ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 1682–1688
Published online 18 February 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13801

ORIGINAL ARTICLE

Characterization of heart failure patients with reverse left ventricular remodelling post-angiotensin receptor blockers/neprilysin inhibitors therapy

Leonid Maizels[1,2,3], Yishay Wasserstrum[1,2], Boris Fishman[1,2,3], Amitai Segev[1,2], David Ben-Nun[2], Anan Younis[1,2], Dov Freimark[1,2], Israel Mazin[1,2] and Avishay Grupper[1,2]*

[1]*Division of Cardiology, Leviev Center of Cardiovascular medicine, Sheba Medical Center in Tel-HaShomer, Sheba Rd. 2, Ramat-Gan, Israel;* [2]*The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; and* [3]*The Talpiot Sheba Medical Leadership Program, Tel-Aviv, Israel*

Abstract

Aims To assess the effect of angiotensin receptor blockers/neprilysin inhibitors (ARNI) on left ventricular (LV) ejection fraction (LVEF) and LV dimensions in a real-life cohort of heart failure and reduced ejection fraction (HFrEF) patients, while analysing patient characteristics that may predict reverse LV remodelling.

Methods and results The ARNI-treated HFrEF patients followed at a single tertiary medical centre HF-outpatient clinic were included in the study. Clinical and echocardiographic parameters were evaluated prior to ARNI initiation, and while on ARNI therapy, assessing patient characteristics associated with reverse LV remodelling. The cohort included 91 patients (mean age 60.5 years, 90% male) and 47 (52%) patients exhibited ARNI responsiveness, defined as an increase in LVEF during therapy. Overall, LVEF increased by 19% post-ARNI (23.8 to 28.4%, $P < 0.001$). Subgroup analysis revealed several parameters associated with significant LVEF improvement, including baseline LVEF <30%, non-ischaemic HF aetiology, lack of cardiac resynchronization therapy (CRT), better initial functional class and ARNI initiation within 3 years from HF diagnosis ($P \leq 0.001$ for all). Significant reduction in LV dimensions was noted in patients with lower initial LVEF, non-ischaemic HF and no CRT. Further combined subgrouping of the study population demonstrated that patients with both LVEF <30% and a non-ischaemic HF gained most benefit from ARNI with an average of 51% improvement in LVEF (19.9 to 30%, $P < 0.001$).

Conclusions The ARNI treatment response is not uniform among HFrEF patient subgroups. More pronounce reverse LV remodelling is associated with early ARNI treatment initiation in the course of HFrEF, and in those with LVEF <30%, non-ischaemic HF and no CRT.

Keywords Reverse remodelling; ARNI; LV function; LV dimensions; Early treatment initiation

Received: 4 September 2021; Revised: 13 December 2021; Accepted: 18 December 2021
**Correspondence to: Avishay Grupper, Division of Cardiology, Leviev Center of Cardiovascular Medicine, Sheba Medical Center in Tel-HaShomer, Sheba Rd. 2, Ramat-Gan, Israel. Email: avishay.grupper@sheba.health.gov.il*
Leonid Maizels, Yishay Wasserstrum, and Boris Fishman contributed equally to the manuscript.

Introduction

The use of combined angiotensin receptor blockers/neprilysin inhibitors (ARNI) as a therapeutic option for patients with heart failure (HF) and reduced ejection fraction (HFrEF) has been introduced following the PARADIGM-HF trial,[1] which demonstrated the superiority of ARNI in reducing morbidity, HF hospitalizations, and mortality in chronic HFrEF patients, compared with angiotensin-converting enzyme inhibitor (ACEi) therapy, and was hence adopted by clinical guidelines as a recommended treatment in HFrEF patients.[2,3] Further, real-world observational studies confirmed the benefits of the ARNI in term of clinical outcomes.[4–6]

The beneficial role of ACEi, angiotensin receptor blockers (ARB), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA) and cardiac resynchronization therapy (CRT) in HFrEF is attributed at least in part to reverse myocardial remodelling, and ARNI was postulated to potentially exert a similar effect.[7] Indeed, several studies have demonstrated reverse myocardial remodelling with ARNI therapy, as

manifested by improvement in left ventricular (LV) ejection fraction (LVEF),[8–13] decrease in LV diameters,[8–13] reduction of mitral regurgitation (MR) severity,[8,14] left atrial reverse remodelling[15] and even improvement in metrics of diastolic function.[8,16] Therefore, HFrEF patients either hospitalized[17] or ambulatory are potential candidates for ARNI initiation, with sacubitril/valsartan as the only currently approved medication in this class.

Importantly, such prior studies as well as the clinical practice suggest that not all HFrEF patients demonstrate the same level of clinical improvement following ARNI treatment, and therefore, differentiating patients who would benefit most from such therapy is of interest. Previous attempts to identify patients who may respond to ARNI therapy with reverse LV remodelling found conflicting results.[9,12,13] Hence, the questions whether ARNI may possess a more pronounced reverse remodelling effect in specific HFrEF patient-subgroups, and whether responsiveness to ARNI treatment may be predicted by different patient characteristics remain uncertain.

In this real-life cohort study, we aim to elucidate the baseline demographic, clinical and echocardiographic patients' parameters that are associated with significant improvement of echocardiographic parameters following ARNI treatment.

Methods

Study population

The study population was based on an ARNI registry of adult (≥18 years old) patients treated at the Sheba Medical Center HF outpatient clinic. The registry comprised of patients who were eligible for commencement of ARNI treatment by the Israeli national reimbursement criteria for ARNI: symptomatic HFrEF patients (LVEF ≤ 35%) with New York Heart Association (NYHA) Class II–IV despite optimal medical therapy with beta-blockers, and ACEi or ARB. The current study analysis included all consecutive HFrEF patients with ARNI therapy initiation between 1 February 2016 and 31 August 2019. The registry inclusion criteria were active ARNI therapy as well as two documented 2-D echocardiography studies conducted within 6 months prior to ARNI initiation and at least 1 month while on active ARNI therapy. Follow-up echocardiography was carried out as part of a scheduled periodic follow up by the treating cardiologist at the Sheba Medical Center.

Study variables

The registry was created based on the data available from the patient electronic medical records. The collected information included demographic and clinical data, prior medical diagnoses, 2-D echocardiography data including visually estimated LVEF, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD) and MR severity, NYHA functional class, chronic medications, prior CRT and/or ICD, as documented during patient visits and follow-up in the HF outpatient clinic. All echocardiography studies were conducted by certified echocardiography technicians and were examined by board certified cardiologists with subspecialty in echocardiography. Echocardiography data were obtained retrospectively from the patient records and echocardiography reports. All reported echocardiographs were carried out based on the American Society of Echocardiography guidelines. The Institutional Review Board of the Sheba Medical Center approved this study based on strict maintenance of participants' anonymity during database analyses.

Statistical analysis

The study population was grouped by LVEF response: (i) responders, presenting any LVEF increase following ARNI therapy; and (ii) non-responders, presenting either no change or deterioration of the LVEF following ARNI therapy. Baseline characteristics were compared between responder and non-responder patient populations and presented as means and standard deviations or percentages for continuous and binary data, respectively. To evaluate the subgroups of patients who would potentially benefit the most following ARNI treatment, changes in LVEF, LVESD, and LVEDD were evaluated in each subgroup by age ($<$60 vs. $\geq$60), HF aetiology (ischaemic vs. non ischaemic), baseline LVEF ($>$30% vs. $\leq$30%), prior CRT, and the timing of ARNI initiation since HF diagnosis ($\leq$3 years vs. $>$3 years). Additional combined subgroup analyses were conducted by two of the following factors: HF aetiology, baseline LVEF, and baseline CRT status. Differences between the groups were analysed using paired *T*-test. Statistical significance was set at a two-tailed probability level of $<$0.05. Statistics were performed using SPSS version 23 (IBM, Chicago, IL, USA). The Institutional Review Board Committee of the Sheba Medical Center approved this study.

Results

Baseline patient characteristics

The study included 91 patients with the man age of 60.5 (SD 10.6) years, 82 patients (90%) were male (*Table 1*). Overall, patients were treated according to current guidelines including BB (95%), ACEi or ARB (89%), MRA (81%), and CRT (41%). Forty-seven (52%) patients exhibited an LVEF increase on ARNI and were classified as responders. Responders were less likely to have an implantable cardioverter defibrillator (ICD) (57% vs. 77%, *P* = 0.04), were marginally more likely to be hypertensive (70% vs. 50%, P = 0.05), and had slightly lower

DOI: 10.1002/ehf2.13801

Table 1 Baseline characteristics of study population by responsiveness to ARNI defined as increase of left ventricular ejection fraction following the initiation of the treatment

		Total (N = 91)	Non-responsive (N = 44)	Responsive (N = 47)	P value
Age		60.5 (±10.5)	59.7 (±9.4)	60.8 (±11.8)	0.65
Sex (male)		82 (90%)	42 (96%)	40 (85%)	0.10
Body-mass index		29.0 (±5.6)	29.4 (±6.4)	28.6 (±4.7)	0.48
Heart failure aetiology	Ischaemic	47 (52%)	26 (59%)	21 (45%)	0.17
	Non-ischaemic	44 (48%)	18 (41%)	26 (55%)	
NYHA functional class	II	46 (51%)	19 (43%)	27 (57%)	0.21
	III	45 (49%)	25 (57%)	20 (43%)	
Hypertension		55 (60%)	22 (50%)	33 (70%)	0.05
Diabetes mellitus		57 (62%)	27 (61%)	30 (64%)	0.81
Beta-blocker therapy		86 (95%)	43 (98%)	43 (91%)	0.19
ACE inhibitors/ARB		84 (92%)	42 (96%)	42 (90%)	0.28
Mineralocorticoid antagonist		73 (80%)	34 (77%)	39 (83%)	0.50
SGLT-2 inhibitors		17 (19%)	8 (18%)	9 (19%)	0.91
Furosemide %		79 (87%)	40 (91%)	39 (83%)	0.26
Daily furosemide (median; IQR)		40 (40–80)	40 (40–80)	40 (40–80)	0.49
Digoxin		9 (10%)	4 (9%)	5 (11%)	0.81
ICD		61 (67%)	34 (77%)	27 (57%)	0.04
Resynchronization therapy		39 (43%)	23 (52%)	16 (34%)	0.08
Beginning of therapy within 3 years of HFrEF diagnosis		51 (57%)	23 (52%)	28 (61%)	0.41
Ejection fraction % (mean + SD)		23.9 (7.4)	24.6 (7.4)	23.2 (7.5)	0.37
LVEDD, cm (mean + SD)		6.2 (0.8)	6.3 (0.7)	6.0 (0.8)	0.04
LVESD, cm (mean + SD)		5.1 (1.0)	5.3 (1.0)	4.9 (1.0)	0.17
Moderate to severe MR*		23 (29%)	15 (39%)	8 (20%)	0.07

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitors; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NYHA, New York Heart Association; SD, standard deviation; SGLT, sodium glucose transporter.

LVEDD (6 vs. 6.3 cm, P = 0.04) compared with non-responders. Other baseline characteristics did not differ between the two groups.

Response to angiotensin receptor blockers/neprilysin inhibitors therapy by subgroup analysis

Changes in LVEF, LVEDD, and LVESD following ARNI therapy in our study population are presented in *Table 2*. Overall, LVEF increased by 19% (from 23.8% to 28.4%, $P < 0.001$) with no difference between age groups or ARNI dosing. Further univariate analysis revealed several parameters associated with significant LVEF improvement, including (i) initiation of ARNI treatment within 3 years from HF diagnosis (25% LVEF increase from 23.9% to 29.9%, P = 0.001); (ii) Baseline LVEF <30% (29% LVEF increase from 20.1% to 25.9%, P = 0.001); (iii) non-ischaemic HF aetiology (29% LVEF increase from 23.8% to 30.6%, P = 0.001); (iv) lack of CRT (25% LVEF increase from 24.3% to 30.3%, P = 0.001); (v) hypertension (20% LVEF increase from 24.3% to 29.1%, P = 0.001); and (vi) Better initial functional class (NYHA Class II, 22% LVEF increase from 25% to 30.6%, P = 0.03).

In the overall study cohort, no significant changes in LV dimensions were noted following ARNI therapy. In a univariate analysis, patients with LVEF <30% and patients with non-ischaemic HF aetiology presented significant LVESD decrease and a numerical LVEDD decrease. A significant reduction in both indices was noted in patients with no CRT (LVEDD 6 to 5.8 cm, P = 0.043 and LVESD 5 to 4.7 cm, P = 0.011).

Response to angiotensin receptor blockers/neprilysin inhibitors therapy by combined subgroup analysis

Because significant LVEF improvement was noted in several univariate parameters, we aimed to further characterize specific patient populations demonstrating the most benefit from ARNI therapy. Hence, we analysed the study population by combined subgrouping according to LVEF, HF aetiology, and the presence of CRT (*Figures 1 and 2*). Patients characterized by both LVEF <30% and a non-ischaemic HF aetiology were found to benefit most from ARNI therapy with an average 51% improvement in LVEF (from 19.9% to 30%, $P < 0.001$). Additional combined patient subgroups demonstrating significant gain from ARNI treatment were those with LVEF <30% and no CRT (33% LVEF increase from 20.4% to 27.2%, $P < 0.01$), and those without CRT regardless of HF aetiology ($P < 0.01$). The subgroup analyses highlight the individual improvement in LVEF among most patients with the combination of LVEF <30%, no CRT and a non-ischaemic HF aetiology (*Figure 1*).

Table 2 Echocardiography parameters before and after the initiation of ARNI therapy by subgrouping

			Ejection fraction (%)			LV end-diastolic diameter (CM)			LV end-systolic diameter (CM)		
		Number	Before ARNI	After ARNI	*P*	Before ARNI	After ARNI	P	Before ARNI	After ARNI	*P*
Overall		91.00	23.84	28.42	<0.01	6.17	6.07	0.15	5.13	4.93	0.07
Age (years)	<60	43.00	24.76	29.59	0.01	6.14	6.01	0.24	4.99	4.89	0.45
	≥60	48.00	23.03	27.03	<0.01	6.19	6.01	0.40	5.26	5.0	0.06
Baseline LVEF (%)	≥30	25.00	33.62	34.50	0.66	5.78	5.78	0.97	4.41	4.41	0.96
	<30	66.00	20.14	25.87	0.00	6.32	6.18	0.09	5.41	5.15	0.04
Ischaemic heart disease	Yes	47.00	23.86	26.00	0.07	6.24	6.22	0.87	5.11	5.10	0.91
	No	44.00	23.82	30.63	<0.01	6.10	5.90	0.06	5.14	4.77	0.01
Resynchronization therapy	Yes	39.00	23.19	25.37	0.24	6.45	6.47	0.86	5.29	5.33	0.82
	No	52.00	24.33	30.29	<0.01	6.01	5.84	0.04	5.03	4.71	0.01
Beginning ARNI therapy within 3 years of	Yes	51.00	23.88	29.87	<0.01	6.04	5.86	0.06	4.89	4.67	0.16
HFrEF diagnosis	No	40.00	23.88	26.66	0.07	6.34	6.33	0.98	5.41	5.27	0.24
Hypertension	Yes	55.00	24.29	29.1	<0.01	6.12	5.95	0.08	4.97	4.78	0.21
	No	36.00	23.17	26.93	0.06	6.24	6.24	0.97	5.35	5.16	0.15
NYHA functional class	II	46	25.00	30.57	0.03	6.08	5.93	0.11	5.07	4.8	0.06
	III	45	22.67	25.86	0.03	6.27	6.23	0.7	5.19	5.1	0.53
ARNI daily dose (mg)	100	39	23.57	28.12	0.02	6.08	6.03	0.69	5.03	4.98	0.73
	200–400	52	24.05	28.33	0.03	6.26	6.1	0.13	5.21	4.91	0.03

Abbreviations: ARNI, angiotensin receptor neprilysin inhibitors; CM, centimetres; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 1 (A–L) Changes in ejection fraction (EF) before and after angiotensin receptor blockers/neprilysin inhibitors (ARNI) in different subgroups according to LVEF, heart failure (HF) aetiology, and the presence of cardiac resynchronization therapy (CRT).

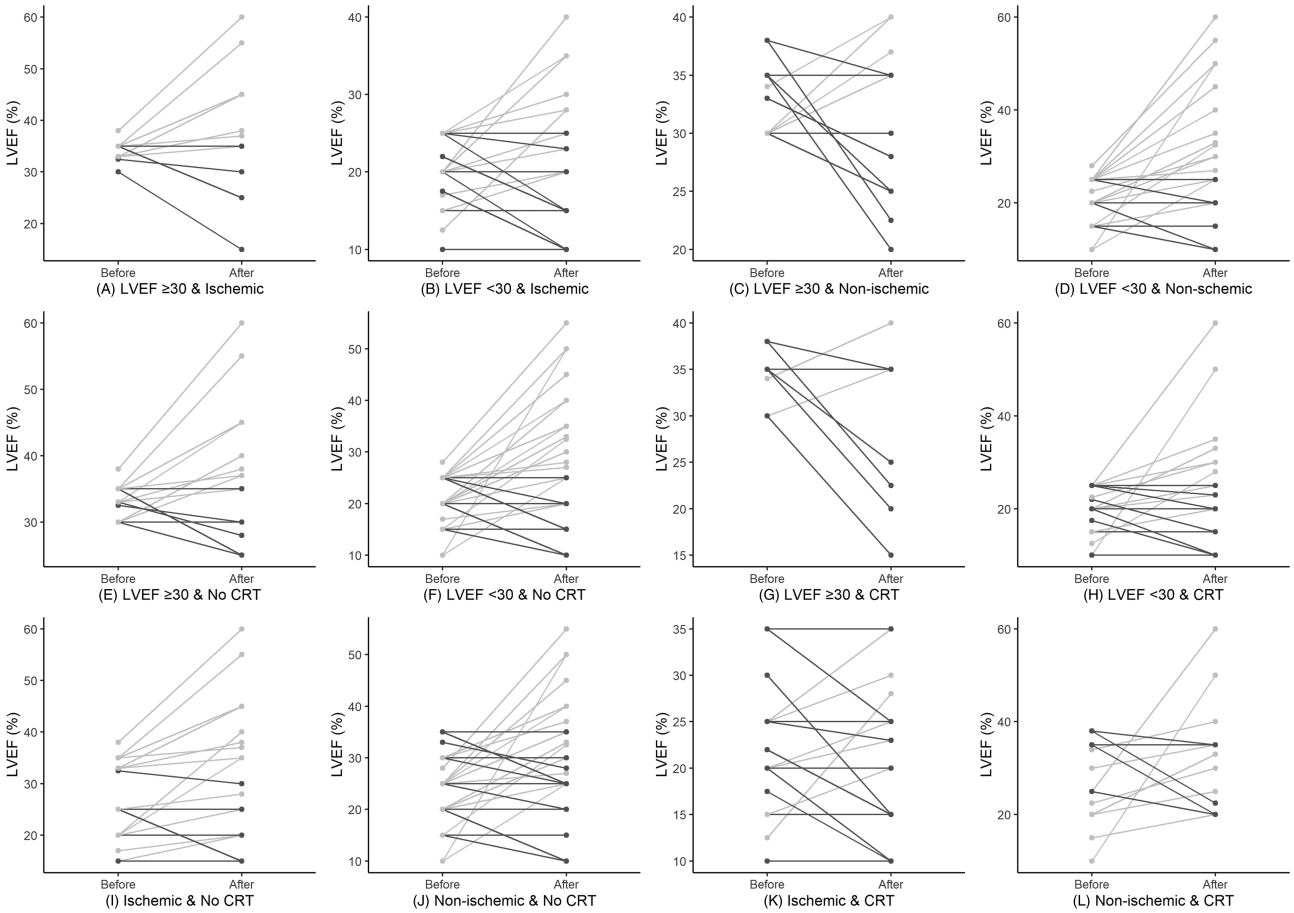
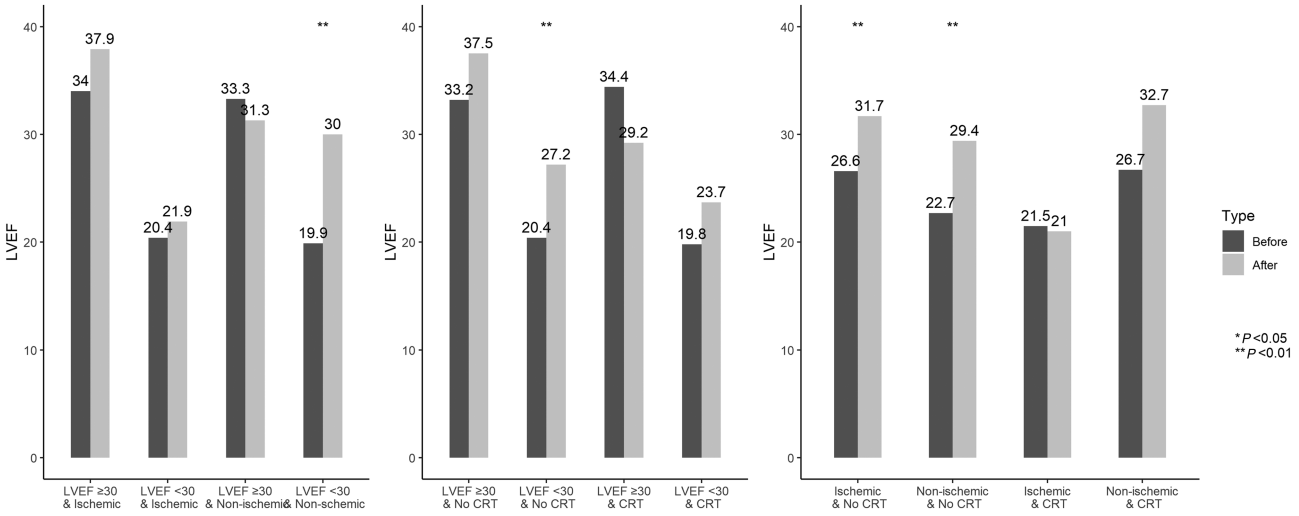


Figure 2 Ejection fraction (EF) before and after angiotensin receptor blockers/neprilysin inhibitors (ARNI) in different subgroups according to left ventricular (LV) EF, heart failure (HF) aetiology and the presence of cardiac resynchronization therapy (CRT).



Discussion

In the current report, we aimed to determine whether ARNI therapy is associated with reverse LV remodelling in a real-life cohort of HFrEF patients, and to characterize specific patient subgroups who could potentially benefit most from such treatment. We found that while ARNI initiation was associated with improved EF in the overall cohort, the extent was more pronounced and accompanied with a reduction in LV dimension indices in selected patients with specific characteristics including baseline EF <30%, non-ischaemic HF aetiology, lack of CRT and early initiation of ARNI treatment in the course of the HFrEF.

Similar to previous reports,[8–13] we found that ARNI treatment is associated with LVEF improvement. Importantly, while the overall absolute LVEF increase was of 4%, this improvement was associated with an upward shift of the LVEF sub-class (e.g. from 20–25% to 25–30%), suggesting an actual clinical benefit. Importantly, in our study, ARNI treatment was associated with improved LVEF when started 3 years or less from HF diagnosis, in concordance with previous reports of the safety and benefit of early commencement of ARNI therpay.[17–20] The differential LV remodelling response according to HF duration emphasizes the need for early ARNI initiation in HFrEF patients, a concept that have been implemented in recent clinical practice guidelines.[21]

An important aspect of our work is the further analysis of subgroups, which exhibit more significant benefit from ARNI treatment, suggesting that reverse LV remodelling effect was more pronounced in selected patient populations. Similarly to previous reports,[13] we have demonstrated that patients with a non-ischaemic HF aetiology exhibited better LV response post-ARNI. A possible explanation is that non-viable myocardial scar resulting from prolonged sustained ischaemia seems less likely to recover following HF therapy.[13,22] We found that patients with an LVEF <30% exhibited better LV response. This finding was not shown in previous reports of remodelling post-ARNI therapy,[13] but has been demonstrated in a large cohort of HF patients treated with the standard HF medications in the pre-ARNI era.[22] The only subgroup to exhibit significant reduction in both LV diameter indices was patients with no CRT. This is the largest study to our knowledge to address this question. While most of the previously published work did not include data on CRT, in one smaller cohort, CRT did not predict LV response to ARNI treatment.[12] Our finding may suggest that the potential myocardial reserve is already realized by CRT or that some clinical indication for CRT (e.g. electrical dyssynchrony manifested as intraventricular conduction abnormalities with prolonged QRS complex) might also be associated with decreased ARNI responsiveness.

The role of baseline LV size in predicting response to ARNI treatment is not clear. While most of the previous studies suggested smaller LV's to respond better,[9,13] others did not find an association between LV size and ARNI response.[12] In our study, ARNI responders had smaller LVEDD, adding to the existing body of evidence supporting the importance of baseline LV size and early initiation of ARNI therapy before the beginning of a significant LV pathologic remodelling process.

Nonetheless, we hereby also report parameters in which the response to ARNI remained significant throughout. While patients with better functional status (NYHA II compared with NYHA III) exhibited a more pronounce increase in LVEF, the effect remained significant across all functional classes, supporting the use of ARNI in more debilitated HF patients.

DOI: 10.1002/ehf2.13801

In addition, in our cohort ARNI treatment was associated with improved LVEF regardless of its daily dose. While previous reports suggested a dose response to ARNI therapy,[8,13] others suggested similar benefit across the dosing range.[10] Our report may encourage ARNI use even in lower doses, as it may still provide benefit over discontinuation of the drug.

Study limitations

This analysis has all the inherent limitations of a small-size, single-centre study; nevertheless, the study population size was similar to several previous reports addressing LV reverse remodelling with ARNI treatment.[8–12] Due to the single-centre nature of this study and the small number of patients included, generalization of the results should be applied with caution before confirmation is available from larger population analyses. Although the data were collected prospectively, our study is limited by its retrospective design. Our study design performing a paired analysis of the echocardiographic parameters for each patient was meant to address these issues. In this issue, there is a potential observer bias due to different cardiologists assessing the LVEF. Finally, data collection was performed prior to the recent reports concerning the benefit of sodium-glucose transporter 2 (SGLT2) inhibitors in HF patients, and the subsequent increase in prescription of this drug-class in HFrEF patients. In our cohort, 18% of patients were treated with SGLT2 inhibitors, but such treatment was not associated with augmented reverse LV remodelling combined with ARNI therapy. Hence, with the increasing use of SGLT2 inhibitors in HF patients, it would be important to further investigate whether these agents play a synergistic role with ARNI or not.

Conclusions

The current study demonstrates that in a real-life scenario ARNI treatment is associated with reverse LV remodelling in HFrEF patients. Our findings add to previous reports by recognizes specific patient characteristics that could potentially predict those who would benefit most from ARNI therapy, including those with LVEF $<30\%$, non-ischaemic HF and no CRT. Our findings support early ARNI initiation in the course of HFrEF and may help to better guide treatment in HFrEF patients. Further randomized trials are warranted to confirm these observations and elucidate their mechanisms.

References

1. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**: 2129–2200.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld JA, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; **70**: 776–803.
4. Chang PC, Wang CL, Hsiao FC, Wen MS, Huang CY, Chou CC, Chu PH. Sacubitril/valsartan vs. angiotensin receptor inhibition in heart failure: a real-world study in Taiwan. *ESC Hear Fail* 2020; **7**: 3003–3012.
5. Thomas M, Khariton Y, Fonarow GC, Arnold SV, Hill L, Nassif ME, Chan PS, Butler J, Thomas L, DeVore AD, Hernandez AF, Albert NM, Patterson JH, Williams FB, Spertus JA. Association between sacubitril/valsartan initiation and real-world health status trajectories over 18 months in heart failure with reduced ejection fraction. *ESC Hear Fail* 2021; **8**: 2670–2678.
6. She J, Lou B, Liu H, Zhou B, Jiang GT, Luo Y, Wu H, Wang C, Yuan Z. ARNI versus ACEI/ARB in reducing cardiovascular outcomes after myocardial infarction. *ESC Hear Fail* 2021 Online ahead of print.
7. Docherty KF, Vaduganathan M, Solomon SD, McMurray JJV. Sacubitril/valsartan: neprilysin inhibition 5 years after PARADIGM-HF. *JACC Heart Fail* 2020; **8**: 800–810.
8. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovasc Ther* 2018; **36**: e12435.
9. Bayard G, Da Costa A, Pierrard R, Roméyer-Bouchard C, Guichard JB, Isaaz K. Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation. *IJC Heart Vasc* 2019; **25**: 100418.
10. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, Mielniczuk L. Ejection fraction improvement and reverse remodeling achieved with sacubitril/valsartan in heart failure with reduced ejection fraction patients. *Am J Cardiovasc Dis* 2017; **7**: 108–113.
11. Liu LW, Wu PC, Chiu MY, Tu PF, Fang CC. Sacubitril/valsartan improves left ventricular ejection fraction and reverses cardiac remodeling in Taiwanese patients with heart failure and reduced ejection fraction. *Acta Cardiol Sin* 2020; **36**: 125–132.
12. Castrichini M, Manca P, Nuzzi V, Barbati G, De Luca A, Korcova R, Stolfo D, Di Lenarda A, Merlo M, Sinagra G, De Luca A, Korcova R, Stolfo D, Di Lenarda A, Merlo M, Sinagra G. Clinical medicine Sacubitril/valsartan induces global cardiac reverse remodeling in long-lasting heart failure with reduced ejection fraction: standard and advanced echocardiographic evidences. *J Clin Med* 2020; **9**: 906.
13. Lee Y-H, Chiou W-R, Hsu C-Y, Lin P-L, Liang H-W, Chung F-P, Liao C-T, Lin W-Y, Chang H-Y. Different left ventricular remodelling patterns and clinical outcomes between non-ischaemic and

ischaemic aetiologies in heart failure patients receiving sacubitril/valsartan treatment. *Eur Hear J Cardiovasc Pharmacother* 2020 Online ahead of print.
14. Kang D-H, Park S-J, Shin S-H, Hong G-R, Lee S, Kim M-S, Yun S-C, Song J-M, Park S-W, Kim J-J. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019; **139**: 1354–1365.
15. Sun Y, Song S, Zhang Y, Mo W, Zhang X, Wang N, Xia Y, Tse G, Liu Y. Effect of angiotensin receptor neprilysin inhibitors on left atrial remodeling and prognosis in heart failure. *ESC Hear Fail* 2021 Online ahead of print.
16. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJV. Prospective comparison of ARNI with ARB on management of heart failUre with preserved ejectioN fracTion (PARAMOUNT) investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380**: 1387–1395.
17. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E. Angiotensin–-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019; **380**: 539–548.
18. Senni M, Wachter R, Witte KK, Straburzynska-Migaj E, Belohlavek J, Fonseca C, Mueller C, Lonn E, Chakrabarti A, Bao W, Noe A, Schwende H, Butylin D, Pascual-Figal D. Initiation of sacubitril/valsartan shortly after hospitalisation for acutely decompensated heart failure in patients with newly diagnosed (*de novo*) heart failure: a subgroup analysis of the TRANSITION study. *Eur J Heart Fail* 2020; **22**: 303–312.
19. Abdin A, Anker SD, Butler J, Coats AJS, Kindermann I, Lainscak M, Lund LH, Metra M, Mullens W, Rosano G, Slawik J, Wintrich J, Böhm M. 'Time is prognosis' in heart failure: time-to-treatment initiation as a modifiable risk factor. *ESC Heart Failure* 2021 Online ahead of print.
20. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, Fonseca C, Goncalvesova E, Karabsheh S, Cavusoglu Y, Fernandez A, Chaaban S, Bøhmer E, Pouleur AC, Mueller C, Tribouilloy C, Lonn E, Buraiki ALJ, Gniot J, Mozheiko M, Lelonek M, Noè A, Schwende H, Bao W, Butylin D, Pascual-Figal D, TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail* 2019; **21**: 998–1007.
21. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **2021**: 3599–3726.
22. Lupón J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, López-Ayerbe J, Domingo M, Núñez J, Zamora E, Moliner P, Díaz-Ruata P, Santesmases J, Bayés-Genís A. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol* 2018; **72**: 591–601.