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Research paper

Influence of angiotensin receptor-neprilysin inhibition on the efficacy of Empagliflozin on cardiac structure and function in patients with chronic heart failure and a reduced ejection fraction: The Empire HF trial

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ABSTRACT

Study objective: The objective was to assess the effect of ongoing angiotensin receptor-neprilysin inhibitor(ARNI) on the effect of the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin on left ventricular (LV) size and function in patients with heart failure and reduced ejection fraction(HFrEF).
Design: Post hoc analysis of the Empire HF trial, an investigator-initiated, double-blind, randomized controlled trial.
Participants: 190 patients with HFrEF with New York Heart association class I-III symptoms with an ejection fraction of 40 % or below. Patients were stratified according to ongoing ARNI treatment at baseline.
Intervention: Empagliflozin 10 mg daily or placebo for 12 weeks. Echocardiography at baseline and follow-up.
Main outcome measures: Left ventricular end-systolic volume index (LVESVI), end-diastolic volume index (LVEDVI), left atrial volume index (LAVI), left ventricular ejection fraction (LVEF).
Results: A total of 58 patients (31 %) received ARNI at baseline. Compared to with placebo, empagliflozin reduced the LVESVI ([−6.2 (−14.1 to 1.6); $p = 0.12$] and [−3.3 (−8.2 to 1.6); $p = 0.19$], interaction $P = 0.49$), LVEDVI ([−11.2 (−21.2 to −1.2); $p = 0.03$] and [−2.9 (−8.7 to 2.9); $p = 0.32$], interaction $P = 0.13$), and LAVI ([−3.9 (−9.1 to 1.2); $p = 0.14$] and. [−1.8 (−4.4 to 0.7); $p = 0.16$], respectively, interaction $P = 0.9$) in patients treated with and without ARNI at baseline, respectively. No treatment-by-ARNI subgroup interaction were found. Unaffected by baseline ARNI treatment, empagliflozin did not improve LVEF.
Conclusion: The effect of empagliflozin on cardiac structure and function compared to placebo was not affected by background treatment with ARNI.

Abbreviations: ACEi, Angiotensin converting enzyme inhibitors; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; CVD, Cardiovascular death; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LAVI, Left atrial volume index; LV, Left ventricle; LVEF, Left ventricular ejection fraction; LVEDVI, Left ventricular end-diastolic volume index; LVESVI, Left ventricular end-systolic volume index; NT-proBNP, N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association; RAAS, Renin angiotensin aldosterone system; SBP, Systolic blood pressure; SGLT2, Sodium-glucose cotransporter 2.

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1. Introduction

In progression of cardiovascular disease, pathological cardiac remodeling [1] characterized by progressive enlargement of the left ventricle and loss of myocardial function is a fundamental pathophysiological process associated with adverse outcomes. [2–5] Remodeling in heart failure with reduced ejection fraction (HFrEF) is characterized by a decline in left ventricular ejection fraction (LVEF) and increase in left ventricular end-systolic volume index (LVESVI) [6] An increase in left atrial (LA) volume in HF is commonly the result of LA pressure overload which has been found to be associated with higher risk of cardiovascular death (CVD), all-cause mortality, congestive heart failure and atrial fibrillation [3] In heart failure patients, an increase in N-terminal-pro B-type natriuretic peptide (NT-proBNP) has been associated with higher risk of death from any cause, CVD, sudden death and heart failure hospitalization [7,8].

A cornerstone in management of patients with heart failure with reduced ejection fraction (HFrEF) is inhibition of the renin angiotensin aldosterone system (RAAS) using angiotensin converting enzyme inhibitors (ACEi) [9,10] to attenuate cardiac remodeling. In 2014, the *Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure* (PARADIGM-HF) study demonstrated that treatment with Angiotensin Receptor-Neprilysin Inhibitor (ARNI) reduced the risk of cardiovascular death and rehospitalization for heart failure in patients with HFrEF compared with ACEi [11]. Sodium glucose cotransporter 2 (SGLT2) inhibitors empagliflozin and dapagliflozin were originally developed as antidiabetic drugs. SGLT2 inhibitors have shown to reduce the risk of cardiovascular death and hospital admission for heart failure in stable patients with HFrEF irrespective of the presence of type 2 diabetes [12–15]. Since 2021, SGLT2 inhibitors have been a class 1A recommendation in European and American heart failure guidelines [16,17]. Thus, it can be anticipated that SGLT2 inhibitors and ARNI frequently will be co-prescribed in patients with HFrEF. In the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR Reduced) trial, 11 % and 20 % of enrolled patients were receiving an ARNI at baseline, respectively [18,19]. Based on a post-hoc analysis of the EMPEROR Reduced trial, the efficacy of empagliflozin treatment on cardiac death and hospitalization for worsening heart failure was unaffected of background treatment with ARNI or ACEi and did not increase the risk of renal adverse events [19]. Efficacy of dapagliflozin compared with placebo on cardiovascular death or heart failure worsening in the DAPA-HF trial were similar in patients with or without background treatment with ARNI [18].

The Empagliflozin in Heart Failure Patients with Reduced Ejection Fraction (Empire HF) trial was designed to investigate the mechanistic effects of SGLT2 inhibitor in patients with HFrEF [20]. No significant effect of empagliflozin was demonstrated on the primary endpoint which was the between group change of NT-proBNP after 12 weeks of treatment [20]. Although the mechanism of empagliflozin to improve outcomes in HFrEF is not fully understood, attenuated remodeling has been suggested as one pathway which also has been demonatrated for ARNI. Thus, it is unclear whether simultaneous treatment with ARNI leads to an additive, synergistic or reduced effect of empagliflozin on the cardiac remodeling. This post hoc analysis of Empire HF investigated whether background therapy with ARNI influenced the effect of empagliflozin on cardiac function and structure (LVEF, LVESVI, left ventricular end-diastolic volume index (LVEDVI), LA volume index (LAVI), left ventricular global longitudinal strain (LVGLS), systolic blood pressure (SBP) and NT-proBNP in stable HFrEF patients after 12 weeks of treatment.

2. Method

2.1. Trial design

This is an exploratory post hoc analysis of the Empagliflozin in Heart Failure Patients with Reduced Ejection Fraction (Empire HF) trial, which was an investigator-initiated, multicenter, double blinded, placebo-controlled randomized clinical trial, assigning patients (1:1) to 12 weeks treatment with either empagliflozin 10 mg daily or matching placebo. In this analysis, participants were further divided into groups according to background treatment with ARNI. The four groups were treated with 1) empagliflozin and ARNI 2) empagliflozin and no ARNI 3) Placebo and ARNI 4) Placebo and no ARNI.

The trial design, conduction, and reporting complied with the Declaration of Helsinki. The locally appointed ethics committee for Capital Region in Denmark (reference number H-17010756) approved the trial protocol. Independent monitoring was conducted according to Good Clinical Practice. All participants provided written informed consent. Previously, the full study protocol has been published [20].

2.2. Study participants

Complete in- and exclusion criteria have been published [20]. In brief, stable adult patients with HFrEF receiving guideline-directed HF therapy, LVEF$\leq$40 %, New York Heart Association (NYHA) classification I-III and estimated GFR >30 mL/min/1,73 m^2 were included. Key exclusion criteria were hospitalization for heart failure within 30 days, or a systolic blood pressure below 95 mmHg. During the treatment period, adverse events and medical adherence were assessed at two telephone contacts and one study visit. Furthermore, biomarkers, physical examination and vital signs were conducted at the study visit during the treatment period.

2.3. Randomization and blinding

Eligible patients were assessed at a screening visit, and if eligible, patients were randomly assigned in a 1:1 ratio to empagliflozin 10 mg daily or matching placebo within 30 days of screening. The allocation sequence was generated using computer-generated random numbers in blocks of 10 without stratification. Data analysis was performed blinded to treatment allocation.

2.4. Outcomes

Outcomes in this post hoc analysis were between empagliflozin and placebo group differences in the change in LVESVI, LVEDVI, LAVI, LVEF, LV GLS, SBP and NT-proBNP.

2.5. Transthoracic echocardiography

Transthoracic echocardiography was performed on a Vivid E9 ultrasonography system (General Electric, Horten, Norway) on all 190 patients at baseline and after 90 days of treatment. Images were stored digitally for offline analysis blinded for treatment allocation, and in a random order. LV end systolic and end diastolic volumes and LVEF were assessed using Simpson's biplane method. Maximal left atrial (LA) volume was assessed using the Simpsons method of disks. Two-dimensional speckle tracking was performed in the three standard apical views with automated tracking of speckles throughout the cardiac cycle. Peak LV GLS was calculated as the mean systolic strain in 17 segments. A more detailed description of the echocardiography protocol is found elsewhere [21].

2.6. Measurement of NT-proBNP

Fasting blood samples, were obtained before randomization and

after 12 weeks treatment and were immediately centrifuged upon collection and stored at -80 °C. Plasma concentrations of NT-proBNP were analyzed at a central laboratory blinded to treatment allocation (Atellica IM NT-proBNP assay on Atellica IM analyzer platform, Siemens Healthineers, Erlangen, Germany).

2.7. Statistical analysis

In this post hoc analysis of the Empire HF trial [20], baseline characteristics of the subgroups treated with or without ARNI at baseline were reported as number (%) for categorical variables, mean ± standard deviation (SD) for normally distribution and interquartile range (IQR) for non-normally distributed variables, and analyzed using student's *t*-test and Wilcoxon rank sum test, respectively. For the selected outcomes, we used a linear mixed model with a random intercept to account for repeated measurements from the same individual, and to adjust for possible differences between groups at baseline. The effects of treatment were assessed by examining two-way interactions in an intention-to-treat analysis. Adjusted interaction *P*-values were furthermore adjusted for the baseline value of the specific outcome, age (continues variable), sex, atrial fibrillation and treatment with mineralocorticoid-receptor antagonist (MRA). The effect of empagliflozin in subgroups treated with or without ARNI were interpreted with mean change and 95 % confidence interval (CI) as the change between the groups and the P-value denotes the two-way interaction between subgroups. All outcomes were tested at a two-sided significance level of 0.05 and estimates

Table 1
Baseline characteristics.

	Patients not taking ARNI		Patients taking ARNI		P-value*
	(n = 132)		*(n = 58)*		
	Placebo	Empagliflozin	Placebo	Empagliflozin	
	(n = 68)	*(n = 64)*	*(n = 27)*	*(n = 31)*	
Age, mean (SD), years	61 ± 12	63 ± 10	68 ± 10	68 ± 10	<0.001
Gender, Male, No. (%)	59 (87 %)	52 (81 %)	24 (89 %)	27 (87 %)	0.49
Caucasian, NO (%)	67 (99 %)	63 (98 %)	27 (100 %)	29 (94 %)	0.32
Body mass index, median (IQR)[a]	29 (26–33)	29 (27–32)	27 (26–33)	28 (26–33)	0.42
Systolic blood pressure, mean (SD), mmHg	122 ± 16	121 ± 19	116 ± 16	114 ± 17	0.011
Diastolic blood pressure, mean (SD), mmHg	75 ± 11	72 ± 12	69 ± 13	72 ± 10	0.082
Heart rate, mean (SD), beats/min	73 ± 12	68 ± 11	71 ± 15	71 ± 13	0.69
Heart failure characteristics					
Duration of heart failure, mean (SD), months	33 (13–76)	37 (11–64)	18 (13–51)	33 (13–98)	0.64
Heart failure cause, No. (%)					0.85
Ischemic heart failure	32 (47 %)	36 (56 %)	17 (63 %)	12 (39 %)	
Non-ischemic heart failure	36 (53 %)	28 (44 %)	10 (37 %)	19 (61 %)	
Left Ventricle Ejection Fraction, mean (SD), (%)	31 ± 7	30 ± 8	28 ± 8	25 ± 8	0.11
NYHA class, No. (%)					0.97
I	4 (6 %)	4 (6 %)	3 (11 %)	1 (3 %)	
II	56 (82 %)	48 (75 %)	21 (78 %)	24 (77 %)	
III	8 (12 %)	12 (19 %)	3 (11 %)	6 (19 %)	
Comorbidities, No. (%)					
Type 2 diabetes	11 (16 %)	11 (17 %)	2 (7 %)	0 (0 %)	0.012
Hypertension	29 (43 %)	25 (39 %)	12 (44 %)	10 (32 %)	0.70
Atrial fibrillation	17 (25 %)	18 (28 %)	16 (59 %)	15 (48 %)	<0.001
Ischemic heart disease	34 (50 %)	37 (58 %)	19 (70 %)	13 (42 %)	0.86
Chronic kidney disease[b]	5 (7 %)	9 (14 %)	7 (26 %)	4 (13 %)	0.12
Laboratory variables					
NT-proBNP, Median (IQR), ng/l	599 (254–1030)	414 (277–850)	658 (422–1470)	915 (612–1740)	<0.001
In sinus rhythm	420 (207–854)	333 (227–548)	509 (354–777)	726 (479–996)	0.021
In atrial fibrillation	1020 (592–1450)	997 (381–1230)	990 (556–2235)	1260 (885–2990)	0.082
Estimated glomerular filtration rate, median (IQR), ml/min/1.73 m^2)	76 (62–90)	75 (57–90)	69 (54–78)	71 (56–88)	0.031
Hemoglobin A1c, median (IQR), mmol/mol	39 (36–43)	40 (37–49)	38 (37–41)	39 (36–41)	0.23
Hematocrit, median (IQR), %	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.42
Hemoglobin, mmol/l	9 (8–9)	9 (8–9)	8 (8–9)	9 (8–9)	0.20
Estimated plasma volume, mean(SD), ml	3183 ± 475	3061 ± 423	3178 ± 428	2995 ± 381	0.53
Heart Failure Medication, No. (%)					
ACE inhibitors/ARBs	65 (96 %)	58 (91 %)	0 (0 %)	0(0 %)	<0.001
β blockers	64 (94 %)	60 (94 %)	25 (93 %)	30 (97 %)	0.81
Mineralocorticoid-receptor antagonist	41 (60 %)	36 (56 %)	22 (81 %)	26 (84 %)	0.001
Diuretics[c]	44 (65 %)	40 (63 %)	18 (67 %)	23 (74 %)	0.35
Device, No (%)	38 (56 %)	35 (55 %)	14 (52 %)	17 (55 %)	0.53
Device type					
Cardiac resynchronization therapy without ICD	2 (5 %)	5 (14 %)	2 (14 %)	2 (12 %)	
Cardiac resynchronization therapy with ICD	11 (29 %)	7 (20 %)	3 (21 %)	4 (24 %)	
ICD only	24 (63 %)	23 (66 %)	7 (50 %)	11 (65 %)	
Quality of life					
KCCQos	74.3 ± 18.5	73.9 ± 19.9	76.3 ± 16.5	78.9 ± 14.4	0.21
KCCQts	77.3 ± 16.6	75.1 ± 21.2	78.4 ± 16.8	80.8 ± 16.6	0.23

Abbreviations: NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; ACE inhibitors, angiotensin-converting enzyme; ARB, angiotensin-II-receptor blockers; ICD, implantable cardioverter defibrillator, KCCQos; Kansas City Cardiomyopathy Questionnaire overall score, KCCQts; Kansas City Cardiomyopathy Questionnaire total score.

* P-values refer to the difference between patients treated or not treated with ARNI at baseline, combining patients in the two randomized treatment groups.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Chronic kidney disease was defined with an estimated glomerular filtration rate under 60 mL/min/1.73 m^2.

[c] Diuretics includes Loop diuretics or Thiazide.

calculated with their 95 % CIs. Statistical analysis was conducted using Stata statistical software, version 16 (StataCorp LLC, College Station, Texas). The Empire HF trial is registered with ClinicalTrials.gov, NCT03198585, and EudraCT, 2017–001341-27.

3. Results

Of the 190 patients studied, 58 patients (31 %) received ARNI treatment at baseline. Patients with ARNI treatment at baseline were older, had higher NT-proBNP, higher usage of the guideline directed HF medical therapy with MRA and lower systolic blood pressure (Table 1). Furthermore, patients with ARNI treatment had higher frequency of atrial fibrillation, lower rates of type 2 diabetes and lower estimated glomerular filtration rate compared to those without ARNI treatment (Table 1)., Stratified on ARNI treatment at baseline, patients in the two groups had similar LVEF and HFrEF etiology, no differences in diuretics or cardiac device implantation (Table 1). During the double-blind treatment period, no patients were changed from ACEi to ARNI.

3.1. Cardiac structure and function

In the whole cohort, empagliflozin treatment reduced the LVESVI, LVEDVI, and LAVI, but not LVEF or LV GLS, compared to placebo (Fig. 1). Baseline LVESVI, LVEDVI and LAVI were larger in patients treated with ARNI and randomized to empagliflozin compared with the other groups (Table 2). Furthermore, patients treated with empagliflozin and ARNI at baseline had the lowest LVEF compared to the other groups (Table 2).

Combined treatment with both empagliflozin and background ARNI therapy significantly reduced LVEDVI by 11 % compared to the placebo-treated ARNI patients (LVEDVI [−11.2 (−21.2 to −1.2) ml/m^2; p = 0.03]).No significant changes in LVEDVI were demonstrated in patients randomized to empagliflozin when not treated with ARNI at baseline (LVEDVI [−2.9 (−8.7 to 2.9) ml/m^2; p = 0.32] (Table 3, Fig. 1). No treatment-by-ARNI subgroup interaction were found on LVEDVI. Empagliflozin combined with background ARNI therapy had a greater reduction on LVESVI and LAVI compared to the placebo-treated group without ARNI treatment at baseline, however, the treatment effects between the groups were not significant. No treatment-by-ARNI

Table 2
Outcomes stratified on baseline ARNI treatment.

ARNI at baseline				
	Empagliflozin		Placebo	
	Baseline	Follow-up	Baseline	Follow-up
LVESVI	64.3 ± 40.3	51.9 ± 25.0	48.8 ± 21.1	50.1 ± 24.1
LVEDVI	91.6 ± 48.6	75.7 ± 28.2	75.1 ± 26.3	79.2 ± 29.9
LAVI	46.4 ± 20.7	46.4 ± 20.8	39.8 ± 16.9	42.6 ± 17.3
LVEF	32.1 ± 7.3	33.8 ± 10.5	36.0 ± 12.3	38.8 ± 11.1
LVGLS	−10.1 ± 3.6	−10.0 ± 3.0	−11.5 ± 3.7	−11.7 ± 3.7
SBP	114 ± 17	109 ± 12	116 ± 16	117 ± 12
NT-proBNP	915 (612–1740)	805 (423–1450)	658 (422–1470)	603 (395–1630)
Not ARNI at baseline				
LVESVI	49.7 ± 22.1	46.9 ± 22.1	49.5 ± 22.6	47.7 ± 19.4
LVEDVI	76.0 ± 27.3	74.5 ± 25.0	75.5 ± 27.9	74.6 ± 24.7
LAVI	38.2 ± 16.9	37.0 ± 14.4	35.0 ± 11.3	35.0 ± 10.4
LVEF	36.3 ± 9.7	39.2 ± 10.8	36.5 ± 8.0	37.6 ± 8.1
LVGLS	−11.9 ± 3.8	−11.9 ± 4.1	- 11.3 ± 3.4	−11.9 ± 3.2
SBP	121 ± 19	118 ± 14	122 ± 16	122 ± 15
NT-proBNP	414 (277–850)	455 (259–627)	599 (254–1030)	502 (199–1040)

Abbreviations: LVESVI, left ventricular end-systolic volume index: LVEDVI, left ventricular end-diastolic volume index: LAVI, left atrial volume index: LVEF, left ventricular ejection fraction: LVGLS, left ventricular global longitudinal strain; SBP, systolic blood pressure; NT-proBNP, N-terminal-pro B-type natriuretic.

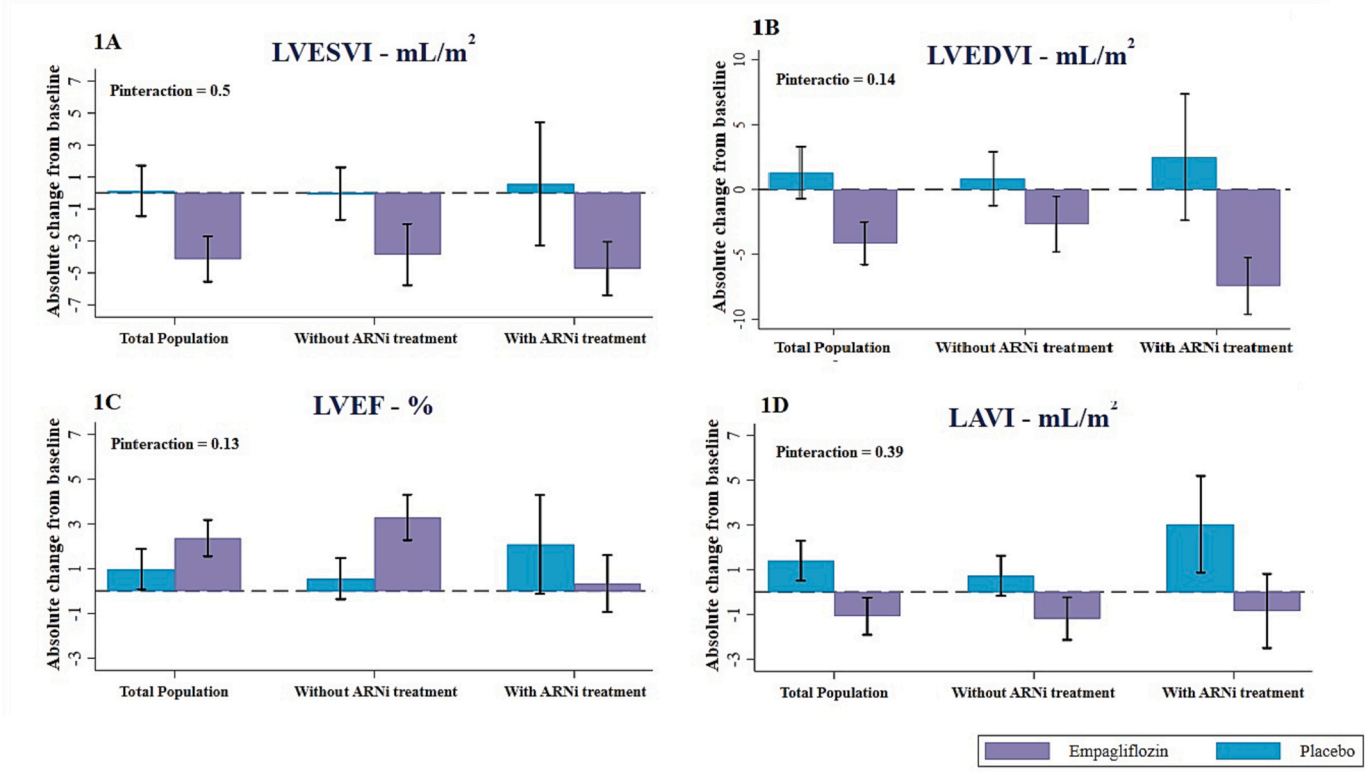

Fig. 1. Absolute change from baseline in LVEDVI, LVESVI, LAVI and LVEF with and without ARNI treatment at baseline
Abbreviations: ARNI, Angiotensin Receptor-Neprilysin Inhibitor; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction. P-interaction values are adjusted for age, sex, atrial fibrillation and MRA.

Table 3
Outcomes changes from baseline and interaction.

		ARNI		Not ARNI			
		Empagliflozin	Placebo	Empagliflozin	Placebo	p interaction	Adjusted p interaction[a]
LVESVI	Change from baseline	−4.7 ± 8.7	0.6 ± 18.8	−3.9 ± 14.8	−0.1 ± 12.9		
	Difference (coef. (95%CI))	−6.2 (−14.1 to 1.6); p = 0.12		−3.3 (−8.2 to 1.6); p = 0.19		0.48	0.5
LVEDVI	Change from baseline	−7.4 ± 11.4	2.5 ± 23.9	−2.7 ± 16.5	0.8 ± 16.4		
	Difference (coef. (95%CI))	−11.2 (−21.2 to −1.2); p = 0.03		−2.9 (−8.7 to 2.9); p = 0.32		0.13	0.14
LAVI	Change from baseline	−0.8 ± 8.9	3.0 ± 10.8	−1.2 ± 7.4	0.7 ± 7.0		
	Difference (coef. (95%CI))	−3.9 (−9.1 to 1.2); p = 0.14		−1.8 (−4.4 to 0.7); p = 0.16		0.42	0.39
LVEF	Change from baseline	0.3 ± 6.6	2.1 ± 10.8	3.3 ± 7.8	0.5 ± 7.2		
	Difference (coef. (95%CI))	−1.4 (−6.2 to 3.3); $p = 0.54$		2.4 (−0.2 to 5.1); $p = 0.07$		0.13	0.13
LVGLS	Change from baseline	−0.0 ± 2.5	−0.2 ± 2.1	−0.1 ± 2.2	−0.4 ± 2.3		
	Difference (coef. (95%CI))	0.2 (−1.1 to 1.5); $p = 0.77$		0.4 (−0.4 to 1.2); $p = 0.37$		0.82	0.85
SBP	Change from baseline	−5.7 ± 14.1	1.2 ± 13.1	−3.8 ± 15.3	−0.2 ± 12.8		
	Difference (coef. (95%CI))	6.9 (−13.9 to 0.01); p = 0.05		−3.6 (−8.4 to 1.2); p = 0.14		0.45	0.45
NT-proBNP	Change from baseline	−0.16 (−0.32–0.07)	0.02 (−0.22–0.19)	−0.03 (−0.39–0.27)	−0.08 (0.31–0.20)		
	Difference (Ratio of change. (95% CI))	0.94 (0.75 to 1.19); $p = 0.62$		1.02 (0.86 to 1.22); $p = 0.76$		0.59	0.68

Abbreviations: LVESVI, left ventricular end-systolic volume index: LVEDVI, left ventricular end-diastolic volume index: LAVI, left atrial volume index: LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; SBP, systolic blood pressure; NT-proBNP, N-terminal-pro B-type natriuretic.
[a] Adjusted for age, sex, atrial fibrillation and MRA.

subgroup interaction were found on LVESVI, and LAVI ($P > 0.05$) (Table 3, Fig. 1). Furthermore, data did not suggest any interaction effect of empagliflozin on LVEF or LV GLS, between ARNI subgroups (Table 3; Fig. 1).

3.2. Changes in systolic blood pressure and brain natriuretic peptide

Baseline systolic blood pressure was lowest in the empagliflozin combined with background ARNI therapy (Table 2), where the combined treatment of empagliflozin and ARNI reduced systolic blood pressure compared to the placebo-treated ARNI group [−6.9 mmHg (−13.9 to 0.01); $p = 0.05$]. The treatment effect of empagliflozin on systolic blood pressure in those without ARNI treatment at baseline was not significant [−3.6 mmHg(−8.4 to 1.2); $p = 0.14$] (Table 3).As aforementioned, no treatment effect was found of empagliflozin on NT-proBNP in HFrEF patients and stratifying the treatment effect to ARNI subgroups, revealed no significant changes (Table 2; Table 3).

4. Discussion

This post hoc study of the Empire HF trial investigated whether background treatment with ARNI affected the effect of empagliflozin treatment on cardiac function and structure in patients with HFrEF. Empagliflozin did not change LVEF, but significantly reduced cardiac volumes after 12 weeks of treatment, and the efficacy of empagliflozin in reducing cardiac volumes was not attenuated in HFrEF patients receiving ARNI at baseline. Thus, independent of the concomitant treatment with ARNI, the benefits of empagliflozin on cardiac structure was consistent after 12 weeks of treatment.

In the DAPA-HF and EMPEROR Reduced trial, a minority (11 % and 20 % of patients respectively) were treated with ARNI at baseline [18,19]. The proportion of patients receiving ARNI at baseline was nearly twice in the EMPEROR Reduced trial compared to DAPA-HF. Substudies of the two large trials demonstrated consistent benefit of the SGLT2 inhibitors of empagliflozin and dapagliflozin in ARNI treated patients. Currently, no other mechanistic studies include as large a proportion of concomitant ARNI and SGLT2 inhibitor treated patients [22]. Furthermore, no study has previously investigated the mechanism of action by the SGLT2 inhibitor focusing on cardiac structures when stratified on background therapy with ARNI.

Reverse cardiac remodeling including reduction of LV volumes is a major pathway for clinical benefits of both pharmacological and device related HF therapy [23] Several studies including the Empire HF trial have demonstrated reductions in LV and LA volumes [21,24,25] in a SGLT2 inhibitor treated patient population. The effect on LVEF has been more conflicting with *Empagliflozin in Non-diabetic Heart Failure Patients With Reduced Ejection Fraction* (EMPA-TROPOISM) suggesting improvement in LVEF after 6 months treatment with empagliflozin [24], whereas Empire HF and *Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction* (SUGAR-DM-HF) failed to find significant changes in LVEF after 12 and 36 weeks treatment with an SGLT2 inhibitor, respectively [21,25].

ARNI has shown overall effect on reverse cardiac remodeling in both patients with HFrEF and heart failure with preserved ejection fraction (HFpEF) [26]. Both SGLT2 inhibitors and ARNI are now central part of the HFrEF therapy strategies, however the exact mechanism of SGLT2 inhibitors remain uncertain, but diuretic properties and favorable cardiac metabolism have been suggested. ARNI with the two active substances (sacubitril and valsartan) blocks the renin-angiotensin system and inhibit the breakdown of natriuretic peptides, where natriuretic peptides cause diuresis and natriuresis [27]. SGLT2 inhibitor on top of background ARNI treatment might have and additive benefit due to reduction of preload and afterload, blunting of cardiac stress/injury with less hypertrophy and fibrosis, which would have further favorable effects on myocardial remodeling [28].

In this analysis, patients receiving ARNI at baseline and randomized to empagliflozin had more dilated ventricles compared with patients not receiving ARNI at baseline and with placebo-treated patients on ARNI likely due to the heart failure therapy guidelines at the time, which required persistent high NT-proBNP despite RAAS-inhibition and conventional HF therapy. Thus, it is likely that these patients had more advanced HF which also could explain the higher use of mineralocorticoid antagonists in these patients. Patients taking ARNI at baseline have lower baseline systolic blood pressure, which is expected due to the fully uptitrated heart failure therapy with blood pressure lowering effect.

In Empire-HF, the treatment duration of 12 weeks was based on findings from analyses of the *Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients* (The EMPA-REG OUTCOME Trial), which demonstrated a significantly reduction in mortality after 59 days treatment with empagliflozin in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease [29]. Later, results from DAPA-HF and the EMPEROR-reduced trial supported these findings in

patients with HFrEF, where the combined endpoints of cardiovascular death and heart failure hospitalization was significantly reduced after 28 and 34 days, respectively [30,31]. Effects of SGLT2 inhibitors on cardiac chamber size and function has been investigated in patients with heart failure and diabetes in SUGARDM-HF and EMPA-TROPISM, where LVESV and LVEDV was significantly reduced meanwhile no significant changes in LVEF was demonstrated after 36 weeks and 6 month of empagliflozin treatment, respectively [24,25]. Data from Empire HF suggest that empagliflozin reduction in cardiac chamber size was apparent already after 12 weeks treatment, and this improvement is likely to be sustained as demonstrated in SUGAR-HF and EMPA-TROPISM [21,24,25].

4.1. Study limitations

In Empire HF, no significant changes were demonstrated in the primary endpoint NT-proBNP, which together with the exploratory post-hoc design render all results hypothesis generating. Still, this paper attempt to elucidate the mechanism of action of SGLT2 inhibitors with or without ARNI, adding novel findings to the literature. Further, power is low. LV volumes and LVEF were assessed by echocardiography with well-known greater variability than for example cardiac magnetic resonance imaging, which should be taken into account when interpreting the cardiac reverse remodeling results. Significantly more patients treated with ARNI at baseline received treatment with MRA. Interaction analysis did not suggest that MRA use influenced the effect of empagliflozin in ARNI treated patients. The power of this analysis is low and an additive effect on the reverse cardiac remodeling cannot be ruled out. In the Empire HF trial, males were overrepresented. Thus, caution should be made when extrapolating the results to a HF population with more women. The gender distribution was similar in the group receiving ARNI and not receiving ARNI treatment at baseline and therefore it is not expected to affect the results in this analysis and no interaction between gender and effects of empagliflozin has been noted previously in Empire HF or other trials.

5. Conclusion

This post-hoc analysis of the Empire HF trial suggested no interaction between treatment with ARNI and empagliflozin on reverse cardiac remodeling or neurohormonal activation in patients with stable HFrEF. Thus, current study adds mechanistic insight to the existing evidence from randomized trials on clinical endpoints on combination of SGLT2 inhibitors and ARNI.

Ethical statement

The trial design, conduction, and reporting complied with the Declaration of Helsinki. The locally appointed ethics committee for Capital Region in Denmark (reference number H-17010756) approved the trial protocol. Independent monitoring was conducted according to Good Clinical Practice. All participants provided written informed consent.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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