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ORIGINAL INVESTIGATIONS

Mineralocorticoid Receptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction

João Pedro Ferreira, MD, PhD,[a,b] Javed Butler, MD,[c] Faiez Zannad, MD, PhD,[b] Gerasimos Filippatos, MD, PhD,[d] Elke Schueler, Dipl Math,[e] Dominik Steubl, MD,[f,g] Cordula Zeller, Dipl Math,[h] James L. Januzzi, MD,[i,j,k] Stuart Pocock, PhD,[l] Milton Packer, MD,[m,n] Stefan D. Anker, MD, PhD[o]

ABSTRACT

BACKGROUND Mineralocorticoid receptor antagonists (MRAs) may be beneficial in reducing heart failure (HF) hospitalizations in patients with HF with preserved ejection fraction. The effect of sodium-glucose cotransporter 2 inhibitors in patients with HF with preserved ejection fraction according to MRA background therapy has not been reported.

OBJECTIVES The aim of this study was to examine the effect of empagliflozin in MRA users and nonusers in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial.

METHODS Survival analyses were conducted comparing the effects of empagliflozin vs placebo in MRA users and nonusers at baseline with treatment-by-MRA use interaction terms.

RESULTS A total of 5,988 patients were included, of whom 2,244 (37.5%) were using MRAs at baseline. MRA users had higher event rates than MRA nonusers (placebo group primary outcome 9.4 vs 8.2 events per 100 person-years). The benefit of empagliflozin to reduce the primary outcome was not significantly different between MRA nonusers and MRA users (HR: 0.73 [95% CI: 0.62-0.87] and HR: 0.87 [95% CI: 0.71-1.06]; interaction $P = 0.22$). The effect of empagliflozin to reduce first and recurrent HF hospitalizations was more pronounced in MRA nonusers than in MRA users (HR: 0.60 [95% CI: 0.47-0.77] and HR: 0.90 [95% CI: 0.68-1.19]; interaction $P = 0.038$). MRA users experienced almost twice as many hyperkalemia events as MRA nonusers, and empagliflozin reduced the risk for hyperkalemia or initiation of potassium binders regardless of MRA use (MRA nonusers: HR: 0.90 [95% CI: 0.69-1.19]; MRA users: HR: 0.74 [95% CI: 0.56-0.96]; interaction $P = 0.29$).

CONCLUSIONS The benefit of empagliflozin to reduce the primary outcome was not significantly different between MRA nonusers and MRA users. The effect of empagliflozin to reduce first and recurrent HF hospitalizations was more pronounced in MRA nonusers. Empagliflozin reduced hyperkalemia, with no significant treatment-by-MRA subgroup interaction. (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [EMPEROR-Preserved]; NCT03057951) (J Am Coll Cardiol 2022;79:1129-1137) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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From the [a]Unidade de Investigaçao Cardiovascular, Faculdade de Medicina Universidade do Porto, Porto, Portugal; [b]Centre d'Investigations Cliniques Plurithématique 1433 and Inserm U1116, CHRU, FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Université de Lorraine, Nancy, France; [c]Department of Medicine, University of Mississippi School of Medicine, Jackson, Mississippi, USA; [d]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon,

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR-QoL = health-related quality of life

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

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

NYHA = New York Heart Association

SGLT2 = sodium-glucose cotransporter 2

Mineralocorticoid receptor antagonists (MRAs) reduce heart failure (HF) hospitalizations and mortality in patients with HF with reduced ejection fraction (HFrEF).[1,2] In patients with HF with preserved ejection fraction (HFpEF), the MRA spironolactone had a statistically nonsignificant effect in reducing the composite of cardiovascular mortality or HF hospitalization in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial.[3] Subsequent analysis of TOPCAT showed important geographic variations in patient selection and adherence to treatment, whereby patients enrolled in Russia and Georgia presented neither characteristics nor event rates compatible with HF and often had negligible levels of circulating drug metabolites.[4-6] These geographic differences might have contributed to the lack treatment effect that was seen in patients from Russia and Georgia; however, an 18% reduction in the composite of cardiovascular mortality or HF hospitalization and a 26% reduction in cardiovascular mortality were seen in the remaining patients (ie, those enrolled in the United States, Canada, Brazil, and Argentina).[4] In other subanalyses, patients with ejection fractions <55% in TOPCAT also appeared to benefit from treatment with spironolactone.[7] These findings suggest that spironolactone may improve outcomes in patients with HFpEF, particularly among those with mildly reduced ejection fractions.[7,8] Despite mixed trial results, MRAs remains a commonly used treatment in patients with HFpEF.

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In the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction), the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduced the composite of cardiovascular mortality or HF hospitalization by 21% and first and recurrent HF hospitalizations by 27% on a relative scale, with no significant effect on mortality in patients with HFpEF.[9]

Previous studies of SGLT2 inhibitors in patients with HFrEF suggested that they were effective regardless of MRA therapy and could reduce rates of hyperkalemia and decrease the rate of MRA discontinuation.[10,11] Therefore, it is important to also assess the influence of background MRA use on the efficacy and safety of empagliflozin in patients with HFpEF.

In this prespecified secondary analysis of the EMPEROR-Preserved trial, we examined the influence of MRA use at baseline on the efficacy of empagliflozin and whether empagliflozin influenced the prescribing of MRAs and rates of hyperkalemia following randomization.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The design and primary results of the EMPEROR-Preserved trial have been published previously.[12,13] In brief, the EMPEROR-Preserved trial was a phase III, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial that enrolled adult patients with chronic HF with New York Heart Association (NYHA) functional class II-IV symptoms for at least 3 months and left ventricular ejection fractions (LVEFs) >40% with no prior measurement ≤40% under stable conditions. Patients were required to have elevated N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels (>900 pg/mL and >300 pg/mL in patients with and those without atrial fibrillation, respectively) and evidence of structural heart disease (left ventricular hypertrophy or left atrial size) or documented HF hospitalizations within 12 months. The protocol was

Athens, Greece; [e]mainanalytics, Sulzbach, Germany; [f]Boehringer Ingelheim International, Ingelheim, Germany; [g]Department of Nephrology, Klinikum rechts der Isar, Faculty of Medicine, Technical University Munich, Germany; [h]Boehringer Ingelheim Pharma, Biberach, Germany; [i]Massachusetts General Hospital, Boston, Massachusetts, USA; [j]Harvard Medical School, Boston, Massachusetts, USA; [k]Baim Institute for Clinical Research, Boston, Massachusetts, USA; [l]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, United Kingdom; [m]Baylor University Medical Center, Dallas, Texas, USA; [n]Imperial College, London, United Kingdom; and the [o]Department of Cardiology and Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany.

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approved by the ethics committee of each of the 622 participating sites in 23 countries, and all patients gave written informed consent to participate in the study.

RANDOMIZATION. Patients were randomized in a double-blind manner (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg/d, in addition to their usual therapy. The use of an MRA at baseline was not a stratification variable. Following entry into the trial, all appropriate treatments for HF 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 HF, initiation or discontinuation of new treatments (including MRAs), vital signs and biomarkers reflecting changes in the course of HF or the action of SGLT2 inhibitors, and adverse events.

ENDPOINTS. The primary endpoint was the composite of adjudicated cardiovascular death and hospitalization for HF, analyzed as the time to first event. The first secondary endpoint was the occurrence of all adjudicated hospitalizations for HF (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. Additional analyses included the individual components of the primary endpoint as well as all-cause mortality, health-related quality of life (HR-QoL) as assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), and the initiation and discontinuation of MRAs.

The occurrence of investigator-reported hyperkalemia, serum potassium concentrations of >5.5 and >6.0 mmol/L, and the new initiation of potassium-binding agents (sodium polystyrene sulfonate, calcium polystyrene sulfonate, patiromer, patiromer calcium, zirconium silicate, and sodium zirconium cyclosilicate) was analyzed, overall and according to MRA use.

STATISTICAL ANALYSIS. Baseline characteristics were compared in MRA users and nonusers 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 using a Cox proportional hazards model. For the analysis of total (first and potentially subsequent) events, the differences between the placebo and empagliflozin groups were assessed using a joint frailty model, with cardiovascular death as a competing risk. In KCCQ analyses, the proportions of responders (5-point threshold) at week 52 were compared between treatment groups using a logistic regression model. All analyses included the prespecified baseline covariates of age, sex, geographic region, diabetes, LVEF, and eGFR. To take into account the differences in baseline characteristics between MRA users and nonusers, Cox models with further adjustment on history of HF hospitalization, NYHA functional class, urinary albumin-to-creatinine ratio, use of loop diuretic agents, hemoglobin, sodium, and log NT-proBNP were performed; these variables were retained after applying a stepwise

TABLE 1 Baseline Characteristics of Patients by MRA Use (N = 5,988)

	No MRA (n = 3,744)	MRA[a] (n = 2,244)	*P* Value
Age, y	72.5 ± 9.1	70.9 ± 9.8	<0.0001
Age ≥70 y	2,480 (66.2)	1,358 (60.5)	<0.0001
Women	1,663 (44.4)	1,013 (45.1)	0.59
Region			<0.0001
North America	550 (14.7)	169 (7.5)	
Latin America	912 (24.4)	603 (26.9)	
Europe	1,663 (44.4)	1,026 (45.7)	
Asia	393 (10.5)	293 (13.1)	
Other	226 (6.0)	153 (6.8)	
eGFR, mL/min	60.6 ± 19.8	60.7 ± 19.9	0.93
eGFR <60 mL/min	1,849 (49.4)	1,139 (50.8)	0.31
UACR, mg/g	23.0 (8.0-83.1)	16.8 (7.1-53.9)	<0.0001[b]
Uric acid, mg/dL	6.5 ± 1.9	6.9 ± 2.0	<0.0001
Sodium, mmol/L	141.4 ± 2.8	140.6 ± 3.1	<0.0001
Potassium, mmol/L	4.5 ± 0.5	4.6 ± 0.5	<0.0001
LVEF, %	55.2 ± 8.7	52.8 ± 8.7	<0.0001
LVEF <50%	1,059 (28.3)	924 (41.2)	<0.0001
BMI, kg/m^2	29.8 ± 5.9	29.9 ± 5.9	0.83
Heart rate, beats/min	69.9 ± 11.7	71.1 ± 12.1	0.0002
SBP, mm Hg	133.5 ± 15.4	129.1 ± 15.7	<0.0001
Hemoglobin, g/dL	13.3 ± 1.6	13.3 ± 1.6	0.54
Hypertension	3,433 (91.7)	1,991 (88.7)	0.0001
Diabetes	1,790 (47.8)	1,148 (51.2)	0.012
Atrial fibrillation/flutter[c]	1,933 (51.6)	1,202 (53.6)	0.14
Ischemic HF	1,287 (34.4)	830 (37.0)	0.039
HF duration, y	4.4 ± 5.2	4.3 ± 4.9	0.37
HF hospitalization <12 mo[d]	708 (18.9)	661 (29.5)	<0.0001
NYHA functional class III/IV	625 (16.7)	476 (21.2)	<0.0001
NT-proBNP, pg/mL	927 (486-1,675)	1,051 (522-1,851)	0.029[b]
ACE inhibitors/ARBs	2,966 (79.2)	1,739 (77.5)	0.12
ARNIs	49 (1.3)	85 (3.8)	<0.0001
Beta-blockers	3,196 (85.4)	1,971 (87.8)	0.007
CCBs	1,295 (34.6)	530 (23.6)	<0.0001
Thiazide diuretic agents	942 (25.2)	297 (13.2)	<0.0001
Loop diuretic agents	2,306 (61.6)	1,748 (77.9)	<0.0001

Values are mean ± SD, n (%), or median (IQR). [a]MRAs used at baseline were spironolactone in 83% (n = 1,860), eplerenone in 16% (n = 359), and canrenone, potassium canrenoate, and esaxerenone in the remaining 1%. [b]Based on log-transformed results. [c]Defined as atrial fibrillation or atrial flutter reported on any electrocardiogram before treatment intake or history of atrial fibrillation or atrial flutter reported as medical history. [d]Reported either on HF history and diagnosis or health care resource utilization form.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CCB = calcium-channel blocker; eGFR = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SBP = systolic blood pressure; UACR = urinary albumin-to-creatinine ratio.

TABLE 2 Effect of Empagliflozin on Prespecified Measures of Efficacy, by MRA Use at Baseline

	No MRA					MRA					
	Placebo		Empagliflozin			Placebo		Empagliflozin			
	(n = 1,866)	IR	(n = 1,878)	IR	Treatment Effect	(n = 1,125)	IR	(n = 1,119)	IR	Treatment Effect	Interaction *P* Value
CV death or HF hospitalization	306 (16.4)	8.2	233 (12.4)	6.1	0.73 (0.62-0.87)	205 (18.2)	9.4	182 (16.3)	8.3	0.87 (0.71-1.06)	0.22
Total (first and recurrent) HF hospitalization	308		201		0.60 (0.47-0.77)	233		206		0.90 (0.68-1.19)	0.038
eGFR slope[a]	−2.75 (0.14)		−1.24 (0.14)		1.50 (0.19)	−2.40 (0.22)		−1.27 (0.22)		1.13 (0.25)	0.23
First HF hospitalization	208 (11.1)	5.6	131 (7.0)	3.4	0.60 (0.49-0.75)	144 (12.8)	6.6	128 (11.4)	5.8	0.86 (0.68-1.09)	0.032
Extended endpoint[b]	589 (31.6)	17.8	455 (24.2)	12.9	0.73 (0.64-0.82)	357 (31.7)	18.4	317 (28.3)	15.8	0.85 (0.73-0.99)	0.12
CV death	149 (8.0)	3.7	138 (7.3)	3.4	0.94 (0.74-1.18)	95 (8.4)	4.0	81 (7.2)	3.4	0.86 (0.64-1.16)	0.66
All-cause mortality	257 (13.8)	6.4	251 (13.4)	6.2	0.99 (0.84-1.18)	170 (15.1)	7.1	171 (15.3)	7.3	1.01 (0.82-1.25)	0.91
Increase >5 points in KCCQ CSS from baseline to week 52[c]	882 (47.3)		951 (50.6)		1.14 (1.00-1.32)	514 (45.7)		577 (51.6)		1.27 (1.06-1.52)	0.37
Decrease >5 points in KCCQ CSS from baseline to week 52[c]	596 (31.9)		533 (28.4)		0.84 (0.73-0.98)	363 (32.3)		320 (28.6)		0.84 (0.69-1.02)	0.97

Values are n (%), HR (95% CI), or N, unless otherwise indicated. Cox models included the same terms described for the logistic regression model. We also performed Cox models with further adjustment on history of HF hospitalization, New York Heart Association functional class, urinary albumin-to-creatinine ratio, use of loop diuretic agents, hemoglobin, sodium, and log N-terminal prohormone B-type natriuretic peptide, and the results remained superimposable. [a]Mean slope change from baseline (SE) (mL/min/1.73 m^2 per year). [b]Time to first instance of outpatient diuretic intensification, urgent care or emergency department visit requiring intravenous diuretic therapy, HF hospitalization, or CV death. [c]In KCCQ analyses, the proportions of responders at week 52 were compared between treatment groups using a logistic regression model including terms for age, baseline eGFR, baseline left ventricular ejection fraction, baseline KCCQ score, region, baseline diabetes status, sex, treatment arm, baseline use of MRA, and interaction of treatment and baseline use of MRA. Patients who died before 52 weeks were considered as having deterioration. Missing scores were 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.

CSS = clinical summary score; CV = cardiovascular; IR = incidence rate per 100 person-years (displayed whenever applicable); KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Table 1.

backward selection model including relevant variables with *P* values <0.05 in Table 1 in the model for the primary outcome. For all efficacy measures, subgroup analyses were performed according to the use of MRAs at baseline, and differences in the effect of empagliflozin in users and nonusers were assessed using interaction terms. Further exploratory subgroup analyses were performed according to LVEF and a recent episode of volume overload, defined by either a history of volume overload in the past 4 weeks and/or clinical presentation of volume overload at baseline. *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. All analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

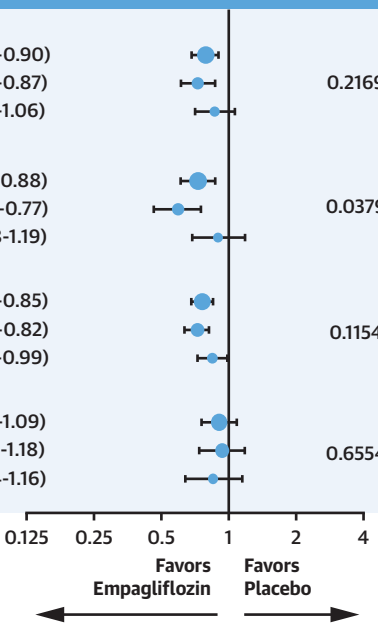
PATIENT CHARACTERISTICS BY MRA USE AT BASELINE. A total of 5,988 patients were included in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), of whom 2,244 (37.5%) were using MRAS. Compared with patients not using MRAs, those on MRA therapy were younger (70.9 years vs 72.5 years), had lower systolic blood pressure (129 mm Hg vs 134 mm Hg), and had lower LVEFs (53% vs 55%), including a higher proportion of patients with LVEFs <50% (41.2% vs 28.3%). MRA users at baseline had also negligibly higher potassium levels (4.6 mmol/L vs 4.5 mmol/L) and a higher frequency of diabetes (51.2% vs 47.8%). Previous HF hospitalizations within the past 12 months (29.5% vs 18.9%), NYHA functional class III-IV (21.2% vs. 16.7%), and treatment with loop diuretic agents (77.9% vs 61.6%) were also more frequent among MRA users, along with lower proportions of patients treated with thiazides (13.2% vs 25.2%) and calcium-channel blockers (23.6% vs 34.6%). The median NT-proBNP concentration was higher among MRA users (1,051 pg/mL vs 927 pg/mL), but the mean eGFR was similar between MRA users and nonusers (61 mL/min/1.73 m^2 in both groups) (Table 1).

EVENTS AND THE EFFECT OF EMPAGLIFLOZIN IN MRA USERS AND NONUSERS. Among placebo-treated patients, MRA nonusers had lower event rates than MRA users (primary composite outcome 8.2 vs 9.4, first HF hospitalization 5.6 vs 6.6, cardiovascular death 3.7 vs 4.0, and all-cause mortality 6.4 vs 7.1 events per 100 person-years) (Table 2).

The benefit of empagliflozin to reduce the primary outcome was not significantly different between MRA nonusers and MRA users (HR: 0.73 [95% CI: 0.62-0.87] in MRA nonusers; HR: 0.87 [95% CI: 0.71-1.06] in MRA users; interaction *P* = 0.22). The benefit of empagliflozin to reduce an extended endpoint that added

CENTRAL ILLUSTRATION **Effect of Empagliflozin Efficacy Outcomes by Mineralocorticoid Receptor Antagonist Use at Baseline**

	Empagliflozin		Placebo				
	n With Event/ N Analyzed (%)	Rate Per 100 Patient-Years	n With Event/ N Analyzed (%)	Rate Per 100 Patient-Years	HR (95% CI)	HR (95% CI)	Interaction *P* Value
Primary outcome							
Overall	415/2,997 (13.8)	6.86	511/2,991 (17.1)	8.67	0.79 (0.69-0.90)		
No MRA	233/1,878 (12.4)	6.05	306/1,866 (16.4)	8.23	0.73 (0.62-0.87)		0.2169
MRA	182/1,119 (16.3)	8.29	205/1,125 (18.2)	9.44	0.87 (0.71-1.06)		
Total HF hospitalization							
Overall	407	-	541	-	0.73 (0.61-0.88)		
No MRA	201	-	308	-	0.60 (0.47-0.77)		0.0379
MRA	206	-	233	-	0.90 (0.68-1.19)		
Extended endpoint							
Overall	772/2,997 (25.8)	13.98	946/2,991 (31.6)	18.04	0.77 (0.70-0.85)		
No MRA	455/1,878 (24.2)	12.95	589/1,866 (31.6)	17.83	0.73 (0.64-0.82)		0.1154
MRA	317/1,119 (28.3)	15.79	357/1,125 (31.7)	18.39	0.85 (0.73-0.99)		
Cardiovascular death							
Overall	219/2,997 (7.3)	3.42	244/2,991 (8.2)	3.81	0.91 (0.76-1.09)		
No MRA	138/1,878 (7.3)	3.41	149/1,866 (8.0)	3.71	0.94 (0.74-1.18)		0.6554
MRA	81/1,119 (7.2)	3.44	95/1,125 (8.4)	3.99	0.86 (0.64-1.16)		



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The primary outcome was a composite of first hospitalization for heart failure (HF) or cardiovascular death. The extended endpoint included the first instance of outpatient diuretic intensification, urgent care or emergency department visit requiring intravenous diuretic therapy, HF hospitalization, or cardiovascular death. Models included terms for age, baseline estimated glomerular filtration rate, baseline left ventricular ejection fraction, region, baseline diabetes status, sex, treatment arm, baseline use of mineralocorticoid receptor antagonist (MRA), and interaction of treatment and baseline use of MRA.

outpatient worsening HF episodes and intravenous diuretic use to the primary outcome was not significantly different between MRA nonusers and MRA users (HR: 0.73 [95% CI: 0.64-0.82] in MRA nonusers; HR: 0.85 [95% CI: 0.73-0.99] in MRA users; interaction $P = 0.12$).

The effect of empagliflozin to reduce HF hospitalizations was more pronounced in MRA nonusers than in MRA users. For first and recurrent HF hospitalizations, the HRs were 0.60 (95% CI: 0.47-0.77) in MRA nonusers and 0.90 (95% CI: 0.68-1.19) in MRA users (interaction $P = 0.038$). For first HF hospitalization, the HRs were 0.60 (95% CI: 0.49-0.75) in MRA nonusers and 0.86 (95% CI: 0.68-1.09) in MRA users (interaction $P = 0.032$). The nonsignificant effect of empagliflozin on cardiovascular death was not modified by MRA use at baseline (HR: 0.94 [95% CI: 0.74-1.18] in MRA nonusers; HR: 0.86 [95% CI: 0.64-1.16] in MRA users) (**Table 2, Central Illustration**). Further adjustment on history of HF hospitalization, NYHA functional class, urinary albumin-to-creatinine ratio, use of loop diuretic agents, hemoglobin, sodium, and log NT-proBNP did not significantly change the results.

In a supplemental analysis according to LVEF subgroup, the differences in treatment effect between MRA users and nonusers were seen mainly in the subgroup of patients with LVEFs ≥50%, with an effect of similar direction and magnitude between MRA users and nonusers among patients with LVEFs between 41% and 49%. In patients with LVEFs between 41% and 49%, the HRs for empagliflozin vs placebo for the primary outcome were 0.69 (95% CI: 0.50-0.94) in MRA nonusers and 0.74 (95% CI: 0.55-1.00) in MRA users (interaction $P = 0.73$), and the HRs for first and recurrent HF hospitalizations were 0.50 (95% CI: 0.31-0.82) in MRA nonusers and 0.60 (95% CI: 0.38-0.96) in MRA users (interaction $P = 0.60$). In patients with LVEFs ≥50%, the HRs for empagliflozin vs placebo for the primary outcome

TABLE 3 Postrandomization Initiation and Discontinuation of MRAs

	Placebo		Empagliflozin			
	n/N (%)	IR	n/N (%)	IR	HR (95% CI)	*P* Value
New MRA initiation	270/1,866 (14.5)	7.6	241/1,878 (12.8)	6.6	0.88 (0.74-1.04)	0.14
MRA discontinuation[a]	251/1,125 (22.3)	12.7	226/1,119 (20.2)	11.2	0.87 (0.73-1.04)	0.12

Cox models included terms for age, baseline estimated glomerular filtration rate, baseline left ventricular ejection fraction, region, baseline diabetes status, sex, and treatment arm. [a]Permanent or temporary discontinuation.

Abbreviations as in Tables 1 and 2.

were 0.75 (95% CI: 0.61-0.92) in MRA nonusers and 0.99 (95% CI: 0.75-1.29) in MRA users (interaction $P = 0.12$), and the HRs for first and recurrent HF hospitalizations were 0.64 (95% CI: 0.48-0.85) in MRA nonusers and 1.19 (95% CI: 0.83-1.71) in MRA users (interaction $P = 0.009$) (Supplemental Table 1).

In another supplemental analysis according to volume overload status, the differences in treatment effect between MRA users and nonusers were seen mainly in the subgroup of patients with volume overload, in whom the effect of empagliflozin to reduce first and recurrent HF hospitalizations was more pronounced among MRA nonusers than in MRA users (HR: 0.60 [95% CI: 0.43-0.86] in MRA nonusers; HR: 1.04 [95% CI: 0.69-1.56] in MRA users; interaction $P = 0.046$). No significant treatment-by-MRA therapy interaction was observed for the primary outcome (interaction $P = 0.53$) and first HF hospitalization (interaction $P = 0.11$). No significant treatment effect heterogeneity was observed for any outcome in patients without volume overload (Supplemental Table 2).

The reduction of the decline in eGFR as measured by the slope favored empagliflozin, without significant differences between MRA nonusers and MRA users (+1.5 mL/min/1.73 m^2 in MRA nonusers and +1.1 mL/min/1.73 m^2 in MRA users; interaction $P = 0.23$) (Table 2).

The improvement of KCCQ clinical summary score >5 points at week 52 with empagliflozin was not significantly different between MRA nonusers and MRA users (OR: 1.14 [95% 1.00-1.32] in MRA nonusers; OR: 1.27 [95% CI: 1.06-1.52] in MRA users; interaction $P = 0.37$) (Table 2).

POSTRANDOMIZATION MRA INITIATION AND DISCONTINUATION. Randomization to empagliflozin did not significantly modify the initiation or discontinuation of MRAs throughout the follow-up period (HR: 0.88 [95% CI: 0.74-1.04; $P = 0.14$] for MRA initiation; HR: 0.87 [95% CI: 0.73-1.04; $P = 0.12$] for MRA discontinuation) (Table 3).

EFFECT OF EMPAGLIFLOZIN ON HYPERKALEMIA AND USE OF POTASSIUM BINDERS. MRA users experienced almost twice as many hyperkalemia events as MRA nonusers. Empagliflozin reduced the incidence of hyperkalemia or initiation of potassium binders regardless of the hyperkalemia definition: 1) new potassium-binder use or investigator-reported hyperkalemia (HR: 0.90 [95% CI: 0.69-1.19] in MRA nonusers; HR: 0.74 [95% CI: 0.56-0.96] in MRA users; interaction $P = 0.29$); 2) serum potassium >5.5 mmol/L or new use of potassium binders (HR: 0.91 [95% CI: 0.72-1.15] in MRA nonusers; HR: 0.69 [95% CI: 0.54-0.88] in MRA users; interaction $P = 0.10$); or 3) serum potassium >6.0 mmol/L or new use of potassium binders (HR: 0.68 [95% CI: 0.47-1.00] in MRA nonusers; HR: 0.61 [95% CI: 0.40-0.93] in MRA users; interaction $P = 0.71$) (Figure 1).

The effect of empagliflozin to reduce hyperkalemia was consistent using the individual components of the aforementioned composite outcomes (Supplemental Table 3).

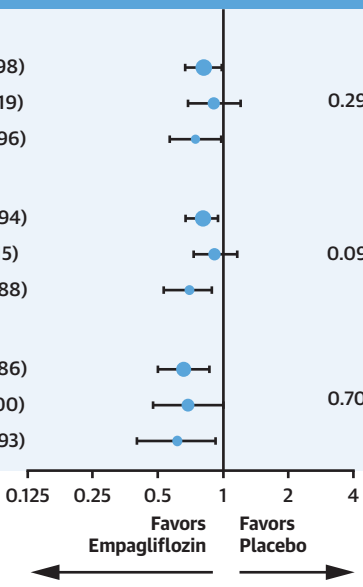
DISCUSSION

In the present analysis of the EMPEROR-Preserved trial, MRAs were used in 37% of study participants. MRA use was higher in those with a more congested clinical picture, with more hospitalizations for HF within the past 12 months, worse HF symptoms, mildly reduced ejection fractions, higher NT-proBNP levels, and more use of loop diuretic agents. These findings indicate more advanced HF presentation among MRA users, which is supported by the higher placebo event rates seen in this subgroup. Empagliflozin reduced the primary composite outcome, reduced the decline in eGFR as measured by the slope and improved HR-QoL, with no significant treatment-by-MRA subgroup interaction. However, the effect of empagliflozin to reduce HF hospitalizations was more pronounced in MRA nonusers than in MRA users, particularly in the subgroup of patients with LVEFs ≥50%. Importantly, MRA users had higher rates of hyperkalemia compared with MRA nonusers, but empagliflozin reduced hyperkalemia events and the use of potassium-binding agents.

In patients with HFrEF, MRAs are recommended to reduce HF hospitalizations and mortality.[1,2] In

FIGURE 1 Effect of Empagliflozin on Hyperkalemia Events by MRA Use at Baseline

	Empagliflozin		Placebo				
	n With Event/ N Analyzed (%)	Rate Per 100 Patient-Years	n With Event/ N Analyzed (%)	Rate Per 100 Patient-Years	HR (95% CI)	HR (95% CI)	Interaction *P* Value
Initiation of potassium binders or investigator-defined hyperkalemia*							
Overall	195/2,986 (6.5)	3.61	235/2,980 (7.9)	4.41	0.81 (0.67-0.98)		
No MRA	101/1,870 (5.4)	2.94	107/1,857 (5.8)	3.21	0.90 (0.69-1.19)		0.2905
MRA	94/1,116 (8.4)	4.76	128/1,123 (11.4)	6.43	0.74 (0.56-0.96)		
Initiation of potassium binders or potassium >5.5 mmol/L†							
Overall	251/2,860 (8.8)	5.29	303/2,864 (10.6)	6.49	0.80 (0.67-0.94)		
No MRA	138/1,800 (7.7)	4.54	146/1,799 (8.1)	4.92	0.91 (0.72-1.15)		0.0984
MRA	113/1,060 (10.7)	6.65	157/1,065 (14.7)	9.23	0.69 (0.54-0.88)		
Initiation of potassium binders or potassium >6.0 mmol/L‡							
Overall	81/2,919 (2.8)	1.61	121/2,928 (4.1)	2.41	0.65 (0.49-0.86)		
No MRA	46/1,834 (2.5)	1.44	63/1,829 (3.4)	2.02	0.68 (0.47-1.00)		0.7098
MRA	35/1,085 (3.2)	1.92	58/1,099 (5.3)	3.06	0.61 (0.40-0.93)		



The Cox model includes terms for age, sex, baseline estimated glomerular filtration rate, baseline left ventricular ejection fraction, region, diabetes status, and randomized treatment (empagliflozin or placebo) and for the subgroup analyses additionally baseline use of mineralocorticoid receptor antagonist (MRA) and treatment-by-MRA interaction. Considered potassium-binding drugs were sodium polystyrene sulfonate, calcium polystyrene sulfonate, patiromer, patiromer (sorbitex) calcium, zirconium silicate, and sodium zirconium cyclosilicate. *Only patients without the use of potassium binders at baseline are considered. †Analysis performed in patients with potassium levels <5.5 mmol/L and without the use of potassium binders at baseline only. ‡Analysis performed in patients with potassium levels <6.0 mmol/L and without the use of potassium binders 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.

contrast, in patients with HFpEF, MRAs have weaker evidence. In the TOPCAT trial, the only large trial performed in this population to date, spironolactone did not reduce the primary composite outcome of first HF hospitalization or cardiovascular death in the overall analysis, but this result was confounded by marked regional differences.[4,5] These differences in the strength of evidence for MRA use between HFrEF and HFpEF were reflected in the EMPEROR program; in EMPEROR-Reduced, more than 70% of patients were using MRAs at baseline,[10] whereas in EMPEROR-Preserved, an MRA was used in <40% of patients, typically in the patients who had the most advanced HF presentation.

Empagliflozin reduced the primary outcome and outpatient worsening HF or intravenous diuretic use added to the primary outcome, slowed the eGFR decline, and improved HR-QoL without a significant treatment-by-MRA interaction. However, the effect of empagliflozin to reduce HF hospitalizations (first and recurrent) was more pronounced in MRA nonusers than in MRA users. The differences in symptom severity, natriuretic peptide levels, recent HF hospitalization, NYHA functional class, loop diuretic use, and volume overload between MRA users and nonusers suggest that MRA users were more congestive, which may have influenced the observed treatment effect differences between MRA users and nonusers. Although it is possible to hypothesize that MRA and empagliflozin might have limited additive effects, this seems unlikely, as empagliflozin reduced major HF outcomes in the EMPEROR-Reduced trial, in which >70% of patients were using MRAs at baseline, and the effect appeared to be more pronounced among MRA users.[10] Still, it should be noted that in EMPEROR-Preserved, the difference in treatment effect in total HF hospitalizations between MRA users and nonusers was seen particularly in the subgroup of patients with LVEFs ≥50%, but not among those with LVEFs between 41% and 49% in whom the treatment effect was more homogeneous. Of note, secondary analysis from TOPCAT suggested that the effect of

spironolactone was attenuated in patients with LVEFs >50%-55%.[7]

Randomization to empagliflozin was accompanied by a modest and statistically nonsignificant reduction in MRA discontinuation or initiation throughout the follow-up, findings that were directionally concordant with those of EMPEROR-Reduced, in which patients were less likely to discontinue or initiate MRAs throughout the follow-up period.[10] The lower rate of postrandomization MRA initiation may be related to the improved clinical stability of patients randomized to empagliflozin, with less outpatient treatment intensifications and fewer hospital visits.[14,15]

The effect of empagliflozin to reduce hyperkalemia was statistically significant and clinically important. In EMPEROR-Preserved, the new use of potassium binder or investigator-reported hyperkalemia and serum potassium >5.5 mmol/L or serum potassium >6.0 mmol/L were all reduced with empagliflozin treatment (vs placebo) by 20%-35%. MRA users experienced higher rates of hyperkalemia, particularly when defined by serum potassium >5.5 mmol/L, and the effect of empagliflozin to prevent hyperkalemia was particularly notable among MRA users. These findings were concordant with, albeit more pronounced than, those of EMPEROR-Reduced and DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), in which empagliflozin and dapagliflozin reduced the incidence of hyperkalemia, particularly among MRA users.[10,11] Furthermore, in the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) trial, enrolling patients with type 2 diabetes and chronic kidney disease, the SGLT2 inhibitor canagliflozin reduced hyperkalemia rates by 20%-25% using a wide range of hyperkalemia definitions.[16] Thus, the effect of SGLT2 inhibitors to mitigate hyperkalemia has been noted in several independent studies, with different agents, and across different patient populations, thus supporting a true effect of this drug class to prevent clinically meaningful hyperkalemia. Thus, although SGLT2 inhibitors may modestly lower eGFR after their initiation, aggregate results from numerous trials suggest that clinicians should not withhold these agents merely because of concerns about hyperkalemia; in fact, SGLT2 inhibitors may prevent hyperkalemia, which may enable the use of MRAs in patients with HFpEF.

STUDY LIMITATIONS. This was a secondary analysis of a randomized trial studying subgroups of patients in whom the decision to use MRAs was determined by the prescribing practitioners and was not randomized; as consequence, the characteristics of MRA users and nonusers differ in many important aspects. Moreover, our *P* values are nominal and have not been corrected for multiplicity of comparisons, and our findings should be considered exploratory. The analyses of ejection fraction and volume overload subgroups are even more limited because of the small number of MRA users within subgroups, and these findings should be interpreted with caution.

CONCLUSIONS

The benefit of empagliflozin to reduce the primary outcome was not significantly different between MRA nonusers and MRA users. The effect of empagliflozin to reduce first and recurrent HF hospitalizations was more pronounced in MRA nonusers. Empagliflozin reduced hyperkalemia, with no significant treatment-by-MRA subgroup interaction.

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ADDRESS FOR CORRESPONDENCE: Prof João Pedro Ferreira, Unidade de Investigaçao Cardiovascular, Faculdade de Medicina Universidade do Porto, Alameda Prof Hernâni Monteiro, 4200-319 Porto, Portugal. E-mail: jpferreira@med.up.pt. Twitter: @unic_cardiovasc.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with HFpEF, treatment with empagliflozin improves clinical outcomes regardless of background mineralocorticoid receptor antagonist therapy.

TRANSLATIONAL OUTLOOK:

Further studies are needed to determine the optimal sequence of initiation and intensity of SGLT2 inhibitor treatment in the course of guideline-directed medical therapy for patients with HFpEF.

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