosorbide dinitrate to perform a meaningful analysis.

In summary, we found a consistent benefit of dapagliflozin, over placebo, regardless of background drug and device therapy. These findings suggest that the effects of dapagliflozin are incremental and complementary to conventional therapies for HFrEF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Table 3 Change in KCCQ total symptom score, systolic blood pressure, and creatinine at 8 months by randomized treatment and background heart failure therapy

	≥5-point improvement in KCCQ-TSS		≥5-point deterioration in KCCQ-TSS		Systolic blood pressure		Creatinine	
	Odds ratio (95% CI)	Interaction P-value	Odds ratio (95% CI)	Interaction P-value	Placebo corrected change (mmHg) (95% CI)	Interaction P-value	Placebo corrected change (mg/dL) (95% CI)	Interaction P-value
Diuretic								
Yes (*n* = 4008)	1.15 (1.08–1.23)	0.92	0.84 (0.78–0.91)	0.55	-1.45 (-2.36 to -0.54)	0.78	0.02 (0.01 to 0.04)	0.26
No (*n* = 736)	1.16 (0.99–1.36)		0.80 (0.67–0.95)		-1.14 (-3.26 to 0.98)		0.02 (-0.01 to 0.05)	
MRA								
Yes (*n* = 3370)	1.15 (1.07–1.24)	0.97	0.84 (0.77–0.91)	0.97	-1.59 (-2.55 to -0.63)	0.89	0.02 (-0.001 to 0.03)	0.32
No (*n* = 1374)	1.16 (1.03–1.29)		0.84 (0.74–0.95)		-1.02 (-2.68 to 0.64)		0.03 (0.01 to 0.06)	
Digoxin								
Yes (*n* = 887)	1.08 (0.94–1.24)	0.32	0.86 (0.74–1.00)	0.69	-4.24 (-6.11 to -2.38)	0.52	0.06 (0.03 to 0.09)	0.97
No (*n* = 3857)	1.17 (1.09–1.25)		0.83 (0.77–0.89)		-0.77 (-1.70 to 0.17)		0.01 (-0.003 to 0.03)	
ARNI								
Yes (*n* = 508)	1.18 (0.98–1.42)	0.79	0.89 (0.73–1.09)	0.54	-1.47 (-3.92 to 0.98)	0.50	0.02 (-0.03 to 0.06)	0.45
No (*n* = 4236)	1.15 (1.08–1.23)		0.83 (0.77–0.89)		-1.41 (-2.30 to -0.51)		0.02 (0.01 to 0.04)	
Ivabradine								
Yes (*n* = 228)	1.25 (0.96–1.64)	0.54	0.78 (0.58–1.05)	0.63	-2.56 (-6.27 to 1.16)	0.86	-0.04 (-0.10 to 0.02)	0.80
No (*n* = 4516)	1.15 (1.08–1.22)		0.84 (0.78–0.90)		-1.35 (-2.21 to -0.49)		0.02 (0.01 to 0.04)	
ACE–I/ARB target dose								
<50% (*n* = 2435)	1.14 (1.05–1.25)	0.81	0.86 (0.78–0.94)	0.27	-0.76 (-1.87 to 0.36)	0.35	0.02 (-0.003 to 0.04)	0.02
≥50% (*n* = 1517)	1.16 (1.05–1.29)		0.79 (0.70–0.89)		-2.62 (-4.22 to -1.01)		0.03 (0.01 to 0.06)	
Beta-blocker target dose								
<50% (*n* = 2209)	1.16 (1.06–1.27)	0.86	0.84 (0.77–0.93)	0.80	-0.78 (-1.99 to 0.42)	0.87	0.02 (-0.01 to 0.04)	0.43
≥50% (*n* = 2349)	1.15 (1.05–1.25)		0.83 (0.75–0.91)		-2.15 (-3.36 to -0.94)		0.03 (0.01 to 0.05)	
MRA target dose								
<50% (*n* = 417)	1.36 (1.10–1.69)	0.11	0.77 (0.61–0.97)	0.52	-0.06 (-2.86 to 2.74)	0.17	0.01 (-0.04 to 0.05)	0.84
≥50% (*n* = 2953)	1.13 (1.04–1.22)		0.84 (0.77–0.92)		-1.81 (-2.84 to -0.78)		0.02 (-0.001 to 0.04)	
ICD[a]								
Yes (*n* = 1242)	1.27 (1.13–1.43)	0.06	0.79 (0.69–0.89)	0.28	-1.31 (-2.94 to 0.32)	0.54	0.01 (-0.02 to 0.04)	0.19
No (*n* = 3502)	1.11 (1.03–1.20)		0.85 (0.79–0.93)		-1.43 (-2.40 to -0.45)		0.02 (0.01 to 0.04)	
CRT[b]								
Yes (*n* = 354)	1.09 (0.87–1.35)	0.60	0.81 (0.64–1.03)	0.79	-0.23 (-3.30 to 2.83)	0.11	0.01 (-0.05 to 0.08)	0.36
No (*n* = 4390)	1.16 (1.09–1.24)		0.84 (0.78–0.90)		-1.48 (-2.35 to -0.61)		0.02 (0.01 to 0.04)	
ACEi/ARB + beta-blocker + MRA								
Yes (*n* = 2765)	1.15 (1.06–1.25)	0.97	0.83 (0.76–0.91)	0.72	-1.52 (-2.59 to -0.45)	0.45	0.02 (0.0002 to 0.04)	0.77
No (*n* = 1979)	1.16 (1.05–1.27)		0.85 (0.76–0.94)		-1.31 (-2.66 to 0.03)		0.03 (0.003 to 0.05)	

Continued

Table 3 *Continued*

	≥5-point improvement in KCCQ-TSS		≥5-point deterioration in KCCQ-TSS		Systolic blood pressure		Creatinine	
	Odds ratio (95% CI)	Interaction P-value	Odds ratio (95% CI)	Interaction P-value	Placebo corrected change (mmHg) (95% CI)	Interaction P-value	Placebo corrected change (mg/dL) (95% CI)	Interaction P-value
ACEi/ARB ≥50% + beta-blocker ≥50%								
Yes (*n* = 975)	1.21 (1.06–1.38)	0.45	0.75 (0.64–0.88)	0.13	-3.07 (-5.10 to -1.04)	0.88	0.05 (0.01 to 0.08)	0.38
No (*n* = 3769)	1.14 (1.06–1.22)		0.86 (0.80–0.93)		-0.96 (-1.87 to -0.04)		0.02 (-0.001 to 0.03)	
ACEi/ARB ≥50% + beta-blocker ≥50% + MRA								
Yes (*n* = 711)	1.19 (1.02–1.39)	0.68	0.78 (0.65–0.94)	0.41	-2.59 (-4.91 to -0.28)	0.79	0.03 (-0.01 to 0.07)	0.14
No (*n* = 4033)	1.15 (1.07–1.23)		0.85 (0.79–0.91)		-1.20 (-2.10 to -0.31)		0.02 (0.005 to 0.04)	
ACEi/ARB ≥50% + beta-blocker ≥50% + ICD[a]								
Yes (*n* = 244)	1.65 (1.26–2.17)	0.006	0.65 (0.49–0.88)	0.09	-2.98 (-6.87 to 0.91)	0.21	-0.01 (-0.06 to 0.05)	0.52
No (*n* = 4500)	1.13 (1.06–1.21)		0.85 (0.79–0.91)		-1.31 (-2.16 to -0.45)		0.02 (0.01 to 0.04)	
ARNI + beta–blocker + MRA								
Yes (*n* = 332)	1.15 (0.90–1.47)	0.92	0.93 (0.72–1.20)	0.45	-2.62 (-5.61 to 0.37)	0.46	0.01 (-0.05 to 0.07)	0.22
No (*n* = 4412)	1.15 (1.08–1.23)		0.83 (0.77–0.89)		-1.31 (-2.19 to -0.44)		0.02 (0.01 to 0.04)	

Odds ratio presented are for dapagliflozin vs. placebo. For a ≥5-point, improvement in KCCQ total symptom score a value of >1.0 favours dapagliflozin, and for a ≥5-point, deterioration a value of <1.0 favours dapagliflozin.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score—range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or above is considered to reflect satisfactory health status.; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.
[b]Cardiac-resynchronization therapy with or without a defibrillator.

Table 4 Volume depletion or renal adverse events by randomized treatment and background heart failure therapy

	Volume depletion			Renal adverse event		
	Dapagliflozin	Placebo	Interaction *P*-value	Dapagliflozin	Placebo	Interaction *P*-value
Diuretic						
Yes	162/1999 (8.1)	131/2004 (6.5)	0.004	145/1999 (7.3)	149/2004 (7.4)	0.02
No	16/369 (4.3)	31/364 (8.5)		8/369 (2.2)	21/364 (5.8)	
MRA						
Yes	129/1694 (7.6)	107/1673 (6.4)	0.25	102/1694 (6.0)	113/1673 (6.8)	0.89
No	49/674 (7.3)	55/695 (7.9)		51/674 (7.6)	57/695 (8.2)	
Digoxin						
Yes	41/445 (9.2)	36/442 (8.1)	0.87	33/445 (7.4)	30/442 (6.8)	0.37
No	137/1923 (7.1)	126/1926 (6.5)		120/1923 (6.2)	140/1926 (7.3)	
ARNI						
Yes	27/250 (10.8)	31/258 (12.0)	0.38	25/250 (10.0)	25/258 (9.7)	0.59
No	151/2118 (7.1)	131/2110 (6.2)		128/2118 (6.0)	145/2110 (6.9)	
Ivabradine						
Yes	9/118 (7.6)	9/109 (8.3)		14/118 (11.9)	9/109 (8.3)	
No	169/2250 (7.5)	153/2259 (6.8)	0.70	139/2250 (6.2)	161/2259 (7.1)	0.23
ACE-I/ARB target dose						
<50%	89/1202 (7.4)	81/1228 (6.6)	0.32	59/1202 (4.9)	85/1228 (6.9)	0.01
≥50%	57/792 (7.2)	36/722 (5.0)		62/792 (7.8)	43/722 (6.0)	
Beta-blocker target dose						
<50%	78/1097 (7.1)	76/1108 (6.9)	0.54	64/1097 (5.8)	70/1108 (6.3)	0.69
≥50%	95/1177 (8.1)	80/1169 (6.8)		82/1177 (7.0)	96/1169 (8.2)	
MRA target dose						
<50%	12/215 (5.6)	21/200 (10.5)	0.01	10/215 (4.7)	10/200 (5.0)	0.92
≥50%	117/1479 (7.9)	86/1473 (5.8)		92/1479 (6.2)	103/1473 (7.0)	
ICD[a]						
Yes	60/621 (9.7)	61/619 (9.9)	0.43	44/621 (7.1)	63/619 (10.2)	0.09
No	118/1747 (6.8)	101/1749 (5.8)		109/1747 (6.2)	107/1749 (6.1)	
CRT[b]						
Yes	19/190 (10.0)	19/164 (11.6)	0.42	16/190 (8.4)	18/164 (11.0)	0.61
No	159/2178 (7.3)	143/2204 (6.5)		137/2178 (6.3)	152/2204 (6.9)	
ACEi/ARB + beta-blocker + MRA						
Yes	104/1399 (7.4)	72/1363 (6.5)	0.02	79/1399 (5.6)	88/1363 (6.5)	0.76
No	74/969 (7.6)	90/1005 (9.0)		74/969 (7.6)	82/1005 (8.2)	
ACEi/ARB ≥50% + beta-blocker ≥50%						
Yes	45/521 (8.6)	22/451 (4.9)	0.03	43/521 (8.3)	26/451 (5.8)	0.03
No	133/1847 (7.2)	140/1917 (7.3)		110/1847 (6.0)	144/1917 (7.5)	
ACEi/ARB ≥50% + beta-blocker ≥50% + MRA						
Yes	39/371 (10.5)	11/339 (3.2)	<0.001	30/371 (8.1)	19/339 (5.6)	0.07
No	139/1997 (7.0)	151/2029 (7.4)		123/1997 (6.2)	151/2029 (7.4)	
ACEi/ARB ≥50% + beta-blocker ≥50% + ICD[a]						
Yes	15/134 (11.2)	4/109 (3.7)	0.04	7/134 (5.2)	9/109 (8.3)	0.46
No	163/2234 (7.3)	158/2259 (7.0)		146/2234 (6.5)	161/2259 (7.1)	
ARNI + beta-blocker + MRA						
Yes	18/161 (11.2)	20/171 (11.7)	0.63	15/161 (9.3)	16/171 (9.4)	0.77
No	160/2207 (7.2)	142/2197 (6.5)		138/2207 (6.3)	154/2197 (7.0)	

Data are presented as *n*/*N* (%). Safety population included all patients who had undergone randomization and received at least one dose of dapagliflozin (*n* = 2368) or placebo (*n* = 2368).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

[a]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

[b]Cardiac-resynchronization therapy with or without a defibrillator.

speakers bureau, and participating in clinical trials for Boehringer Ingelheim; lecture fees from Pfizer; participation in clinical trials for Amgen, gran support, paid to his institution; fees for serving on a speakers bureau, consulting fees, and participation in clinical trials for Vifor Pharma; fees for serving on a speakers bureau and consulting fees from Servier; fees for serving on a speakers bureau, consulting fees, and participation in clinical trials for Bayer; fees for serving on a speakers bureau, consulting fees, and participation in clinical trials for BMS; fees for serving on a speakers bureau and consulting fees from Respicardia; fees for serving on a speakers bureau from Berlin-Chemie; fees for serving on a speakers bureau, consulting fees, and participation in clinical trials for Cibiem; fees for serving on a speakers bureau, consulting fees, and participation in clinical trials for Novartis; and fees for serving on a speakers bureau, consulting fees, and participation in clinical trials for RenalGuard. D.L.D. receiving consulting fees from Frontier Science, Actelion, BMS, Medtronic, Boston Scientific, GSK, and Merck; and consulting fees and being owner of D L DeMets Consulting. M.S.S. receiving grant support, paid to Brigham and Women's Hospital, and consulting fees from Amgen, AstraZeneca, Intarcia, Janssen Research and Development, The Medicines Company, MedImmune, Merck, and Novartis; consulting fees from Anthos Therapeutics, Bristol-Myers Squibb, CVS Caremark, DalCor, Dynamix, Esperion, IFM Therapeutics, and Ionis, grant support, paid to Brigham and Woman's Hospital, from Bayer, Daiichi Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Quark Pharmaceuticals, and Takeda; and serving as a member of the TIMI Study Group, which receives grant support, paid to Brigham and Women's Hospital, from Abbott, Aralez, Roche, and Zora Biosciences. O.B. and M.S. being employed by AstraZeneca. A.M.L. being employed and holding shares in AstraZeneca. A.S.D. receiving consulting fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Dalcor Pharma, and Regeneron, grant support, paid to BWH, and consulting fees from Alnylam and Novartis, and advisory board fees from Corvidia and Relypsa. M.D. receiving personal fees from AstraZeneca during the conduct of the study. J.G.H. receiving grant support, consulting fees, and lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Servier; consulting fees and lecture fees from Novo Nordisk; consulting fees from Janssen, and grant support, consulting fees, lecture fees, and provision of drugs from Pfizer. T.K. receiving fees for serving as national coordinator of a trial from Novartis and AstraZeneca. C.E.A.L. receiving lecture fees and advisory board fees from AstraZeneca, lecture fees from Novartis, and advisory board fees from Pfizer. E.O.M. receiving fees for serving on a clinical trial, paid to her institution, consulting fees, and lecture fees from AstraZeneca, Bayer, Amgen, and Novartis, consulting fees from Merck, fees for serving on a clinical trial, paid to her institution, from American Regent, and consulting fees and lecture fees from Pfizer and Boehringer Ingelheim. M.C.P. reports receiving lecture fees from AstraZeneca, Novartis, and Lilly, grant support, advisory board fees, and fees for serving on an endpoint committee from Boehringer Ingelheim, advisory board fees, lecture fees, and fees for serving on an endpoint committee from Novo Nordisk, advisory board fees from Napp, and fees for serving on an endpoint committee from Takeda and Bayer. M.S. receiving personal fees and nonfinancial support from Astra Zeneca, and personal fees from Novo Nordisk and Boehringer Ingelheim. S.V. receiving grant support, lecture fees, and advisory board fees from AstraZeneca, Boehringer Ingelheim, Bayer, Janssen, and Merck; lecture fees from Sun Pharmaceuticals and EOCI Pharmacomm, grant support and advisory board fees from Amgen; and lecture fees and advisory board fees from Sanofi and Eli Lilly. S.D.S. receiving grant support and consulting fees from Alnylam, Amgen, AstraZeneca, BMS, Gilead, GSK, MyoKardia, Novartis, Theracos, Bayer, and Cytokinetics; grant support from Bellerophon, Celladon, Ionis, Lone Star Heart, Mesoblast, Sanofi Pasteur, and Eidos; consulting fees from Akros, Corvia, Ironwood, Merck, Roche, Takeda, Quantum Genomics, AoBiome, Caridac Dimensions, Tenaya, and Daiichi Sankyo; and fees for serving on a DSMB from Janssen. J.J.V.M. receiving fees (all fees listed paid to Glasgow University) for serving on a steering committee from Bayer, fees for serving on a steering committee, fees for serving on an endpoint committee, and travel support from Cardiorentis, fees for serving on a steering committee and travel support from Amgen, fees for serving on a steering committee and travel support from Oxford University/Bayer, fees for serving as principal investigator of a trial and travel support from Theracos, fees for serving on a steering committee and travel support from AbbVie, fees for serving on a steering committee from DalCor, fees for serving on a data safety monitoring committee from Pfizer, fees for serving on a data safety monitoring committee from Merck, fees for serving on an executive committee, fees for serving as co-principal investigator of a trial, fees for serving on a steering committee, fees for serving on an executive committee, travel support, and advisory board fees from Novartis, fees for serving as co-principal investigator for a trial, fees for serving on a steering committee, and travel support from GlaxoSmithKline, fees for serving on a steering committee from Bristol-Myers Squibb, fees for serving on a steering committee, fees for serving on an endpoint adjudication committee, and travel support from Vifor-Fresenius. 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