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Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure

EMPEROR-Reduced

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ABSTRACT

BACKGROUND Mineralocorticoid receptor antagonists (MRAs) and sodium glucose co-transporter 2 inhibitors favorably influence the clinical course of patients with heart failure and reduced ejection fraction.

OBJECTIVES This study sought to study the mutual influence of empagliflozin and MRAs in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction).

METHODS Secondary analysis that compared the effects of empagliflozin versus placebo in 3,730 patients with heart failure and a reduced ejection fraction, of whom 71% used MRAs at randomization.

RESULTS The effects of empagliflozin on the primary endpoint, on most efficacy endpoints, and on safety were similar in patients receiving or not receiving an MRA (interaction $p > 0.20$). For cardiovascular death, the hazard ratios for the effect of empagliflozin versus placebo were 0.82 (95% confidence interval [CI]: 0.65 to 1.05) in MRA users and 1.19 (95% CI: 0.82 to 1.71) in MRA nonusers (interaction $p = 0.10$); a similar pattern was seen for all-cause mortality (interaction $p = 0.098$). Among MRA nonusers at baseline, patients in the empagliflozin group were 35% less likely than those in the placebo group to initiate treatment with an MRA following randomization (hazard ratio: 0.65; 95% CI: 0.49 to 0.85). Among MRA users at baseline, patients in the empagliflozin group were 22% less likely than those in the placebo group to discontinue treatment with an MRA following randomization (hazard ratio: 0.78; 95% CI: 0.64 to 0.96). Severe hyperkalemia was less common in the empagliflozin group.

CONCLUSIONS In EMPEROR-Reduced, the use of MRAs did not influence the effect of empagliflozin to reduce adverse heart failure and renal outcomes. Treatment with empagliflozin was associated with less discontinuation of MRAs. (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; NCT03057977) (J Am Coll Cardiol 2021;77:1397–407) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

eGFR = estimated glomerular filtration rate

KCCQ = Kansas City Cardiomyopathy Questionnaire

MRA = mineralocorticoid receptor antagonist

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

NYHA = New York Heart Association

SGLT2 = sodium glucose co-transporter 2

Mineralocorticoid receptor antagonists (MRAs) reduce the morbidity and mortality of patients with heart failure and reduced ejection fraction. The EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) and RALES (Randomized Aldactone Evaluation Study) trials demonstrated that both eplerenone and spironolactone decreased the risk of cardiovascular death and the risk of hospitalization for heart failure in patients with mild and moderate to severe symptoms, respectively (1,2).

More recently, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial and the EMPEROR-Reduced (Cardiovascular and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) showed that the sodium glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin reduced the composite risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, with and without diabetes, with similar effects in patients receiving or not receiving an MRA before randomization (3–5). However, it is not clear how MRAs influence other measures of efficacy (as well as the safety) of SGLT2 inhibitors and whether SGLT2 inhibition may influence the utilization of MRAs.

In this secondary analysis of EMPEROR-Reduced, we examined the influence of MRA use at baseline on the efficacy and safety of empagliflozin and whether empagliflozin influenced the prescribing of MRAs following randomization.

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METHODS

EMPEROR-Reduced was a randomized, double-blind, parallel-group, placebo-controlled, and event-driven study, the design of which has been described previously (4). Participants were men or women with chronic heart failure (functional class II, III, or IV) with a left ventricular ejection fraction of ≤40% who were receiving appropriate background treatment for heart failure. We preferentially enrolled patients with an ejection fraction of ≤30% by requiring those with a higher ejection fraction to have been hospitalized for HF within 12 months or to have markedly increased levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), that is, ≥1,000 pg/ml or ≥2,500 pg/ml in those with an ejection fraction of 31% to 35% or 36% to 40%, respectively; these thresholds were doubled in patients with atrial fibrillation. The ethics committee of each of the 520 sites in 20 countries approved the protocol, and all patients gave written informed consent.

RANDOMIZATION. Patients were randomized in a double-blind manner (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy. The use of MRAs at baseline was not a stratification variable. Following entry into the trial, all appropriate treatments for heart failure or other medical conditions (including MRAs) could be initiated, discontinued, or altered at the clinical discretion of the investigator. Patients were periodically assessed at study visits for major outcomes, symptoms, and functional capacity related to heart failure, initiation or discontinuation of new treatments for heart failure (including MRAs), vital signs and biomarkers reflecting changes in the course of heart failure or the action of SGLT2 inhibitors, and adverse events. All randomized patients were followed for the occurrence of pre-specified outcomes for the entire duration of the trial, regardless of whether the study participants were taking their study medications or adhered to the schedule of study visits.

TRIAL ENDPOINTS. The primary endpoint was the composite of adjudicated cardiovascular death hospitalization for heart failure, analyzed as the time to first event. The first secondary endpoint was the occurrence of all adjudicated hospitalizations for heart failure (including first and recurrent events). The second secondary endpoint was the analysis of the slope of the change in estimated glomerular filtration rate (eGFR) during double-blind treatment, which was supported by an analysis of a composite of serious adverse renal events, defined by the need for chronic dialysis or renal transplant, or a sustained ≥40% drop in eGFR, or a sustained eGFR of <15 ml/min/1.73 m^2 (if the baseline eGFR was ≥30 ml/min/1.73 m^2) or <10 ml/min/1.73 m^2 (if the baseline eGFR was <30 ml/min/1.73 m^2). Additional analyses included the individual components of the primary endpoint as well as all-cause mortality, health status as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), systolic blood pressure, body weight, and laboratory parameters.

The pre-specified safety analyses included serious adverse events, adverse events associated with discontinuation of a trial treatment, and adverse events of special interest (i.e., volume depletion, renal events, and hypotension). The occurrence of a serum potassium concentration of >5.5 mmol/l and >6.0 mmol/l as well as investigator-reported hyperkalemia were also analyzed.

STATISTICAL ANALYSIS. Baseline characteristics were compared in MRA users and nonusers by using the chi-square test for categorical variables and Student's *t*-test for continuous variables. For time-to-first-event analyses, differences between the placebo and empagliflozin groups were assessed by using a Cox proportional hazards model with pre-specified baseline covariates of age, sex, geographic region, diabetes, left ventricular ejection fraction, and eGFR. For the analysis of total (first and repeated) events, the differences between the placebo and empagliflozin groups were assessed by using a joint frailty model, with cardiovascular death (for recurrent heart failure hospitalizations) or all-cause mortality (for recurrent hospitalization for any reason) as competing risks. For the analysis of changes in vital signs and laboratory measurements, treatment effects were assessed based on changes from baseline by using a mixed model for repeated measures. Between-group differences in the slope of change in eGFR were analyzed based on data on double-blind treatment and using a random intercept random slope model. All analyses used the same covariates as in the Cox model and included the baseline variable as an additional covariate, where applicable. For all efficacy measures, separate analyses were performed according to the use or nonuse of MRAs at baseline, and differences in the effect of empagliflozin in users and nonusers were assessed by interaction terms. Analyses of safety were performed based on all patients who had received at least 1 dose of the study medication. The p values and 95% confidence intervals (CIs) presented in this report have not been adjusted for multiplicity, and therefore, inferences drawn from these statistics may not be reproducible. All analyses were performed with SAS, version 9.4 (SAS Institute, Cary, North Carolina).

DATA SHARING. Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the corresponding author. The executive committee of EMPEROR has developed a comprehensive analysis plan and numerous pre-specified analyses, which will be presented in future scientific meetings and publications. At a later time point, the full database will be made available in adherence with the transparency policy of the sponsor.

RESULTS

In EMPEROR-Reduced, 71% of patients were treated with an MRA at the time of randomization. In general, MRA users were younger with better renal function but with a lower ejection fraction, systolic blood pressure, and NT-pro BNP. Additionally, MRA users were more likely to have been hospitalized for heart failure within 12 months and be treated with a loop diuretic, but they were less likely to have received a

TABLE 1 Clinical Characteristics, According to the Use of an MRA at Baseline

	No MRA Use at Randomization (n = 1,069)	MRA Use at Randomization (n = 2,661)	p Value
Age, yrs	69.6 ± 10.5	65.7 ± 11.1	<0.0001
Women	238 (22.3)	655 (24.6)	0.13
Race			
White	727 (67.7)	1905 (71.6)	0.003
Black	81 (7.6)	176 (6.6)	
Asian	226 (21.1)	446 (16.8)	
Other/missing	38 (3.5)	134 (5.1)	
Region			
North America	215 (20.1)	210 (7.9)	<0.0001
Latin America	254 (23.8)	1032 (38.8)	
Europe	378 (35.4)	975 (36.6)	
Asia	169 (15.8)	324 (12.2)	
Other	53 (5.0)	120 (4.5)	
Body mass index, kg/m^2	27.5 ± 5.3	28.0 ± 5.4	0.013
Heart rate, beats/min	71.3 ± 11.8	71.2 ± 11.7	0.85
Systolic blood pressure, mm Hg	125.1 ± 16.1	120.7 ± 15.3	<0.0001
NYHA functional class			
II	815 (76.2)	1985 (74.6)	0.29
III-IV	254 (23.6)	676 (25.4)	
Duration of heart failure, yrs	4.2 (1.6-9.2)	3.9 (1.4-8.7)	0.35
Left ventricular ejection fraction, %	28.4 ± 6.0	27.1 ± 6.0	<0.0001
NT-proBNP, pg/ml*	2,015 (1,192-3,814)	1,866 (1,077-3,349)	0.0038
Medical history			
Heart failure hospitalization within 12 months	284 (26.6)	867 (32.6)	0.0003
Coronary artery disease	543 (50.8)	1167 (43.9)	0.0001
CABG/PCI	495 (46.3)	1028 (38.6)	<0.0001
Atrial fibrillation/flutter	455 (42.6)	986 (37.1)	0.0018
Hypertension	815 (76.2)	1883 (70.8)	0.0007
Diabetes	556 (52.0)	1300 (48.9)	0.081
Clinical and laboratory assessments			
HbA1c, %	6.6 ± 1.3	6.6 ± 1.5	0.99
eGFR, ml/min/1.73 m^2	57.3 ± 21.0	63.9 ± 21.6	<0.0001
KCCQ clinical summary score	71.9 ± 21.4	70.2 ± 22.2	0.034
Serum potassium, mmol/l	4.6 ± 0.5	4.7 ± 0.5	<0.0001
Heart failure medications			
Loop diuretics	840 (78.6)	2310 (86.8)	<0.0001
ACE inhibitor	453 (42.4)	1250 (47.0)	0.011
ARB without neprilysin inhibitor	276 (25.8)	632 (23.8)	0.18
Sacubitril/valsartan	190 (17.8)	537 (20.2)	0.093
Beta-blocker	1005 (94.0)	2528 (95.0)	0.22
Devices for heart failure			
Implantable cardioverter-defibrillator†	368 (34.4)	803 (30.2)	0.012
Cardiac resynchronization therapy‡	149 (13.9)	293 (11.0)	0.012

Values are mean ± SD, n (%), or median (interquartile range). *Values for NT-proBNP were log transformed. †Includes all patients with an implantable cardioverter-defibrillator regardless of the presence or absence of cardiac resynchronization therapy. ‡Includes all patients who were receiving cardiac resynchronization therapy regardless of the presence or absence of a defibrillator.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin A1c; KCCQ = Kansas City Cardiomyopathy Questionnaire; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

TABLE 2 Effect of Empagliflozin on Pre-Specified Measures of Efficacy, According to the Use of MRAs at Baseline

	MRA Nonusers (n = 1,069)			MRA Users (n = 2,661)			
	Placebo (n = 512)	Empagliflozin (n = 557)	Treatment Effect	Placebo (n = 1,355)	Empagliflozin (n = 1,306)	Treatment Effect	Interaction p Value
Cardiovascular death or heart failure hospitalization	132 (25.8)	118 (21.2)	0.76 (0.59–0.97)	330 (24.4)	243 (18.6)	0.75 (0.63–0.88)	0.93
Total number of heart failure hospitalizations	165	126	0.69 (0.48–0.97)	388	262	0.71 (0.56–0.89)	0.88
Slope of decline in eGFR, ml/min/1.73 m^2/yr	−2.74 ± 0.43	−0.55 ± 0.40	2.19 (1.04–3.35)	−2.09 ± 0.27	−0.55 ± 0.28	1.55 (0.79–2.30)	0.36
Composite kidney endpoint	12 (2.3)	11 (2.0)	0.80 (0.35–1.82)	46 (3.4)	19 (1.5)	0.41 (0.24–0.71)	0.18
Time to first hospitalization for heart failure	106 (20.7)	82 (14.7)	0.65 (0.49–0.87)	236 (17.4)	164 (12.6)	0.71 (0.58–0.87)	0.66
Cardiovascular death	51 (10.0)	67 (12.0)	1.19 (0.82–1.71)	151 (11.1)	120 (9.2)	0.82 (0.65–1.05)	0.10
All-cause mortality	68 (13.3)	87 (15.6)	1.15 (0.84–1.59)	198 (14.6)	162 (12.4)	0.84 (0.68–1.03)	0.098
Change in KCCQ clinical summary score at 52 weeks							
Increase of >5*	227 (44.3)	292 (52.5)	1.39 [1.06–1.83]	650 (48.0)	665 (50.9)	1.16 [0.97–1.37]	0.26
Decrease of >5*	175 (34.2)	159 (28.6)	0.77 [0.58–1.03]	432 (31.9)	385 (29.5)	0.87 [0.73–1.05]	0.48
Change in NYHA functional class at 52 weeks							
Odds ratio for improvement†	81/425 (19.1)	109/479 (22.8)	1.25 [0.88–1.78]	222/1,110 (20.0)	251/1,057 (23.7)	1.32 [1.06–1.66]	0.81
Odds ratio for worsening†	71/425 (16.7)	78/479 (16.3)	0.97 [0.68–1.38]	208/1,110 (18.7)	164/1,057 (15.5)	0.78 [0.62–0.98]	0.31

Values are n (%), hazard ratio (95% confidence interval), n, absolute difference ± SD, odds ratio [95% confidence interval], or n/N (%). The proportions of responders were compared between treatment groups by using a logistic regression model including for age, baseline eGFR, baseline KCCQ value, region, baseline diabetes status, sex, baseline left ventricular ejection fraction, treatment arm, baseline use of MRA, and treatment arm by baseline use of MRA interaction. Multiple imputations were used to impute missing data. The observed number and proportion of responders, OR between treatment groups, 95% CI, and 2-sided p value estimated from each imputed dataset were combined by using Rubin's rule, and the combined results are presented. The p values and 95% CIs presented in this report have not been adjusted for multiplicity, and therefore, inferences drawn from these statistics may not be reproducible. *Patients who died before 52 weeks are considered as having not improved or deteriorated. Missing scores are imputed for surviving patients. Ceiling effects were managed as follows: if a patient had a baseline value of ≤5 points, he or she was defined as having a 5-point deterioration if the value was ≤5 points at 52 weeks; conversely, if a patient had a baseline value of ≥95 points, he or she was defined as having a 5-point improvement if the value was ≥95 points at 52 weeks. †Logistic regression analysis adjusted for age, baseline eGFR, treatment arm, region, baseline diabetes status, sex, baseline left ventricular ejection fraction, baseline NYHA functional class, baseline use of MRA, and baseline use of MRA by treatment interaction. No improvement/deterioration was imputed for patients who died or had missing data due to being lost to follow-up or withdrawal of consent at 52 weeks.

Abbreviations as in Table 1.

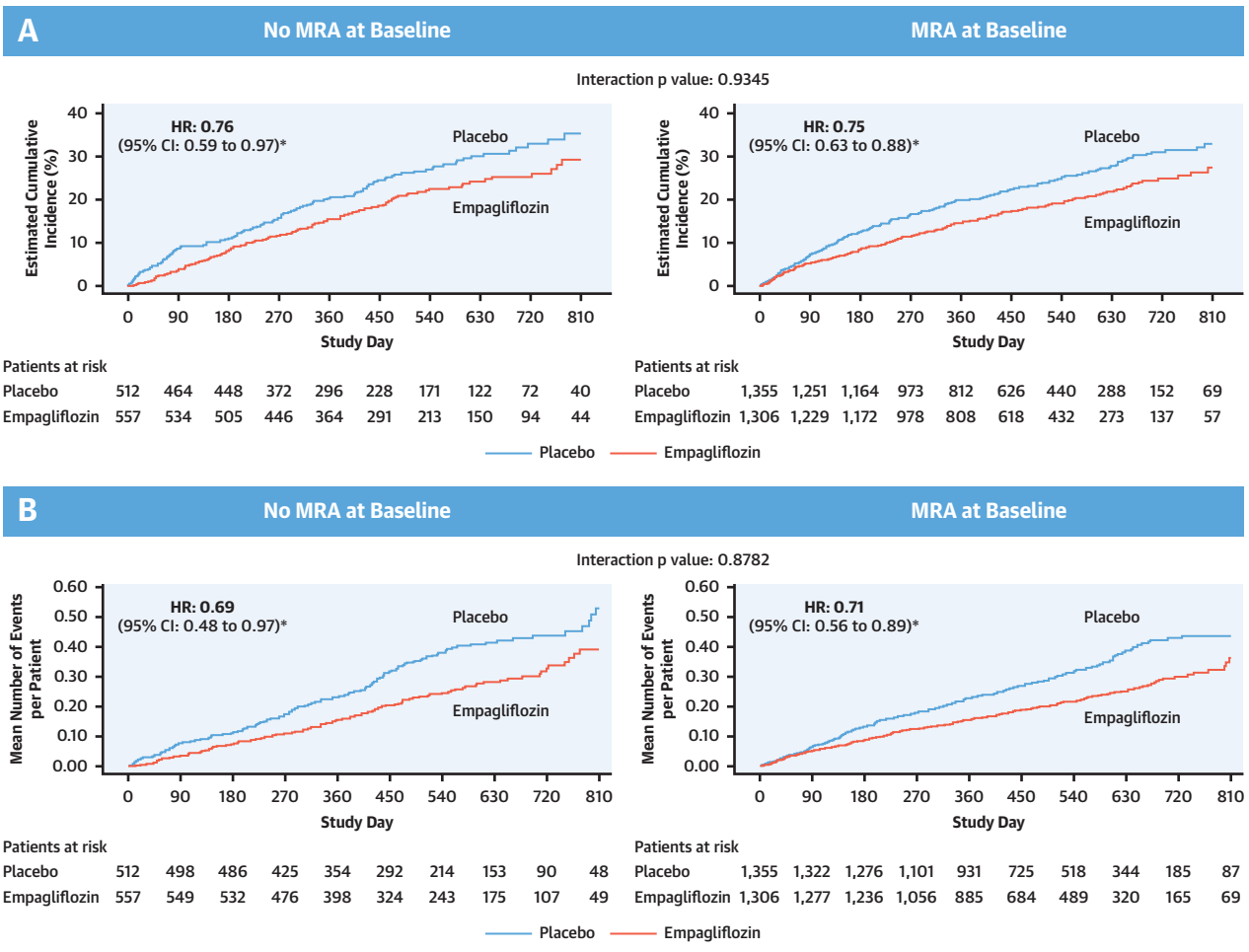
cardiac device for the treatment of heart failure. Other clinical features are shown in Table 1. MRA users were prescribed spironolactone in 2,091 (78.6%) and eplerenone in 570 (21.4%) patients. Of the patients treated with an MRA, 1,355 were randomized to placebo and 1,306 to empagliflozin; of the patients not treated with an MRA, 512 were randomized to placebo and 557 to empagliflozin.

EFFECT OF EMPAGLIFLOZIN ON MEASURES OF EFFICACY ACCORDING TO MRA USE. With respect to heart failure and renal outcomes, when compared with placebo, the effect of empagliflozin was similar regardless of the use of an MRA at baseline (Table 2, Figure 1). The hazard ratios for the effect of empagliflozin on the primary composite outcome of cardiovascular death or hospitalization for heart failure were 0.75 (95% CI: 0.63 to 0.88) and 0.76 (95% CI: 0.59 to 0.97) in MRA users and MRA nonusers, respectively (interaction p = 0.93) (Figure 1). The hazard ratios for the effect of empagliflozin on total hospitalizations for heart failure were 0.71 (95% CI: 0.56 to 0.89) and 0.69 (95% CI: 0.48 to 0.97), respectively (interaction p = 0.88). Additionally, baseline use of an MRA did not influence the effect of empagliflozin on health status (assessed by KCCQ score), New York Heart Association (NYHA) functional class, and the severity of heart failure hospitalizations (i.e., hospitalizations requiring intensive care or receiving treatment with intravenous positive inotropic drugs, vasopressor agents, or mechanical interventions) (Table 2, Supplemental Table 1).

The use of MRAs also did not influence the effect of empagliflozin to retard the worsening of renal function during double-blind therapy. As compared with placebo, empagliflozin slowed the rate of decline in eGFR in both MRA users and nonusers: +1.55 ± 0.39 in MRA users and +2.19 ± 0.59 in MRA nonusers (interaction p = 0.36) (Table 2). The use of MRAs did not influence the effect of empagliflozin on the composite of serious adverse renal outcomes (interaction p = 0.18), although the number of events in MRA nonusers was small (<25 events) (Table 2).

In contrast, for cardiovascular death and all-cause mortality, the hazard ratios for the effect of empagliflozin versus placebo appeared to be directionally different for MRA users and nonusers. The hazard ratio for the effect of empagliflozin was 0.82 (95% CI: 0.65 to 1.05) in MRA users and 1.19 (95% CI: 0.82 to 1.71) in MRA nonusers (interaction p = 0.10). Similarly, for all-cause mortality, the hazard ratios for the effect of empagliflozin versus placebo were 0.84 (95% CI: 0.68 to 1.03) in MRA users and 1.15 (95% CI: 0.84 to 1.59) in MRA nonusers (interaction p = 0.098) (Figure 2, Table 2).

FIGURE 1 Effect of Empagliflozin on Major Heart Failure Endpoints, According to Use of Mineralocorticoid Receptor Antagonist at Baseline



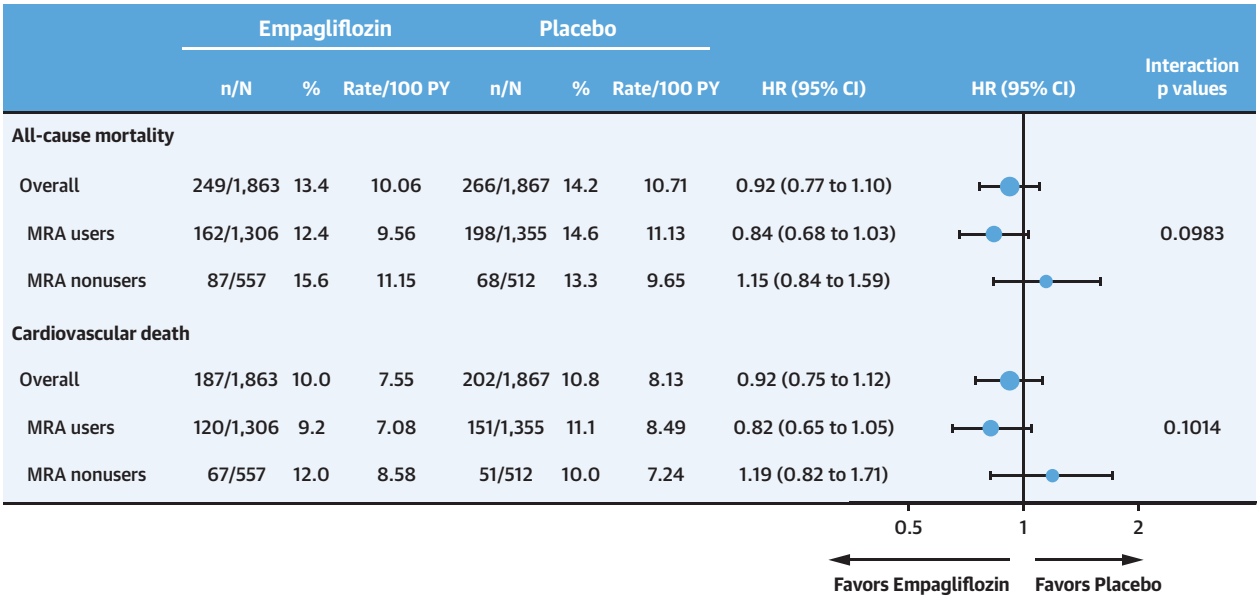
(A) Time-to-first-event analysis of the effect of empagliflozin on cardiovascular death or hospitalizations for heart failure, according to use of mineralocorticoid receptor antagonist at baseline. **(B)** Effect of empagliflozin on total (first and recurrent) hospitalizations for heart failure, according to use of mineralocorticoid-receptor antagonist at baseline using a joint frailty model. *Model includes age, baseline estimated glomerular filtration rate, region, baseline diabetes status, sex, baseline left ventricular ejection fraction, treatment, baseline use of MRA, and treatment by baseline use of MRA interaction. CI = confidence interval; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist.

EFFECT OF EMPAGLIFLOZIN ON UTILIZATION OF MRAs FOLLOWING RANDOMIZATION. Among the 1,069 MRA nonusers at baseline (512 on placebo and 557 on empagliflozin), those randomized to empagliflozin were 35% less likely to be initiated on treatment with an MRA during the follow-up (122 on placebo and 90 on empagliflozin) (hazard ratio: 0.65; 95% CI: 0.49 to 0.85; p = 0.0019). This differential post-randomization utilization was apparent shortly following the initiation of double-blind treatment (**Table 3, Central Illustration**). Conversely, among the 2,661 MRA users at baseline (1,355 in the placebo and 1,306 in the empagliflozin group), those randomized to empagliflozin were less likely to discontinue or interrupt treatment with MRAs during double-blind therapy following randomization (210 in the placebo and 164 in the empagliflozin group) (hazard ratio: 0.78; 95% CI: 0.64 to 0.96; p = 0.018).

INFLUENCE OF MRA ON THE EFFECT OF EMPAGLIFLOZIN ON VITAL SIGNS, BIOMARKERS, AND SAFETY. The effects of empagliflozin on systolic blood pressure, body weight, glycated hemoglobin, uric acid, NT-proBNP, and hematocrit were not influenced by use of MRA at baseline (Supplemental Table 2).

When MRA users and nonusers were combined, the risk of hyperkalemia was lower in the empagliflozin

FIGURE 2 Effect of Empagliflozin on Cardiovascular Death and All-Cause Mortality, According to Use of Mineralocorticoid-Receptor Antagonist at Baseline



The p values and 95% CIs presented in this report have not been adjusted for multiplicity, and therefore, inferences drawn from these statistics may not be reproducible. PY = person-years; other abbreviations as in Figure 1.

than in the placebo group (Table 4). The effect of empagliflozin was particularly noteworthy in preventing the occurrence of severe hyperkalemia (hazard ratio: 0.70; 95% CI: 0.47 to 1.04); however, the effect of empagliflozin on the risk of severe hyperkalemia did not differ in MRA users and nonusers at baseline (interaction p = 0.56). For all other assessments, the use of MRA at baseline did not influence the safety profile of empagliflozin (Supplemental Table 3).

DISCUSSION

In large-scale randomized controlled trials in patients with type 2 diabetes, with chronic kidney disease, and with heart failure and a reduced ejection fraction, SGLT2 inhibitors have had a remarkably consistent effect to reduce the risk of hospitalizations for heart failure and to slow the progression of renal disease (3-9). Most patients in the cardiovascular outcomes trials with type 2 diabetes were not treated with MRAs.

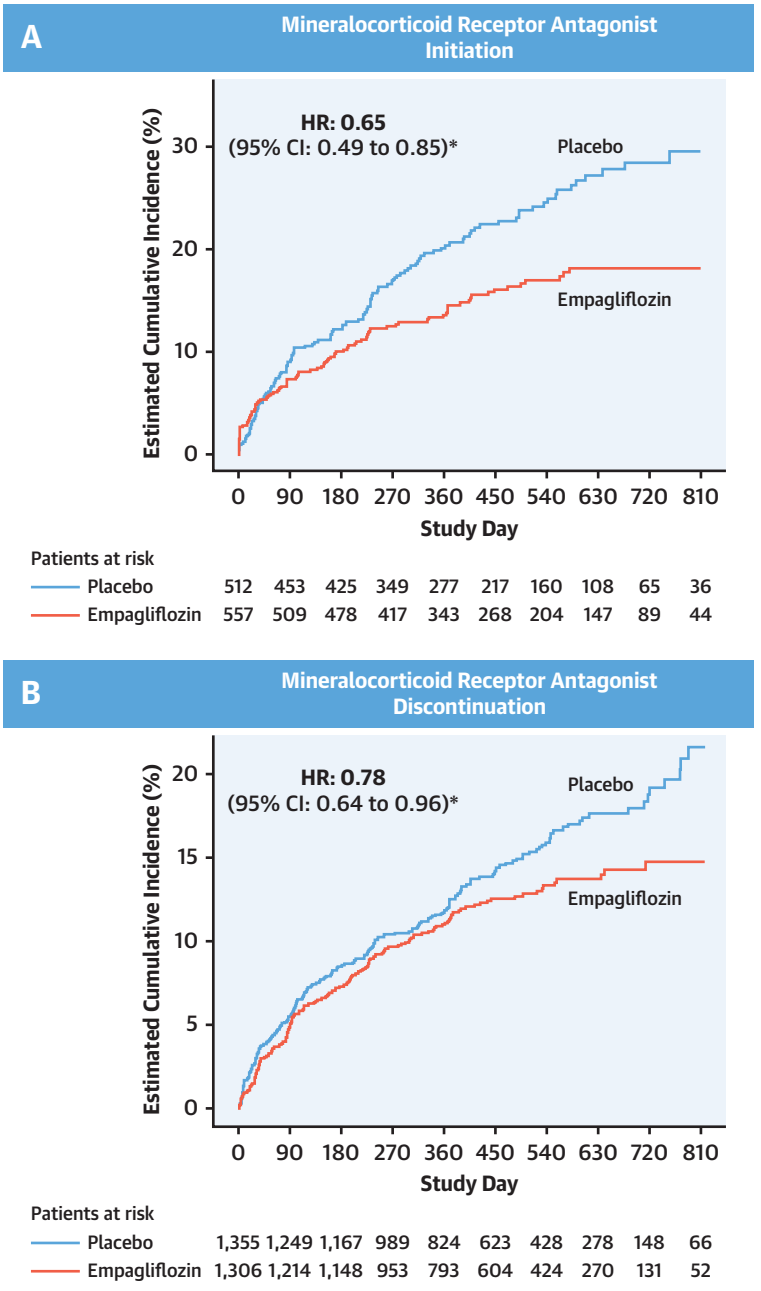
In the original publications of both the DAPA-HF trial and EMPEROR-Reduced, background use of MRAs at baseline did not influence the effect of dapagliflozin and empagliflozin on the primary composite of cardiovascular death or hospitalization for heart failure (3,4). However, more data are needed to assess whether the use of spironolactone or eplerenone might influence the effects of SGLT2 inhibitors on other measures of efficacy or on safety. The current study demonstrates that the use of MRAs at

TABLE 3 Post-Randomization Initiation and Discontinuation of MRAs in the Placebo and Empagliflozin Groups

	Placebo		Empagliflozin			
	n/N (%)	Rate per 100 Patient-Years	n/N (%)	Rate per 100 Patient-Years	HR (95% CI)	p Value
Initiation of MRA in patients not receiving an MRA at baseline	122/512 (23.8)	21.2	90/557 (16.2)	13.2	0.65 (0.49–0.85)	0.0019
Discontinuation or interruption of MRA in patients receiving an MRA at baseline	210/1,355 (15.5)	13.2	164/1,306 (12.6)	10.7	0.78 (0.64–0.96)	0.018

CI = confidence interval; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist.

CENTRAL ILLUSTRATION **Effect of Empagliflozin on the Use of Mineralocorticoid Receptor Antagonists Following Randomization**



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Among MRA nonusers, the empagliflozin group was 35% less likely than the placebo group to initiate treatment with an MRA following randomization. Among MRA users, the empagliflozin group was 22% less likely than the placebo group to discontinue treatment with an MRA following randomization. **(A)** Time to initiation of MRA treatment in patients not using an MRA at baseline. **(B)** Time to discontinuation or temporary interruption of MRA in patients using MRA at baseline. *Model includes age, baseline estimated glomerular filtration rate, region, baseline diabetes status, sex, baseline left ventricular ejection fraction, and treatment. CI = confidence interval; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist.

TABLE 4 Effect of Empagliflozin on the Occurrence of Hyperkalemia

	All Patients					No Use of MRA at Baseline					Use of MRA at Baseline					
	Placebo		Empagliflozin		HR	Placebo		Empagliflozin		HR	Placebo		Empagliflozin		HR	Interaction
	n/N (%)	Rate	n/N (%)	Rate	(95% CI)	n/N (%)	Rate	n/N (%)	Rate	(95% CI)	n/N (%)	Rate	n/N (%)	Rate	(95% CI)	p Value
Serum potassium >5.5 mmol/l*	179/1,750 (10.2)	10.3	164/1,752 (9.4)	9.2	0.89 (0.72–1.09)	53/484 (11.0)	11.0	47/527 (8.9)	8.4	0.79 (0.53–1.17)	126/ 1,266 (10.0)	10.0	117/ 1,225 (9.6)	9.5	0.93 (0.72–1.20)	0.48
Serum potassium >6.0 mmol/l†	57/1,824 (3.1)	3.0	42/1,811 (2.3)	2.2	0.70 (0.47–1.04)	18/501 (3.6)	3.4	17/543 (3.1)	2.8	0.81 (0.42–1.58)	39/1,323 (2.9)	2.8	25/1,268 (2.0)	1.9	0.64 (0.38–1.05)	0.56
Hyperkalemia as adverse event reported by investigator	127/1,863 (6.8)	5.9	109/1,863 (5.9)	5.0	0.82 (0.64–1.06)	32/512 (6.3)	5.3	31/557 (5.6)	4.6	0.87 (0.53–1.42)	95/1,351 (7.0)	6.2	78/1,306 (6.0)	5.2	0.81 (0.60–1.09)	0.82

Rate is expressed as events per 100 person-years. *Analysis performed in patients with potassium level of <5.5 mmol/L at baseline only. †Analysis performed in patients with potassium level of <6.0 mmol/L at baseline only. Shown are adverse events up to 7 days and serum potassium levels up to 3 days following discontinuation of the study medication.

Abbreviations as in Table 3.

randomization did not influence the benefits of empagliflozin to reduce the number or severity of heart failure hospitalizations and to improve health status (as assessed by the KCCQ) or functional capacity (as assessed by NYHA functional class). Furthermore, empagliflozin slowed the decline in glomerular filtration rate and reduced the risk of serious adverse renal outcomes similarly in patients who did or did not receive spironolactone or eplerenone, although the number of adverse renal events in MRA nonusers was small. Finally, the use of MRAs did not modify the effect of empagliflozin on physiological measures or biomarkers that reflect the actions of SGLT2 inhibitors, and MRA use did not adversely affect the safety of the drug when given to patients with heart failure and a reduced ejection fraction.

Nevertheless, empagliflozin had a meaningful influence on the utilization of MRAs following randomization in 2 important ways. First, patients in the empagliflozin group who had not been treated with spironolactone or eplerenone at baseline were 35% less likely to be initiated on an MRA following randomization; that is, among nonusers of an MRA at baseline, 23.8% of placebo-treated patients but only 16.2% of empagliflozin-treated patients were initiated on therapy with an MRA during double-blind follow-up. This differential utilization may have been related to the benefits of empagliflozin on health status and NYHA functional class, which may have diminished clinical pressures (on the part of both the patient and the physician) to intensify treatments with drugs known to be effective for the treatment of heart failure. An initial increase in serum creatinine (related to an effect on intrarenal hemodynamics) in empagliflozin-treated patients may have also discouraged initiation of treatment with an MRA (10). Second, patients in the empagliflozin group who had been treated with spironolactone or eplerenone were 22% less likely to discontinue treatment with these drugs following randomization; that is, among users of an MRA at baseline, 15.5% of placebo-treated patients, but only 12.6% of empagliflozin-treated patients stopped or interrupted treatment with an MRA. This differential utilization may have been related to favorable effects of empagliflozin to mitigate the occurrence of hyperkalemia and to prevent worsening renal function during long-term treatment, because increases in serum creatinine or potassium levels can cause physicians to withhold treatment with MRAs in patients who are receiving these drugs (11–13). Additionally, because hospitalizations are known to trigger changes in background therapy, it is possible that the lower rates of hospitalizations for heart failure in patients randomized to empagliflozin might have contributed to our finding of lower rates of initiation or discontinuation of MRAs in the empagliflozin group.

The potential for an effect of empagliflozin to reduce the risk of hyperkalemia is noteworthy, because a similar finding has been reported with the use of dapagliflozin in the patients with heart failure and a reduced ejection fraction who were enrolled in the DAPA-HF trial (14). In that trial, the effect of SGLT2 inhibition to reduce the risk of serum potassium of >6.0 mmol/l was particularly notable in patients who were treated with an MRA at baseline, with a 50% relative reduction, an effect size that was similar to the 36% reduction in this risk seen in the EMPEROR-Reduced, although the latter was not statistically significant. Of note, SGLT2 inhibitors appeared to have little effect on serum potassium in patients with type 2 diabetes without heart failure,

possibly because few patients in the diabetes trials were receiving MRAs (15). The mechanism by which SGLT2 inhibitors may selectively interfere with MRA-induced hyperkalemia is not known. Interestingly, a similar effect has been reported with the use of sacubitril/valsartan in patients with heart failure and a reduced ejection fraction (16).

Might the effect of empagliflozin to promote differential utilization of MRAs following randomization have confounded the analyses of survival in EMPEROR-Reduced? As seen in **Table 3**, when compared with the empagliflozin group, 32 additional patients in the placebo group who were nonusers of an MRA at baseline were initiated on treatment with an MRA, and the differential enrichment was apparent almost immediately after the start of double-blind therapy. Because MRAs reduce mortality in heart failure with a reduced ejection fraction (1,2), it is likely that lives might have been saved preferentially in the placebo group, contributing to the apparent excess estimate of hazard in empagliflozin-treated patients who were MRA nonusers at randomization. Conversely, when compared with the placebo group, 46 additional patients in the empagliflozin group who were users of an MRA at randomization were maintained on treatment with an MRA, potentially contributing to the lower hazard of death observed in empagliflozin-treated patients who were MRA users at randomization. Therefore, differential post-randomization utilization of MRAs in both MRA users and nonusers may help explain our finding of a possible qualitative interaction between baseline MRA use and the effect of empagliflozin on survival (interaction $p = 0.10$, unadjusted for multiple comparisons). It is important to note that post-randomization differential enrichment is not methodologically accounted for in a conventional intention-to-treat analysis (17,18).

If the differential utilization of MRAs following randomization exerted an influence on estimates of a treatment effect on mortality, it is possible that differences that occurred by chance in the use of MRAs at the time of randomization might also have influenced the estimates of the effect of empagliflozin. EMPEROR-Reduced did not stratify randomization according to the use of MRAs, and by the play of chance, patients prescribed an MRA at baseline were more likely to be randomized to placebo, a difference that involved 49 patients. Conversely, in DAPA-HF, the use of MRAs was (by chance) more frequent in the patients randomized to dapagliflozin than placebo (by 22 patients) (3). Because randomization does not ensure balance of all baseline factors that can influence outcomes, imbalances in treatments that can affect outcomes can affect reported estimates of the size of treatment effects. Accordingly, it is important to adjust for prognostically relevant baseline covariates, and such adjustment (even when performed post hoc) can help reconcile conflicting reports of the efficacy of similar treatments (19).

STUDY STRENGTHS AND LIMITATIONS. The current study should be interpreted in light of its strengths and limitations. The use of an MRA at baseline was included as 1 of 12 pre-specified subgroups, but many of the analyses reported herein are post hoc, as is common in secondary manuscripts following the publication of the primary results of a large-scale trial. Given the exploratory nature of this report, we did not perform correction for multiplicity of tests. Notwithstanding, our finding that the use of an MRA did not influence the effects of empagliflozin on most variables is consistent with similar findings in the DAPA-HF trial (20). However, it is not known if differential enrichment of MRA use following randomization was seen in the DAPA-HF trial. Finally, the clinical impact of the differential use of MRAs at baseline and following randomization is dependent on assumptions about the magnitude of the survival advantage of MRAs and the duration of differential use, and these complexities undermine our ability to estimate the potential for post-randomization bias with a reasonable degree of precision.

CONCLUSIONS

With respect to adverse heart failure and renal outcomes, the use of an MRA did not influence the effects of empagliflozin in patients with heart failure and a reduced ejection fraction. This finding indicates that MRAs and SGLT2 inhibitors can be usefully combined to reduce morbidity and mortality and improve symptoms and health status without concerns of an adverse interaction. The observation that treatment with empagliflozin may influence physician decision making regarding the utilization of MRAs may have important implications for the design and analysis of large-scale trials where background therapy with life-prolonging drugs is not tightly controlled and may confound estimates of a treatment effect of the study medication. In the clinical setting, a favorable symptomatic response to SGLT2 inhibition should not obviate the use of MRAs by practitioners. Furthermore, the possibility that the use of SGLT2 inhibitors may enhance the ability of patients to be maintained on treatment with an MRA provides further support for the value of combining these 2 classes of drugs to improve outcomes in patients with heart failure.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In EMPEROR-Reduced, concomitant administration of empagliflozin with MRAs to patients with heart failure was well tolerated, and MRAs did not modify the effect of empagliflozin on cardiac or renal outcomes.

TRANSLATIONAL OUTLOOK: Elucidating the mechanisms by which empagliflozin exerts beneficial effects in patients with heart failure with or without concomitant MRA therapy requires further study.

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APPENDIX For supplemental tables, please see the online version of this paper.