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CLINICAL RESEARCH

Dapagliflozin in HFrEF Patients Treated With Mineralocorticoid Receptor Antagonists

An Analysis of DAPA-HF

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ABSTRACT

OBJECTIVES The purpose of this study was to assess the efficacy and safety of dapagliflozin in patients taking or not taking an mineralocorticoid receptor antagonist (MRA) at baseline in the DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) trial.

BACKGROUND MRAs and sodium glucose co-transporter 2 inhibitors each have diuretic activity, lower blood pressure, and reduce glomerular filtration rate (GFR). Therefore, it is important to investigate the safety, as well as efficacy, of their combination.

METHODS A total of 4,744 patients with heart failure with reduced ejection fraction (HFrEF) were randomized to placebo or dapagliflozin 10 mg daily. The efficacy of dapagliflozin on the primary composite outcome (cardiovascular death or episode of worsening heart failure) and its components was examined according to MRA use, as were predefined safety outcomes.

RESULTS A total of 3,370 patients (71%) were treated with an MRA and they were younger (65 vs. 69 years of age), less often from North America (9% vs. 26%), had worse New York Heart Association functional class (35% vs. 25% in class III/IV), lower left ventricular ejection fraction (30.7% vs. 31.9%) and systolic blood pressure (120.3 vs. 125.5 mm Hg), but higher estimated GFR (67.1 vs. 62.6 ml/min/1.73 m^2), than patients not taking an MRA. The benefit of dapagliflozin compared with placebo was similar in patients taking or not taking an MRA: hazard ratio: 0.74 (95% confidence interval [CI]: 0.63 to 0.87) versus 0.74 (95% CI: 0.57 to 0.95), respectively, for the primary endpoint (p value for interaction = 0.97); similar findings were observed for secondary endpoints. In both MRA subgroups, safety outcomes were similar in patients randomized to dapagliflozin or placebo.

CONCLUSIONS Dapagliflozin was similarly efficacious and safe in patients with HFrEF taking or not taking an MRA, supporting the use of both drugs together. (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]; NCT03036124)
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Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce sodium-coupled glucose reabsorption in the proximal renal tubule, with consequent diuretic and natriuretic actions (1). Until recently, the safety of these agents in patients with heart failure with reduced ejection fraction (HFrEF) was uncertain, as most patients with HFrEF are treated with conventional diuretic agents and renin-angiotensin system blockers, and many have impaired kidney function (2–4). Of special concern were patients treated, in addition, with a mineralocorticoid receptor antagonist (MRA). From a safety perspective, MRAs may result in further volume reduction, immediate decline in kidney function when added to a loop or thiazide diuretic, and increase in serum potassium concentration when added to a renin-angiotensin system blocker (5–7). Therefore, the safety of adding dapagliflozin to 3 other agents acting on volume, sodium, potassium, and glomerular filtration, was uncertain, given the potentially complex renal interactions between these 2 classes of drug (5–10). Whereas SGLT2 inhibitors act in the proximal tubule, MRAs act in the distal tubule and collecting ducts and, therefore, MRAs might amplify any diuretic action of SGLT2 inhibition (5–10). Each of SGLT2 inhibitors and MRAs is also believed to affect the renal microcirculation. Although difficult to prove with certainty in humans, SGLT2 inhibitors are thought to cause afferent glomerular arteriolar constriction by enhancing tubulo-glomerular feedback (5–10). Conversely, MRAs are believed to inhibit the vasoconstrictive action of aldosterone on the glomerular efferent arteriole (8). If correct, these combined actions could lead to a major reduction in intraglomerular pressure and filtration and loss of the ability to autoregulate glomerular filtration rate (GFR), especially in the face of a decrease in arterial (i.e., renal perfusion) pressure. On the other hand, if MRAs exert some of their benefit by augmenting diuresis, there may be less scope for further benefit from this action with SGLT2 inhibitors, if diuresis contributes to their efficacy in HFrEF (5–10). In view of this potentially complex interplay between SGLT2 inhibition and MRAs, subgroup analysis of the effect of SGLT2 inhibition according to MRA use at baseline was prespecified in DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) trial. In DAPA-HF, when compared with placebo, the SGLT2 inhibitor dapagliflozin reduced mortality and worsening heart failure (HF), and improved symptoms, in patients with HFrEF (11).

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

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

NYHA = New York Heart Association

SBP = systolic blood pressure

SGLT2 = sodium glucose co-transporter 2

METHODS

The design and results of DAPA-HF have been published (11). Briefly, DAPA-HF was a randomized, double-blind, 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. The trial was approved by the ethics committee at each study center, and all patients gave written informed consent.

STUDY PATIENTS. Patients with HF were eligible if age ≥18 years, New York Heart Association (NYHA) functional class II to IV, left ventricular ejection fraction (LVEF) ≤40% and an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Patients received guideline-recommended medical and device therapy, unless contraindicated or not tolerated. Key exclusion criteria included symptoms of hypotension or systolic blood pressure (SBP) <95 mm Hg, estimated GFR (eGFR) <30 ml/min/1.73 m^2, and type 1 diabetes.

STUDY OUTCOMES. The primary outcome was a composite of worsening HF or cardiovascular death, whichever occurred first. An episode of worsening HF was defined as either an unplanned hospitalization or an urgent visit requiring intravenous therapy for HF. Secondary outcomes included cardiovascular death, worsening HF events, the total number of HF hospitalizations and cardiovascular death, the change from baseline to 8 months in the Total Symptom Score of

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristic in Patients Taking and Not Taking MRA

	Patients Not on MRA (n = 1,374)	Patients on MRA (n = 3,370)	p Value
Age (yr)	69.0 ± 10.1	65.3 ± 11.0	<0.001
Female	322 (23.4)	787 (23.4)	0.95
Geographic region			<0.001
Europe	508 (37.0)	1,646 (48.8)	
Asia/Pacific	326 (23.7)	770 (22.8)	
North America	364 (26.5)	313 (9.3)	
South America	176 (12.8)	641 (19.0)	
Race			0.004
White	943 (68.6)	2,390 (70.9)	
Black	84 (6.1)	142 (4.2)	
Asian	335 (24.4)	781 (23.2)	
Other	12 (0.9)	57 (1.7)	
Heart rate (beats/min)	71.4 ± 12.0	71.5 ± 11.6	0.74
SBP (mm Hg)	125.5 ± 17.3	120.3 ± 15.7	<0.001
DBP (mm Hg)	74.7 ± 11.3	73.0 ± 10.0	<0.001
BMI (kg/m^2)	28.1 ± 6.0	28.2 ± 5.9	0.82
Medical history			
Hypertension	1,074 (78.2)	2,449 (72.7)	<0.001
Diabetes	579 (42.1)	1,404 (41.7)	0.76
Atrial fibrillation	579 (42.1)	1,239 (36.8)	<0.001
Features of HF			
HF etiology			0.003
Ischemic	776 (56.5)	1,898 (56.3)	
Nonischemic	460 (33.5)	1,227 (36.4)	
Unknown	138 (10.0)	245 (7.3)	
Prior HF hospitalization	635 (46.2)	1,616 (48.0)	0.28
KCCQ-TSS	80 (61-94)	77 (58-92)	<0.001
LVEF (%)	31.9 ± 6.8	30.7 ± 6.8	<0.001
NYHA functional class			<0.001
II	1,025 (74.6)	2,178 (64.6)	
III/IV	349 (25.4)	1,192 (35.4)	
NT-proBNP (pmol/l)	1,438 (901-2,549)	1,437 (838-2,689)	0.84
No AF on ECG	1,284 (811-2,343)	1,294 (755-2,434)	
AF on ECG	1,855 (1,239-3,129)	2,030 (1,276-3,230)	
eGFR (ml/min/1.73 m^2)	62.6 ± 18.6	67.1 ± 19.6	<0.001
eGFR <60 ml/min/1.73 m^2	630 (45.9)	1,296 (38.5)	<0.001
Creatinine (μmol/l)	107.7 ± 31.7	103.1± 29.8	<0.001
Hemoglobin (g/l)	134.1 ± 16.7	136.1 ± 15.9	<0.001
Treatment			
Diuretics	1,063 (77.4)	2,945 (87.4)	<0.001
ACEI	691 (50.3)	1,970 (58.5)	<0.001
ARB	413 (30.1)	894 (26.5)	0.01
ARNI	166 (12.1)	342 (10.1)	0.05
Beta-blockers	1,299 (94.5)	3,259 (96.7)	<0.001
Digoxin	205 (14.9)	682 (20.2)	<0.001
Ivabradine	44 (3.2)	184 (5.5)	<0.001
CRT*	104 (7.6)	250 (7.4)	0.86
ICD†	353 (25.7)	889 (26.4)	0.62

Continued on the next page

the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS), a worsening renal function composite outcome, and death from any cause. The composite worsening renal function outcome consisted of a ≥50% sustained decline in eGFR, end-stage renal disease (i.e., sustained eGFR <15 ml/min/1.73 m^2, chronic dialysis treatment, or renal transplant) or renal death.

The prespecified safety analyses included serious adverse events, adverse events associated with discontinuation of a trial treatment, or adverse events of interest, as reported in the Results section.

STATISTICAL ANALYSES. We compared baseline characteristics between those who were and were not taking MRA at baseline, with Student's *t*-test or Mann-Whitney *U* test, as appropriate for continuous variables and chi-square or Fisher's exact tests for categorical variables. Time-to-event outcomes were analyzed using Cox proportional hazards models, stratified according to diabetes status and adjusted for a history of HF hospitalization and treatment-group assignment, with interaction terms used to assess effect modification by baseline MRA use. The renal outcome and incident hyperkalemia were adjusted for baseline eGFR and serum potassium, respectively, instead of a history of HF hospitalization. Total (including recurrent) events were examined using a semiparametric proportional-rates model (11). We analyzed the differences between treatment groups in the proportion of patients (presented as an odds ratio) who reported a clinically significant (≥5 points) improvement or deterioration in the KCCQ-TSS at 8 months following randomization using the methods described previously (11).

The proportion of patients with specific safety outcomes were compared by treatment-group assignment in those who were and were not taking MRAs at baseline using Fisher's exact test. Changes in SBP, weight, hematocrit, and serum creatinine, potassium, NT-proBNP, HbA1c, and eGFR were analyzed using a mixed model for repeated measurements (adjusted for baseline values, visit, treatment-group assignment and interaction of treatment, and visit with a random intercept and slope per patient). The least-squares mean differences with 95% confidence intervals between treatment groups were estimated in patients with and without baseline MRA use. We plotted the change in eGFR during study visits and calculated its slope as per ml/min/1.73 m^2 per year in the first 2 weeks since randomization and thereafter.

All analyses were performed using Stata version 16 (College Station, Texas) and SAS, version 9.4 (SAS Institute, Cary North Carolina).

RESULTS

At baseline, 3,370 patients (71.0%) were receiving MRAs. Of these, 2,674 (56.4%) were prescribed spironolactone, 692 (14.6%) eplerenone, and 7 (0.1%)

another MRA (potassium canrenoate or canrenone). The mean dose taken at baseline was 31.4 ± 18.8 mg of spironolactone and 32.5 ± 13.0 mg of eplerenone.

BASELINE CHARACTERISTICS. Compared with those not taking MRAs, people taking MRAs were younger (mean 65 vs. 69 years), less likely to have a history of hypertension or atrial fibrillation, and had a considerably lower mean SBP (120.3 vs. 125.5 mm Hg) (Table 1). Patients treated with an MRA also had more advanced NYHA functional class (35% vs. 25% in class III/IV, respectively), lower (worse) median KCCQ-TSS (77 vs. 80), and lower mean LVEF (30.7% vs. 31.9%), despite nearly identical median plasma NT-proBNP concentrations between groups. The mean eGFR was higher in patients taking an MRA compared with those not (67.1 vs. 62.6 ml/min/1.73 m^2). Diuretics were used more frequently in patients treated with an MRA than in those not (87% vs. 77%, respectively), as was digoxin (20% vs. 15%, respectively). Overall, more than 90% of patients were treated with a renin-angiotensin system blocker and a beta-blocker.

CLINICAL OUTCOMES. Patients taking an MRA had a higher rate of cardiovascular death than among those not treated with an MRA (Table 2). The rate of worsening HF (HF hospitalization or an urgent visit) was similar in the 2 MRA subgroups (Table 2). The proportion of patients experiencing a clinically meaningful deterioration (≥5-point decrease) in KCCQ-TSS was greater in patients treated with an MRA, compared with those not (33.8% vs. 30.7% in the placebo group) (Central Illustration).

The benefit of dapagliflozin on the primary endpoint was similar in patients taking or not taking an MRA, with a hazard ratio (HR) for dapagliflozin, compared with placebo, of 0.74 (95% confidence interval [CI]: 0.63 to 0.87) in patients taking an MRA, compared with 0.74 (95% CI: 0.57 to 0.95) in those not taking an MRA (Table 2). The benefit of dapagliflozin was similar in those who were and were not taking MRAs, for the other prespecified endpoints, including KCCQ-TSS (p for interaction >0.60 for all) (Table 2). The composite renal endpoint is described under "Kidney function," later in this paper.

When the effect of dapagliflozin was examined in patients with markedly reduced eGFR (30-45 ml/min/1.73 m^2), the hospitalization and mortality benefits were consistent with the overall benefit in each of the MRA subgroups (Figure 1)

BLOOD PRESSURE. The placebo-corrected reduction in SBP with dapagliflozin was not significantly different between the MRA subgroup and the no MRA subgroup (1.58 vs. 1.00 mm Hg) (Table 3).

TABLE 1 Continued

	Patients Not on MRA (n = 1,374)	Patients on MRA (n = 3,370)	p Value
Diabetes medications‡			
Biguanides	275 (47.5)	741 (52.8)	0.03
DPP-4 inhibitors	116 (20.0)	194 (13.8)	0.001
GLP-1 analogues	14 (2.4)	7 (0.5)	<0.001
Sulfonylureas	129 (22.3)	309 (22.0)	0.90
Insulin	172 (29.7)	368 (26.2)	0.11

Values are mean ± SD, n (%), or mean (interquartile range), unless otherwise indicated. *Cardiac resynchronization therapy with or without a defibrillator. †Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator. ‡Only in patients with a medical history of diabetes (n = 1,983).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; DPP = Dipeptidyl peptidase; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GLP = glucagon-like peptide; HF = heart failure; ICD = implantable cardioverter-defibrillator; 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; SBP = systolic blood pressure.

KIDNEY FUNCTION. Overall, the prespecified composite renal efficacy outcome was infrequent (28 dapagliflozin vs. 39 placebo patients) and was not reduced significantly by dapagliflozin (HR: 0.71, 95% CI: 0.44 to 1.16; p = 0.17). This outcome occurred slightly more frequently in the no MRA subgroup, compared with the MRA-treated subgroup, and did not differ significantly between dapagliflozin and placebo within each MRA subgroup (Table 2).

The placebo-corrected increase in creatinine with dapagliflozin was similar in patients treated and not treated with an MRA at baseline (Table 3).

After randomization, there was a small initial drop in eGFR with dapagliflozin compared with placebo (Figure 2). However, after the 2-week follow-up visit (the first visit after randomization), the rate of decline in eGFR over time was significantly less in the dapagliflozin group than in the placebo group (Figure 2). Overall, this pattern of change in eGFR was essentially the same in patients taking and not taking MRA (p for interaction 0.95).

HYPERKALEMIA. There were only small changes in mean potassium between baseline and 8 months in each MRA subgroup, and this change did not differ between dapagliflozin and placebo (p for interaction 0.60) (Table 3). In the MRA-treated group, mild hyperkalemia (potassium >5.5 mmol/l) occurred in 180 of 1,632 patients (11.0%) in the dapagliflozin group and 204 of 1,625 patients (12.6%) in the placebo group (HR: 0.86, 95% CI: 0.70 to 1.05; p = 0.14). The corresponding numbers in patients not treated with an MRA were 63 of 660 (9.6%) and 57 of 682 (8.4%), respectively (HR: 1.20, 95% CI: 0.84 to 1.72; p = 0.32) (Table 4).

In the MRA group, moderate/severe hyperkalemia (potassium >6.0 mmol/l) occurred in 21 of 1,683

TABLE 2 Clinical Outcomes by Randomized Treatment in Patients Taking and Not Taking MRA

	Patients Not on MRA		Patients on MRA		
	Placebo (n = 697)	Dapagliflozin (n = 677)	Placebo (n = 1,674)	Dapagliflozin (n = 1,696)	p Value for Interaction
Primary outcome					
Events (%)	141 (20.2)	105 (15.5)	361 (21.6)	281 (16.6)	
Event rate per 100 patient-yrs	15.0 (12.7-17.7)	11.1 (9.1-13.4)	16.1 (14.5-17.9)	12.0 (10.7-13.5)	
Unadjusted hazard ratio (95% CI)	0.74 (0.57-0.95); p = 0.019		0.74 (0.63-0.87); p < 0.001		0.97
Cardiovascular death					
Events (%)	66 (9.5)	56 (8.3)	207 (12.4)	171 (10.1)	
Event rate per 100 patient-yrs	6.5 (5.1-8.3)	5.7 (4.4-7.4)	8.7 (7.6-9.9)	7.0 (6.0-8.1)	
Unadjusted hazard ratio (95% CI)	0.87 (0.61-1.24); p = 0.445		0.80 (0.66-0.98); p = 0.035		0.69
HF hosp./urgent visit					
Events (%)	99 (14.2)	69 (10.2)	227 (13.6)	168 (9.9)	
Event rate per 100 patient-yrs	10.5 (8.6-12.8)	7.3 (5.7-9.2)	10.1 (8.9-11.5)	7.2 (6.2-8.4)	
Unadjusted hazard ratio (95% CI)	0.69 (0.51-0.94); p = 0.019		0.70 (0.58-0.86); p = 0.001		0.96
Recurrent HF hosp./CV death					
Events	209	148	533	419	
Event rate per 100 patient-yrs	20.8 (17.3-25.3)	15.0 (12.1-18.8)	22.4 (19.9-25.2)	17.2 (15.1-19.6)	
Unadjusted hazard ratio (95% CI)	0.72 (0.54-0.96); p = 0.028		0.76 (0.64-0.91); p = 0.002		0.77
KCCQ - Total symptom score					
Mean change ± SD at 8 months	2.8 ± 18.2	5.6±18.0	3.5±19.7	6.3±18.9	
Proportion with increase in score ≥5 at 8 months (%)	52.1	59.5	50.4	57.8	
Odds ratio (95% CI)	1.16 (1.04-1.29); p = 0.0104		1.15 (1.07-1.24); p = 0.0001		0.98
Proportion with decrease in score ≥5 at 8 months (%)	30.7	23.6	33.8	26.0	
Odds ratio (95% CI)	0.83 (0.73-0.95); p = 0.0063		0.83 (0.77-0.90); p < 0.0001		0.99
Composite renal outcome*					
Events	16	8	23	20	
Event rate per 100 patient-yrs	1.7 (1.0-2.8)	0.8 (0.4-1.7)	1.0 (0.7-1.5)	0.9 (0.6-1.3)	
Unadjusted hazard ratio (95% CI)	0.51 (0.22-1.20); p = 0.125		0.84 (0.46-1.54); p = 0.581		0.34
All-cause death					
Events (%)	88 (12.6)	66 (9.8)	241 (14.4)	210 (12.4)	
Event rate per 100 patient-yrs	8.7 (7.0-10.7)	6.7 (5.2-8.5)	10.1 (8.9-11.4)	8.6 (7.5-9.8)	
Unadjusted hazard ratio (95% CI)	0.77 (0.56-1.06); p = 0.106		0.85 (0.70-1.02); p = 0.08		0.62

*Adjusted for baseline eGFR and stratified by diabetes status. Hazard ratio represents comparison of dapagliflozin against placebo. Hazard ratios adjusted for previous heart failure hospitalization at baseline (except all-cause death) and stratified by diabetes status. The total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. 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. The total number of hospitalizations for heart failure and cardiovascular deaths was analyzed by means of the semiparametric proportional-rates model, in which the treatment effect is reported as a rate ratio.

CV = cardiovascular; HF = heart failure; hosp. = hospitalization.

(1.3%) patients treated with dapagliflozin and in 40 of 1,666 (2.4%) patients treated with placebo, giving a HR of 0.50 (0.29 to 0.85). The corresponding numbers in patients not treated with an MRA were 13 of 675 (1.9%) and 11 of 695 (1.6%), respectively (HR: 1.17, 0.52 to 2.62); p for interaction = 0.08 (Table 4).

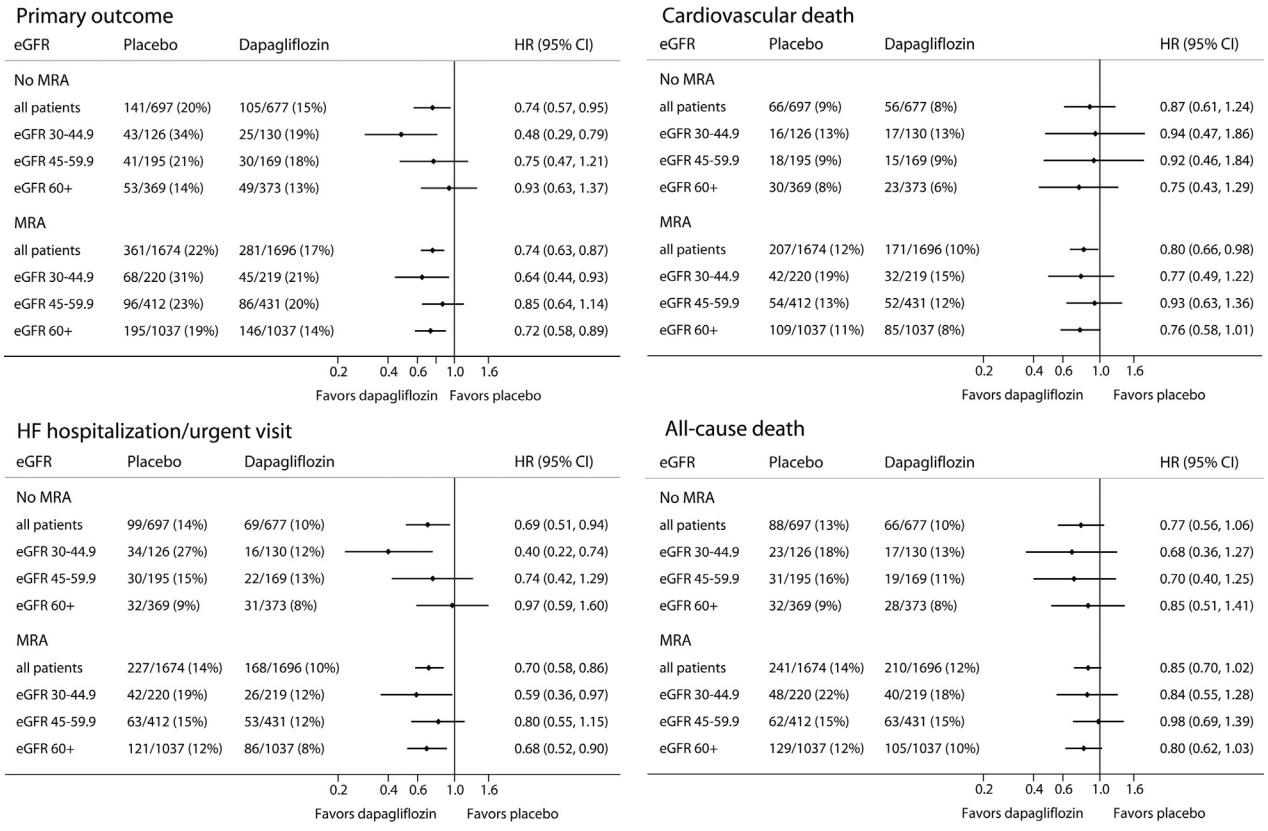
OTHER SAFETY OUTCOMES. When comparing dapagliflozin to placebo, none of the prespecified adverse events were common or significantly more common with dapagliflozin, compared with placebo, irrespective of background MRA therapy (Table 5).

DISCUSSION

In patients with HFrEF, the magnitude of the beneficial effect of dapagliflozin on the primary composite outcome was virtually identical in patients treated and not treated with an MRA at baseline, with an overall relative risk reduction of 26%. The findings were also similar in the MRA and no MRA subgroups for other key secondary endpoints, with no statistically significant interactions identified. Most measures of safety, including adverse events related to volume depletion and change in renal function, were also similar between dapagliflozin and placebo in the 2 MRA-treatment subgroups. The only exception was in patients taking an MRA at baseline, where moderate/severe hyperkalemia (potassium >6.0 mmol/l) was less common among patients assigned to dapagliflozin, compared with placebo.

Aldosterone stimulates reabsorption of sodium and excretion of potassium in the renal distal tubule and

FIGURE 1 Effect of Dapagliflozin on Clinical Outcomes According to Baseline eGFR Category (i.e., eGFR 30 to 44.9, 45 to 59.9, and 60 or Above ml/min/1.73 m^2), in Patients With and Without MRA at Baseline



Clinical outcomes include primary composite outcome, cardiovascular death, heart failure (HF) hospitalization/urgent visit for HF, and all-cause death.
eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist.

for this reason MRAs were originally introduced as potassium-retaining diuretic agents (12). SGLT2 inhibitors reduce glucose (and sodium) reabsorption in the proximal renal tubule and, therefore, also have a diuretic action, among other actions (1,9,10). Because of these distinct renal effects, the interplay between SGLT2 inhibitors and MRAs is potentially complex. Although not completely consistent, most evidence suggests that, as with other diuretics, SGLT2 inhibitors increase aldosterone levels (10,13–17). Because of this, the combination of an MRA with an SGLT2 inhibitor is pharmacologically attractive in the same way the combination of an MRA with conventional potassium-wasting diuretic agents is. However, because both SGLT2 inhibitors and MRAs have a diuretic effect, their combined use could, theoretically, lead to volume depletion, and hypotension, particularly in patients already treated with a loop diuretic, although we did not identify any substantial change in diuretic therapy after randomization in DAPA-HF overall, as reported elsewhere, or a significant risk of hypotension associated with either an MRA or an SGLT2 inhibitor individually (5–7,18–20). Moreover, both SGLT2 inhibitors and MRAs cause a small initial decline in eGFR and this, combined with the potential for volume depletion and hypotension, was a concern when DAPA-HF was designed, especially in patients with HFrEF with impaired kidney function. Indeed, this combination of effects also could have led to an increased risk of hyperkalemia. In contrast, we observed a reduced risk of serious hyperkalemia when dapagliflozin was combined with an MRA, compared with when placebo was added to an MRA, for reasons that are not clear. A possible explanation is that SGLT2 inhibitors do not reduce intravascular volume to the same extent as conventional diuretic agents (21), have minimal effect on SBP in HFrEF, and slow the longer-term rate of decline in eGFR (after causing a small initial decrease) (1,22). This should permit enhanced distal delivery of

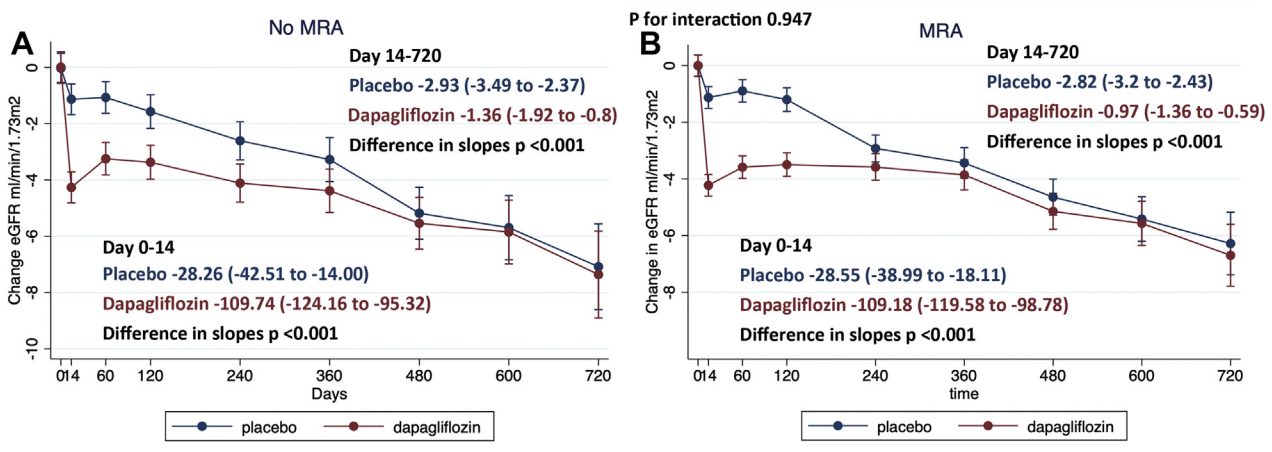
TABLE 3 Changes in Repeated Measurements by Randomized Treatment in Patients Taking and Not Taking MRA

	Patients Not on MRA		Patients on MRA		
	Placebo (n = 697)	Dapagliflozin (n = 677)	Placebo (n = 1,674)	Dapagliflozin (n = 1,696)	p Value for Interaction
Systolic blood pressure, mm Hg					
Change from baseline at 8 months	−2.20 ± 16.90	−3.46 ± 15.78	0.37 ± 14.48	−1.29 ± 14.51	
Difference*	−1.00 (−2.72 to 0.72); p = 0.254		−1.58 (−2.59 to −0.58); p = 0.002		0.88
Creatinine, mg/dl					
Change from baseline at 8 months	0.04 ± 0.26	0.08 ± 0.24	0.04 ± 0.24	0.06 ± 0.24	
Difference*	0.03 (0.01 to 0.06); p = 0.021		0.02 (−0.003 to 0.03); p = 0.103		0.32
Potassium, mmol/l					
Change from baseline at 8 months	0.08 ± 0.52	0.11 ± 0.49	0.1 ± 0.53	0.06 ± 0.54	
Difference*	0.03 (−0.03 to 0.08); p = 0.349		−0.03 (−0.07 to 0.002); p = 0.064		0.60
NT-proBNP, pg/ml					
Change from baseline at 8 months	406 ± 2,949	−286 ± 2,071	−25 ± 2,934	−159 ± 2,503	
Difference*	−690 (−1,121 to −259); p = 0.002		−140 (−662 to 383); p = 0.60		0.55
Weight, kg					
Change from baseline at 8 months	−0.26 ± 4.09	−0.94 ± 3.80	0.24 ± 4.08	−0.86 ± 3.89	
Difference*	−0.67 (−1.11 to −0.23); p = 0.003		−0.98 (−1.28 to −0.68); p < 0.001		0.84
Hematocrit, %					
Change from baseline at 8 months	−0.26 ± 3.83	2.42 ± 3.55	−0.16 ± 3.8	2.27 ± 4.04	
Difference*	2.61 (2.21 to 3.00); p < 0.001		2.42 (2.15 to 2.68); p < 0.001		0.53
Glycated hemoglobin,† %					
Change from baseline at 8 months	0.10 ± 1.28	−0.17 ± 1.22	0.04 ± 1.30	−0.21 ± 1.08	
Difference*	−0.30 (−0.50 to −0.10); p = 0.003		−0.24 (−0.37 to −0.11); p < 0.001		0.43

*Difference between placebo and dapagliflozin at 8 months with 95% confidence interval. †Glycated hemoglobin values are listed only for the patients with medical history of diabetes (n = 1,983).

Abbreviations as in Table 1.

FIGURE 2 Change in eGFR During Study Visits by Randomized Treatment in Patients Taking and Not Taking MRA



(A) Change in eGFR over time by randomized treatment in patients not taking MRA. **(B)** Change in eGFR over time by randomized treatment in patients taking MRA. Changes in eGFR slope are shown as per ml/min per 1.73 m^2 per year. CI = confidence interval; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist.

TABLE 4 Incident Hyperkalemia During Follow-Up by Randomized Treatment in Patients Taking and Not Taking MRA

	Patients Not on MRA		Patients on MRA		
	Placebo (n = 697)	Dapagliflozin (n = 677)	Placebo (n = 1,674)	Dapagliflozin (n = 1,696)	p Value for Interaction
Mild hyperkalemia* (potassium >5.5 mmol/l)					
Events	57/682 (8.4)	63/660 (9.6)	204/1,625 (12.6)	180/1,632 (11.0)	
Rate, per 100 patient-yrs	6.4 (5.0–8.4)	7.2 (5.7–9.3)	10.0 (8.7–11.5)	8.7 (7.5–10.1)	
HR† (95% CI)	1.20 (0.84–1.72); p = 0.316		0.86 (0.70–1.05); p = 0.144		0.13
Moderate/severe hyperkalemia‡ (potassium >6.0 mmol/l)					
Events	11/695 (1.6)	13/675 (1.9)	40/1,666 (2.4)	21/1,683 (1.3)	
Rate, per 100 patient-yrs	1.2 (0.6–2.1)	1.4 (0.8–2.4)	1.8 (1.3–2.4)	0.9 (0.6–1.4)	
HR† (95% CI)	1.17 (0.52–2.62); p = 0.707		0.50 (0.29–0.85); p = 0.01		0.08

*Values are n/N (%), unless otherwise indicated. Excluding patients with baseline serum potassium >5.5 mmol/l (n = 145). †Adjusted for baseline potassium and stratified by diabetes status. ‡Excluding patients with baseline serum potassium >6.0 mmol/l (n = 25).

sodium, as a result of inhibition of proximal reabsorption, preserving sodium/potassium exchange in the distal nephron.

Whatever the explanation, we believe that our findings are clinically important, given that MRAs remain underused in practice, often due to fear of hyperkalemia, especially in patients with renal dysfunction (23). Our other initial concerns about using an SGLT2 inhibitor in patients treated with a conventional diuretic and renin-angiotensin system blocker, as well as an MRA, were not realized either, with no excess of adverse effects related to volume depletion or hypotension. Furthermore, despite evidence of their benefit across the spectrum of severity of HFrEF, many physicians still reserve MRAs for patients with more advanced HF. This was evidenced in DAPA-HF by more severe symptoms, lower SBP, and more frequent use of digoxin, reflecting a patient subgroup likely to be more at risk of adverse effects with any new treatment. The current findings are therefore reassuring with respect to safety in this more vulnerable group.

The further reduction in morbidity and mortality with the addition of dapagliflozin to an MRA suggests these agents have separate but complementary mechanisms of action that lead to added benefit. MRAs block the receptors for aldosterone, which has long been recognized to contribute to the pathophysiology of HF, and possibly other corticosteroids with similar actions (23,24). Corticosteroids, including aldosterone, may promote cardiac hypertrophy and fibrosis, cause

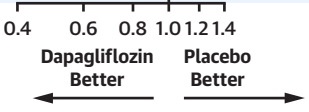
TABLE 5 Discontinuation and Safety Outcomes by Randomized Treatment in Patients Taking and not Taking MRA

	Patients Not on MRA			Patients on MRA		
	Placebo (n = 697)	Dapagliflozin (n = 677)	p Value	Placebo (n = 1,674)	Dapagliflozin (n = 1,696)	p Value
Any discontinuation*						
Events	98/697 (14.1)	76/677 (11.2)	0.11	160/1,674 (9.6)	173/1,696 (10.2)	0.53
Discontinuation due to adverse event						
Events	50/695 (7.2)	37/674 (5.5)	0.22	66/1,673 (3.9)	74/1,694 (4.4)	0.55
Volume depletion						
Events	55/695 (7.9)	49/674 (7.3)	0.68	107/1,673 (6.4)	129/1,694 (7.6)	0.18
Renal adverse event						
Events	57/695 (8.2)	51/674 (7.6)	0.69	113/1,673 (6.8)	102/1,694 (6.0)	0.40
Fracture						
Events	18/695 (2.6)	18/674 (2.7)	1.00	32/1,673 (1.9)	31/1,694 (1.8)	0.90
Amputation						
Events	2/695 (0.3)	3/674 (0.4)	–	10/1,673 (0.6)	10/1,694 (0.6)	–
Major hypoglycemia						
Events	2/695 (0.3)	1/674 (0.1)	–	2/1,673 (0.1)	3/1,694 (0.2)	–

Values are n/N (%), unless otherwise indicated. *Only in the safety set except for discontinuation due to any cause.
Abbreviation as in Table 1.

CENTRAL ILLUSTRATION **Summary of Effects of Dapagliflozin in Patients Taking and Not Taking Mineralocorticoid Receptor Antagonist at Baseline**

	Dapagliflozin	Placebo	Effect Estimate (95% CI) †	Interaction p Value
Primary Outcome	16.3%	21.2%	0.74 (0.65–0.85)	0.97
No MRA	15.5%	20.2%	0.74 (0.57–0.95)	
MRA	16.6%	21.6%	0.74 (0.63–0.87)	
Cardiovascular death	9.6%	11.5%	0.82 (0.69–0.98)	0.69
No MRA	8.3%	9.5%	0.87 (0.61–1.24)	
MRA	10.1%	12.4%	0.80 (0.66–0.98)	
HF hospitalization or urgent HF visit	10.0%	13.7%	0.70 (0.59–0.83)	0.96
No MRA	10.2%	14.2%	0.69 (0.51–0.94)	
MRA	9.9%	13.6%	0.70 (0.58–0.86)	
Recurrent HF hospitalization or CV death	n = 567	n = 742	0.75 (0.65–0.88)	0.77
No MRA	n = 148	n = 209	0.72 (0.54–0.96)	
MRA	n = 419	n = 533	0.76 (0.64–0.91)	
≥5pt. deterioration in KCCQ-TSS	25.3%	32.9%	0.84 (0.78–0.90)	0.99
No MRA	23.6%	30.7%	0.83 (0.73–0.95)	
MRA	26.0%	33.8%	0.83 (0.77–0.90)	
Composite renal outcome*	n = 28	n = 39	0.71 (0.44–1.16)	0.34
No MRA	n = 8	n = 16	0.51 (0.22–1.20)	
MRA	n = 20	n = 23	0.84 (0.46–1.54)	
All-cause death	11.6%	13.9%	0.83 (0.71–0.97)	0.62
No MRA	9.8%	12.6%	0.77 (0.56–1.06)	
MRA	12.4%	14.4%	0.85 (0.70–1.02)	



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Effect estimate = treatment effect of dapagliflozin compared with placebo shown as a hazard ratio (HR) or rate ratio; "all patients" are shown in **blue** for each outcome, with the background MRA therapy and no background MRA therapy subgroups shown in black. 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. The total number of hospitalizations for heart failure and cardiovascular deaths was analyzed by means of the semiparametric proportional-rates model, in which the treatment effect is reported as a rate ratio. The Total Symptom Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ) ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. An HR <1 indicates fewer people with a 5 or greater point deterioration. †HRs adjusted for previous heart failure hospitalization at baseline (except all-cause death) and stratified by diabetes status. *Adjusted for baseline eGFR and stratified by diabetes status. CI = confidence interval; CV = cardiovascular; MRA = mineralocorticoid receptor antagonist; pt. = points.

vascular damage and baroreceptor dysfunction, and prevent the re-uptake of norepinephrine by myocardium (24).

Conversely, the mechanisms responsible for the cardiovascular benefits of SGLT2 inhibitors are unknown (1,9).

It is also important to note that the mean doses of spironolactone and eplerenone taken by patients at baseline in DAPA-HF (31 mg and 33 mg, respectively) were similar to those taken in RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (26 mg and 39 mg, respectively), reinforcing the incremental benefit of dapagliflozin in DAPA-HF.

STUDY LIMITATIONS. The patients studied were selected and those with a low eGFR at screening were excluded. Blood pressure, serum potassium, and renal function were carefully monitored throughout the trial, which may not happen in routine practice.

Patients taking an MRA at baseline had likely taken this treatment for some time and were presumably tolerant of it. Starting an MRA and SGLT2 inhibitor together might not be as well tolerated as in the sequence we studied.

CONCLUSIONS

In summary, we found that the benefit of dapagliflozin on symptoms, worsening HF, and death was similar in patients with HFrEF treated and not treated with an MRA at baseline. Moreover, we found similar safety of dapagliflozin in the 2 MRA subgroups, including with respect to volume depletion and renal dysfunction. Furthermore, we observed a lower rate of serious hyperkalemia with dapagliflozin, compared with placebo, in MRA-treated patients. These findings suggest that dapagliflozin acts in a mechanistically complementary and independent way to MRAs, and the use of these drugs together further reduces morbidity and mortality in HFrEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: When compared with placebo, dapagliflozin substantially reduced cardiovascular morbidity and mortality in patients with HFrEF. Previously, MRAs have also been shown to reduce morbidity and mortality in patients with HF. We assessed the efficacy and safety of dapagliflozin in patients who were and were not taking an MRA and found that the benefit of dapagliflozin was similar, regardless of MRA use. Regarding the safety of combined therapy, dapagliflozin reduced the risk of hyperkalemia in patients treated with an MRA and was not associated with an excess of volume depletion or renal dysfunction. These data show that the combined use of these agents is safe with additive benefit.

TRANSLATIONAL OUTLOOK: Although the exact mechanisms by which SGLT-2 inhibitors benefit patients with HFrEF are unknown, these data strongly suggest that the mechanism of action of these drugs is likely to be distinct and complementary. Further research will help elucidate the specific mechanisms of action of these SGLT-2 inhibitors.

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