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**Mineralocorticoid receptor antagonist use and the effects of empagliflozin on clinical outcomes in patients admitted for acute heart failure: findings from EMPULSE**

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## **Abstract**

*Background:* In patients hospitalized for acute heart failure (AHF) empagliflozin produced greater clinical benefit than placebo. Many patients with AHF are treated with mineralocorticoid receptor antagonists (MRAs). The interplay between empagliflozin and MRAs in AHF is yet to be explored.

*Aims:* To study the efficacy and safety of empagliflozin versus placebo according to MRA use at baseline in the EMPULSE trial (NCT04157751).

*Methods:* In this analysis all comparisons were performed between empagliflozin and placebo, stratified by baseline MRA use. The primary outcome included all-cause death, HF events, and a  $\geq 5$  point difference in KCCQ-TSS at 90 days, assessed using the win ratio (WR). First HF hospitalization or cardiovascular death was a secondary outcome.

*Results:* From the 530 patients randomized, 276 (52%) were receiving MRA at baseline. MRA users were younger, had lower ejection fraction, better renal function, and higher KCCQ scores. The primary outcome showed benefit of empagliflozin irrespective of baseline MRA use (WR=1.46, 95%CI=1.08-1.97 and WR=1.27, 95%CI=0.93-1.73 in MRA users and non-users, respectively; interactionP=0.52). The effect of empagliflozin on first HF hospitalization or cardiovascular death was not modified by MRA use (HR=0.58, 95%CI=0.30-1.11 and HR=0.85, 95%CI=0.47-1.52 in MRA users and non-users, respectively; interactionP=0.39). Investigator-reported and severe hyperkalemia events were infrequent (<6%) irrespective of MRA use.

*Conclusions:* In patients admitted for AHF, initiation of empagliflozin produced clinical benefit and was well tolerated irrespective of background MRA use. These

findings support the early use of empagliflozin on top of MRA therapy in patients admitted for AHF.

*Key-words:* Empagliflozin; Acute Heart Failure; Mineralocorticoid Receptor Antagonists.

## **Introduction**

Mineralocorticoid receptor antagonists (MRAs) reduce heart failure (HF) hospitalizations and mortality in patients with chronic heart failure and a reduced ejection fraction (HFrEF),<sup>1,2</sup> and may reduce HF hospitalizations in selected patients with chronic heart failure and a preserved ejection fraction (HFpEF).<sup>3,4</sup> Therefore, MRAs are frequently used in patients admitted for decompensated heart failure.

In chronic HF, the beneficial effects of sodium glucose co-transporter 2 inhibitors (SGLT2i) on clinical outcomes appear to be independent from background use of MRAs.<sup>5-7</sup> Moreover, SGLT2i may limit the risk of significant hyperkalemia in HF patients using MRAs which may facilitate the implementation and continuation of MRA therapy.<sup>8</sup>

In EMPULSE (A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure; NCT04157751), empagliflozin produced greater clinical benefit than placebo when initiated in patients hospitalized for AHF.<sup>9</sup>

However, the interplay between SGLT2i and MRAs in AHF has not been reported yet. Using the EMPULSE data, we aim to study the patient characteristics related to background MRA use and assess the efficacy and safety of empagliflozin (vs. placebo) according to MRA use at baseline.

## **Methods**

### **Study design**

EMPULSE was a multinational, multicentre, randomized, double-blind trial designed to evaluate the effects of oral empagliflozin compared to placebo on clinical benefit, safety, and tolerability in AHF. In the study, patients admitted to the hospital for AHF

after initial stabilization (between 24 h and 5 days after admission) were randomized 1:1 to receive either empagliflozin (10 mg once daily) or placebo for 90 days. The detailed description of the study design as well as results of the main study have been published elsewhere.<sup>9,10</sup> In brief, to be eligible to enter the study patients had to be admitted to the hospital with the primary diagnosis of AHF and treated with a minimum dose of 40 mg of intravenous (IV) furosemide (20 mg for Japanese patients) or equivalent. Key exclusion criteria were AHF primarily triggered by pulmonary embolism, cerebrovascular accident, acute myocardial infarction, type 1 diabetes mellitus, treatment with SGLT1 or SGLT2 inhibitors in the 90 days prior to randomization and an estimated glomerular filtration rate (eGFR) <20 ml/min/1.73m<sup>2</sup> or dialysis requirement. During the hospitalization the eligible patients were randomized into the study after initial stabilization (between 24h and day 5 from admission) defined by a systolic blood pressure ≥100mmHg with no symptoms of hypotension, no increase in IV diuretic dose and no intravenous vasodilators and/or inotropic drugs.

The primary outcome was defined as clinical benefit in a hierarchical composite including time to all-cause death, number of HF events, time to first HF event, and a ≥5 point difference in change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at 90 days, assessed using the win ratio (WR) method.<sup>9</sup>

The study fulfilled the requirements stated in the Declaration of Helsinki and was independently approved by the ethics committees at each participating centre; written informed consent was obtained from each participant. Boehringer Ingelheim and Eli Lilly sponsored the trial.



## **Endpoints**

In this non-prespecified post-hoc analysis, we studied our original primary hierarchical composite outcome of death from any cause, number of HF events and time to first HF event, and a 5 point or greater difference in change from baseline in the KCCQ-TSS at 90 days using the win ratio method. In addition, we studied 1) the individual components of the primary outcome, 2) a composite of cardiovascular death or HF event, 3) total HF hospitalizations, 4) all-cause hospitalizations, and 5) a clinical congestion score calculated as a sum of the points (on a 0 to 3 scale) for dyspnea, orthopnea and fatigue. We reported the changes over time in systolic blood pressure (SBP), body weight, hemoglobin, uric acid, NT-pro BNP, sodium, potassium, and eGFR. The incidence of hyperkalemia, hypokalemia, adverse events of interest, and MRA initiation and discontinuation were also reported. All comparisons were performed between empagliflozin and placebo, stratified by baseline MRA use.

## **Statistical analyses**

Patient characteristics were described using numbers and proportions, means and standard deviations, or medians and 25-75<sup>th</sup> percentile, as appropriate, and compared between MRA users and non-users at baseline. To evaluate treatment effects on the primary hierarchical composite endpoint of clinical benefit in MRA subgroups, we compared empagliflozin vs. placebo among MRA users and non-users at baseline with the win ratio method. Time-to-first event analyses were performed using Cox proportional hazards models. Total HF hospitalizations were evaluated with a negative binomial model. Adverse events were assessed using descriptive methods. Serially measured variables (measured at randomization, day 15, 30 and 90) were studied using mixed effects models for repeated measures

(MMRM). All models (not including the win ratio) incorporated AHF status ("de novo" vs. "chronic decompensated"), and baseline MRA use (yes vs. no) as covariates along with a treatment-by-baseline MRA use interaction term. All analyses were performed with SAS software, version 9.4 or higher (SAS Institute). P-values <0.05 were considered statistically significant and were not adjusted for multiple comparisons given the exploratory nature of this report.

## **Results**

### **Patient characteristics by baseline MRA use**

From the 530 patients randomized in EMPULSE, 276 (52%) were using MRA at baseline (mostly spironolactone 25 mg/day) and 254 (48%) were not. Baseline MRA users were younger, more frequently from Europe, had longer HF duration, lower blood pressure, lower ejection fraction, had more frequent HF of ischemic etiology, better renal function, higher KCCQ scores (i.e., better health status), and were more frequently treated with ACEi/ARB/ARNi and beta-blockers. Serum potassium levels were similar between MRA users and non-users (**Table 1**).

### **Outcomes by MRA use**

The primary hierarchical composite outcome showed benefit of empagliflozin over placebo irrespective of baseline MRA use: WR 1.46, 95% CI 1.08, 1.97 in MRA users and WR 1.27, 95% CI 0.93, 1.73 in MRA non-users, interaction P=0.52. The composite outcome of cardiovascular death or HF hospitalization, total HF hospitalizations, and all-cause mortality occurred less frequently with empagliflozin than with placebo regardless of baseline MRA use, health status and the clinical congestion score improved more with empagliflozin than with placebo irrespective of

baseline MRA use (interaction  $P > 0.1$  for all). The effect of empagliflozin on all-cause hospitalizations did not significantly differ by baseline MRA use: HR 0.61, 95% CI 0.37, 1.02 in MRA users and HR 0.98, 95% CI 0.62, 1.54 in MRA non-users, interaction  $P = 0.17$  (**Table 2**).

### **Changes in vital signs and biomarkers by baseline MRA use**

Changes in body weight, hemoglobin, uric acid, NT-pro BNP, and sodium were similar irrespective of baseline MRA use (interaction  $P > 0.1$  for all). (**Table 3**).

Changes over time in serum potassium, eGFR, and SBP also did not differ significantly according to baseline MRA use (**Figure 1**).

### **Adverse events by baseline MRA use**

Empagliflozin had a favourable safety profile regardless of baseline MRA use.

Investigator-reported and severe hyperkalemia were infrequent ( $< 6\%$ ) and did not differ by MRA use at baseline. All adverse event  $P$ -values for treatment-by-baseline MRA use interaction were statistically non-significant at the 5% level. (**Table 4**).

### **Initiation and discontinuation of MRA therapy throughout the trial**

At baseline, more patients in the empagliflozin-treated group were receiving a MRA: empagliflozin  $n/N = 151/265$  (57.0%); placebo  $n/N = 125/265$  (47.2%),  $P = 0.024$ . A MRA was initiated on a “de novo” basis during index hospitalization in 24 placebo (17.1% of previously untreated patients) and in 19 empagliflozin (16.7% of previously untreated patients) treated patients. In patients with in-hospital MRA initiation, serum potassium increased by 0.6 mmol/L from baseline and up to day 90 with small (0.1-0.2 mmol/L) absolute differences between placebo and empagliflozin groups.

**Supplementary Table 1.** At 90-days, 152 (57.4%) patients in the placebo group and 168 (63.4%) patients in the empagliflozin group were receiving an MRA.

## Discussion

This post-hoc analysis from the EMPULSE trial demonstrated differences between baseline MRA users and non-users with the former being younger, having better renal function and a more severely depressed ejection fraction with HF of ischemic etiology. Despite these differences, empagliflozin was similarly beneficial in patients with and without background MRA use. No major differences between empagliflozin and placebo were observed in post-baseline serum potassium, eGFR, blood pressure or adverse events according to baseline MRA use. Collective in-hospital initiation of both MRA and empagliflozin did not lead to clinically meaningful potassium changes compared to MRA and placebo initiation. Despite being based on a small subgroup of 43 patients, these findings support the concomitant initiation of MRA and empagliflozin while in-hospital, expanding on the STRONG-HF (safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure) trial, which was performed prior to the routine use of SGLT2i for HF treatment.<sup>11</sup> Together, these findings suggest that empagliflozin is beneficial and well tolerated on top of MRA therapy.

Data on MRA initiation and discontinuation over the 90-day follow-up did not show significant differences between empagliflozin and placebo groups. In the EMPEROR-Reduced and EMPEROR-Preserved trials,<sup>5,6</sup> patients taking empagliflozin were less likely to initiate and more likely to discontinue MRAs, which could be explained by the better clinical status achieved under empagliflozin treatment. Notwithstanding, given different and non-overlapping mechanisms of benefit, in clinical practice it is advisable to continue MRA whenever a clinical indication exists irrespective of SGLT2i use.<sup>12</sup>

In EMPULSE, just above 50% of patients were using MRAs at baseline, these patients were mostly chronic HF<sub>r</sub>EF experiencing a decompensation (rather than a “de novo” AHF event). The MRA doses used (median of 25 mg/day of spironolactone or eplerenone) were not “diuretic” doses but provide aldosterone blockade, anti-remodelling, and anti-fibrotic effects.<sup>13,14</sup> Empagliflozin 10 mg/day has an early natriuretic and diuretic effect later followed by anti-oxidative stress and autophagy promoting effects which seem to act independently from baseline MRA use, thus supporting a different but complementary mode of action of these agents.<sup>15-18</sup> Both SGLT2i and MRAs have pleiotropic effects beyond the heart and kidneys, having the potential for reducing hospitalizations and mortality.<sup>1,2,19</sup>

In chronic HF patients, across a wide range of ejection fractions, enrolled in the EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, and DELIVER trials SGLT2i were generally effective irrespective of baseline MRA use, further supporting the independent effects of these agents.<sup>5-7,20</sup> Importantly, in chronic heart failure, patients randomized to SGLT2i and taking an MRA at baseline experienced lower rates of significant hyperkalemia, suggesting that SGLT2i may also enhance MRA tolerability, therefore allowing better treatment adherence in the chronic setting.<sup>8</sup> In this AHF study, absolute numbers of hyperkalemia (any of investigator reported, potassium >5.5 mmol/L, and potassium >6 mmol/L) were infrequent and without significant treatment-by-baseline MRA interaction (at the 5% level) for any of the hyperkalemia definitions, suggesting that the absolute risk of hyperkalemia was limited irrespective of baseline MRA use. Our findings suggest the concomitant use of empagliflozin plus MRA did not lead to excess hyperkalemia compared to MRA alone. This is clinically important because AHF patients experience frequent medication and dose changes which may cause side-effects, including

hyperkalemia. Using empagliflozin plus MRA did not lead to excess adverse events, including hyperkalemia.<sup>21</sup> Other important parameters to consider in AHF is renal function and blood pressure. Both SGLT2i and MRA may cause an initial ( $\pm$ 4-8 weeks) eGFR “dip” with subsequent eGFR recovery.<sup>22-25</sup> In this regard, our study shows that no excessive eGFR “dip” was found with concomitant empagliflozin and MRA use in AHF, where eGFR is frequently monitored and influences therapeutic decision and prognosis. Additionally, no differences in SBP change or excessive risk of symptomatic hypotension were found among patients taking empagliflozin and an MRA at baseline.

### **Limitations**

Some limitations of this study should be acknowledged. This is a non-prespecified post-hoc analysis of a randomized trial and these data have similar limitations to observational studies, including the inability to infer causality between baseline MRA use and any potential effect modification of empagliflozin, because, contrary to empagliflozin, MRA use was not randomly allocated to patients resulting in a very different patient profile of MRA users and non-users. The MRA doses used herein were chronic HF doses (i.e., not “diuretic” doses) and these findings cannot be generalized to patients using higher MRA doses in AHF (e.g., 100 mg/day of spironolactone). The duration of MRA use before randomization was not recorded, but the MRA doses used were compatible with doses used in chronic HF suggesting that the patients were chronically treated with MRAs before inclusion in the study. Our study has limited power to detect differences in MRA effect between HF<sub>r</sub>EF and HF<sub>mr</sub>EF/HF<sub>p</sub>EF subpopulations, since by design, the trial was not powered to detect these differences. Finally, given the modest size of the subgroups examined, and

exploratory nature of this study we did not perform statistical corrections for multiplicity which may enhance the probability of chance findings.

## **Conclusions**

Empagliflozin was beneficial and well tolerated irrespective of baseline MRA use.

These findings support the use of empagliflozin on top of background MRA therapy in patients admitted for AHF.

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## **Data Sharing Statement**

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major Regulatory Authorities. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

## **Disclosures**



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Table 1. Baseline characteristics of the patients by MRA use at baseline

	No MRA (n=254)		MRA (n=276)		No MRA vs. MRA P-value
	Placebo (n=140)	Empa. (n=114)	Placebo (n=125)	Empa. (n=151)	
Age, years	70.2 ± 12.7	71.0 ± 12.0	65.9 ± 14.6	67.4 ± 12.9	0.001
Age ≥70 years, n. (%)	81 (58)	70 (61)	55 (44)	79 (52)	0.012
Women, n. (%)	56 (40)	37 (32)	37 (30)	49 (32)	0.18
Race, n. (%)					0.020
White	104 (74)	88 (77)	98 (78)	123 (81)	
Black/African American	22 (16)	13 (11)	11 (9)	8 (5)	
Asian	11 (8)	12 (11)	14 (11)	20 (13)	
Other <sup>§</sup>	3 (2)	1 (1)	2 (2)	0	
Region, n. (%)					0.008
North America	42 (30)	38 (33)	27 (22)	28 (19)	
Europe	87 (62)	64 (56)	84 (67)	104 (69)	
Asia	11 (8)	12 (11)	14 (11)	19 (13)	
HF diagnosis time, years	2.8 ± 4.1	3.8 ± 5.5	5.1 ± 7.6	3.9 ± 5.7	0.020
“De novo” HF, n. (%)	49 (35)	36 (32)	38 (30)	52 (34)	0.83
Acute on Chronic decompensated HF, n. (%)	91 (65)	78 (68)	87 (70)	99 (66)	
NYHA class, n. (%)					0.77 <sup>@</sup>
III	79 (56)	58 (51)	66 (53)	76 (50)	
IV	13 (9)	11 (10)	10 (8)	15 (10)	
Clinical congestion score	2.8 ± 2.1	3.0 ± 2.2	2.7 ± 2.2	2.9 ± 2.1	0.47
Weight, kg	85 ± 21	87 ± 27	89 ± 27	86 ± 25	0.44
BMI, kg/m <sup>2</sup>	30 ± 7	30 ± 8	30 ± 8	30 ± 8	0.99
Heart rate, bpm	77 ± 15	75 ± 14	76 ± 12	77 ± 15	0.53
SBP, mmHg	128 ± 20	125 ± 19	121 ± 17	122 ± 16	<0.001
DBP, mmHg	74 ± 12	73 ± 12	73 ± 12	73 ± 13	0.25
LVEF, %	41 ± 17	38 ± 16	30 ± 13	32 ± 13	<0.001
LVEF >40 %, n. (%)	66 (47)	43 (38)	27 (22)	33 (22)	<0.001
NT-proBNP, pg/mL, median (IQR)	3286 (1795-6215)	3447 (1927-6385)	3046 (1414-5328)	3277 (1776-5281)	0.090 <sup>#</sup>
Ischemic HF, n. (%)	32 (23)	31 (27)	43 (34)	44 (29)	0.086
Medical history					
History of CABG/PCI, n. (%)	38 (27)	33 (29)	40 (32)	45 (30)	0.47
Atrial fibrillation, n. (%)	73 (52)	60 (53)	55 (44)	74 (49)	0.20
Hypertension, n. (%)	125 (89)	93 (82)	96 (77)	112 (74)	0.002
Type 2 diabetes, n. (%)	55 (39)	58 (51)	61 (49)	66 (44)	0.72
Laboratory data					
eGFR, ml/min/1.73m <sup>2</sup>	52 ± 20	48 ± 20	60 ± 21	56 ± 19	0.001
eGFR <60, n. (%)	86 (61)	78 (68)	59 (47)	83 (55)	0.001
Uric acid, mg/dL	8.5 ± 2.4	8.8 ± 2.5	8.7 ± 2.2	8.4 ± 2.5	0.82
KCCQ-CSS	43 ± 22	43 ± 24	47 ± 22	44 ± 25	0.24
KCCQ-TSS	40 ± 24	39 ± 24	44 ± 24	40 ± 24	0.25
Hemoglobin, g/L	13 ± 2	13 ± 2	14 ± 2	13 ± 2	0.001

	No MRA (n=254)		MRA (n=276)		No MRA vs. MRA P-value
	Placebo (n=140)	Empa. (n=114)	Placebo (n=125)	Empa. (n=151)	
Sodium, mmol/L	140 ± 3	140 ± 4	140 ± 3	139 ± 4	0.30
Potassium, mmol/L	4.2 ± 0.5	4.2 ± 0.5	4.3 ± 0.5	4.2 ± 0.5	0.29
Potassium <4 mmol/L, n. (%)	45 (32)	31 (27)	22 (18)	34 (23)	0.011
Potassium 4-5.5 mmol/L, n. (%)	85 (61)	72 (63)	92 (74)	107 (71)	
Potassium >5.5 mmol/L, n. (%)	3 (2)	1 (1)	0	1 (1)	
Potassium missing, n. (%)	7 (5)	10 (9)	11 (9)	9 (6)	
Heart failure medication, n. (%)					
ACEi/ARB/ARNi	90 (64)	70 (61)	95 (76)	116 (77)	0.001
Loop-diuretics	104 (74)	95 (83)	100 (80)	138 (91)	0.017
Thiazide diuretics	17 (12)	12 (11)	6 (5)	19 (13)	0.37
Beta blocker	101 (72)	85 (75)	107 (86)	128 (85)	0.001
MRA: spironolactone	-	-	100 (80.0)	130 (86.1)	-
MRA: eplerenone	-	-	24 (19.2)*	21 (13.9)	

Legend: HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; CABG/PCI, coronary artery bypass grafting/percutaneous coronary intervention; eGFR, estimated glomerular filtration rate.

Numbers are mean +/- standard deviation, unless otherwise stated.

P-values are from ANOVA for continuous variables or chi-square test for categorical variables.

\$ includes missing

# based on log-transformed results.

@ Includes comparison with classes I and II.

\*One patient used esaxerenone.

Table 2. Outcomes by MRA use

	No MRA (n=254)			MRA (n=276)			p-value inter.
	Placebo (n=140)	Empagliflozin (n=114)	WR or HR or mean difference or event rate ratio (95% CI)	Placebo (n=125)	Empagliflozin (n=151)	WR or HR or mean difference or event rate ratio (95% CI)	
	n (%)	n (%)		n (%)	n (%)		
Primary outcome at 90 days	Wins = 6603/15960 (41.4%)	Wins = 8359/15960 (52.4%)	1.27 (0.93, 1.73)	Wins = 7179/18875 (38.0%)	Wins = 10466/18875 (55.4%)	1.46 (1.08, 1.97)	0.52
Clinical congestion score <sup>1</sup> change from baseline to 90 days (points)*	-1.56 (-1.81, -1.32)	-1.91 (-2.17, -1.66)	-0.35 (-0.71, 0.00)	-1.75 (-2.00, -1.51)	-1.85 (-2.07, -1.62)	-0.09 (-0.43, 0.24)	0.30
KCCQ-TSS change from baseline to 90 days (points)*	29.2 (25.1, 33.2)	36.4 (32.0, 40.8)	7.3 (1.3, 13.2)	34.4 (30.2, 38.6)	35.7 (31.8, 39.5)	1.25 (-4.5, 7.0)	0.15
First HFE or CV death	27 (19.3)	19 (16.7)	0.85 (0.47, 1.52)	22 (17.6)	15 (9.9)	0.58 (0.30, 1.11)	0.39
Total HFE (number of events)	26	17	0.75 (0.36, 1.58)	26	19	0.69 (0.34, 1.40)	0.86
All-cause hospitalization	42 (30.0)	34 (29.8)	0.98 (0.62, 1.54)	35 (28.0)	26 (17.2)	0.61 (0.37, 1.02)	0.17
All-cause mortality	11 (7.9)	7 (6.1)	0.79 (0.31, 2.04)	11 (8.8)	4 (2.6)	0.32 (0.10, 1.00)	0.23

Legend: HFE, heart failure event; CV, cardiovascular; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score.

\*Adjusted mean (95% confidence interval).



<sup>1</sup> The clinical congestion score is calculated as a sum of the points allocated for the following signs and symptoms: dyspnea, orthopnea, and fatigue, with a 0- to 3-point scale used for each variable i.e., absence =0 points, seldom =1 point, frequent =2 points, and continuous =3 points.



Table 3. Changes in vital signs and biomarkers according to baseline MRA use

Change from baseline to day 90	No MRA (n=254)		MRA (n=276)		Int. P value
	Placebo (n=140)	Empa. (n=114)	Placebo (n=125)	Empa. (n=151)	
Weight, kg	-1.0 (-2.2, 0.2)	-2.7 (-4.0, -1.4)	-0.6 (-1.9, 0.6)	-2.1 (-3.2, -1.0)	0.86
	Diff.= -1.7 (-3.5, 0.1)		Diff.= -1.5 (-3.2, 0.2)		
Hb, g/dL	-0.3 (-0.5, -0.0)	0.4 (0.1, 0.7)	-0.5 (-0.8, -0.3)	0.0 (-0.2, 0.2)	0.47
	Diff.= 0.7 (0.3, 1.1)		Diff.= 0.5 (0.2, 0.9)		
Uric acid, mg/dL	-0.9 (-1.2, -0.5)	-1.9 (-2.3, -1.5)	-0.9 (-1.3, -0.6)	-2.0 (-2.3, -1.6)	0.99
	Diff.= -1.0 (-1.6, -0.5)		Diff.= -1.0 (-1.6, -0.5)		
NT-proBNP, pg/mL*	71 (63, 80)	62 (54, 70)	71 (63, 80)	65 (58, 73)	0.66
	Ratio= 0.87 (0.73, 1.03)		Ratio= 0.91 (0.77, 1.08)		
Sodium, mmol/L	0.3 (-0.2, 0.9)	0.0 (-0.6, 0.6)	0.4 (-0.2, 1.0)	-0.1 (-0.6, 0.4)	0.63
	Diff.= -0.3 (-1.1, 0.5)		Diff.= -0.6 (-1.3, 0.2)		

Legend: Hb, hemoglobin; Int., interaction.

Numbers are adjusted means (95% confidence intervals) unless otherwise stated.

\*Change from baseline in AUC (pg/mL\*days) up to Day 90 (ANCOVA results) – adjusted geometric means.

	No MRA (n=252)		MRA (n=272)		Interaction P*
	Placebo (n=140)	Empa. (n=112)	Placebo (n=124)	Empa. (n=148)	
-	n (%)	n (%)	n (%)	n (%)	-
Hyperkalemia (investigator reported)	1 (0.7)	5 (4.5)	7 (5.6)	6 (4.1)	0.08
Hyperkalemia >5.5 mmol/L	5 (3.6)	13 (11.7)	9 (7.3)	11 (7.5)	0.09
Hyperkalemia >6.0 mmol/L	0	3 (2.7)	2 (1.6)	4 (2.7)	0.34
Hypokalemia (investigator reported)	5 (3.6)	4 (3.6)	4 (3.2)	3 (2.0)	0.64
Hypokalemia <3.5 mmol/L	15 (10.9)	7 (6.6)	6 (5.0)	9 (6.3)	0.27
Any adverse event	114 (81.4)	84 (75.0)	90 (72.6)	98 (66.2)	0.93
Serious adverse event	68 (48.6)	47 (42.0)	47 (37.9)	37 (25.0)	0.24
Adverse event leading to trial drug discontinuation	22 (15.7)	12 (10.7)	12 (9.7)	10 (6.8)	0.96
Acute kidney injury	12 (8.6)	7 (6.3)	7 (5.6)	3 (2.0)	0.39
Volume depletion	15 (10.7)	16 (14.3)	12 (9.7)	17 (11.5)	0.81
Symptomatic hypotension	9 (6.4)	8 (7.1)	5 (4.0)	8 (5.4)	0.80

Table 4. Adverse Events by MRA use at baseline

Urinary tract infection	8 (5.7)	5 (4.5)	9 (7.3)	6 (4.1)	0.66
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Legend: Data are AEs in the treated set of patients classified using MedDRA.

Shown are adverse events up to 7 days and potassium levels up to 3 days following discontinuation of the study medication.

\*Cochran's-Q test for homogeneity of risk ratios (treatment by subgroup interaction).



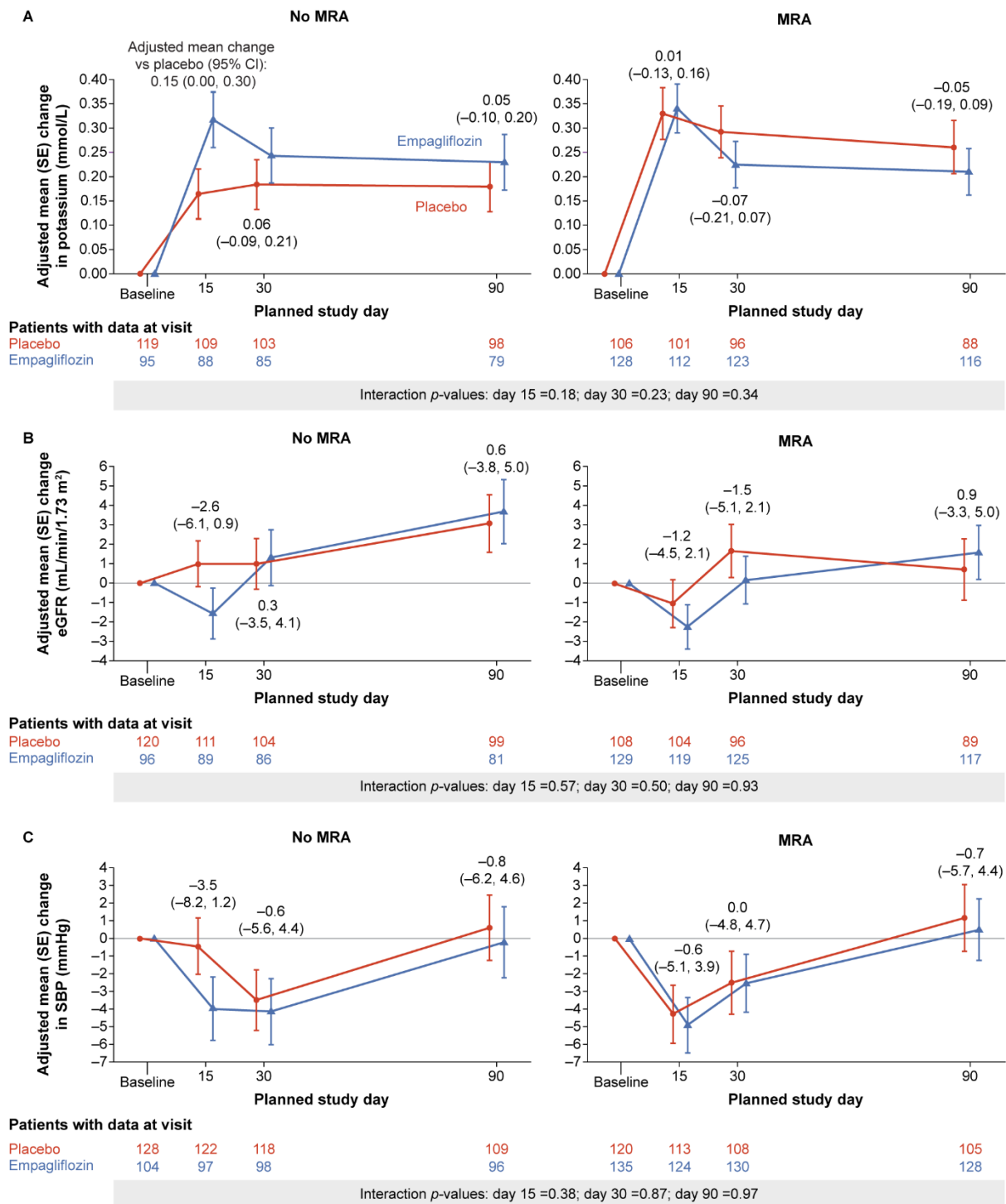
Table 5. First initiation and discontinuation of MRA

<b>MRA initiation/discontinuation</b>	<b>Empagliflozin</b>	<b>Placebo</b>	<b>OR (95% CI)</b>
	<b>n/N (%)</b>	<b>n/N (%)</b>	
First initiation of MRA*	40/114 (35.1)	57/140 (40.7)	0.79 (0.47, 1.32) P =0.37
Discontinuation of MRA**	32/151 (21.2)	22/125 (17.6)	1.27 (0.70, 2.33) P =0.43

\*Among patients not on MRA at baseline

\*\*Temporary or permanent discontinuation among patients on MRA at baseline

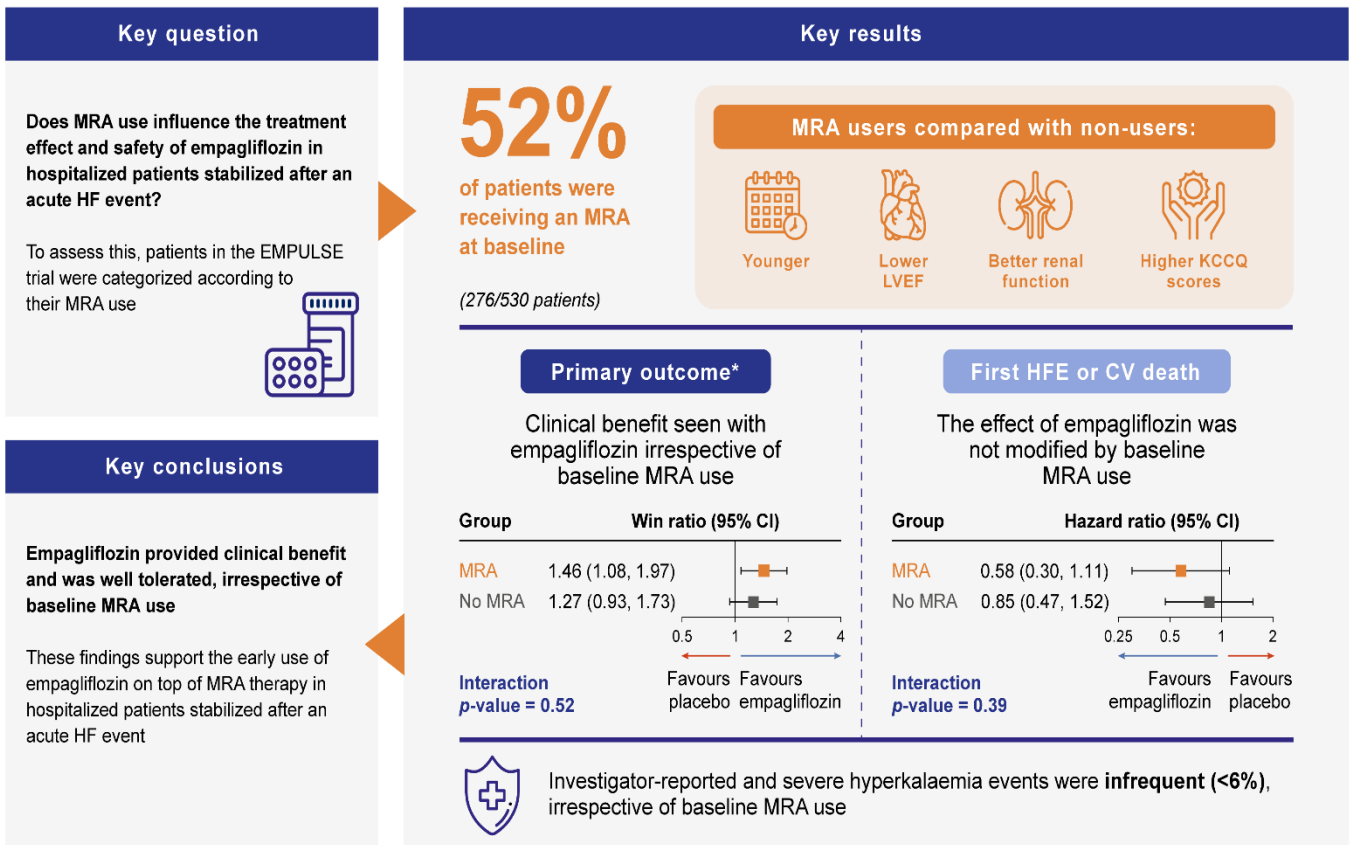
Figure 1. Changes over time in serum potassium, estimated glomerular filtration rate, and systolic blood pressure



Legend: A) serum potassium; B) eGFR, estimated glomerular filtration rate; and C) systolic blood pressure. MRA, mineralocorticoid receptor antagonist.



Graphical abstract. Main findings of the MRA subgroup analysis of the EMPULSE trial



Legend: \*The hierarchy and components of the primary outcome measured by the win ratio were: (1) time to all-cause death; (2) number of HF events; (3) time to first HF event; (4)  $\geq 5$  point difference in change from baseline in KCCQ total symptom score after 90 days of treatment. CI, confidence interval; CV, cardiovascular; HF, heart failure; HFE, heart failure event; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.