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RESEARCH ARTICLE

Short-term effects of sacubitril/valsartan therapy on myocardial oxygen consumption and energetic efficiency of cardiac work in heart failure with reduced ejection fraction: A randomized controlled study

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Aims We sought to evaluate the mechanism of angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril/valsartan therapy and compare it with a valsartan-only control group in patients with heart failure with reduced ejection fraction (HFrEF).

Methods and results The study was a phase IV, prospective, randomized, double-blind, parallel-group study in patients with New York Heart Association class II–III heart failure and left ventricular ejection fraction (LVEF) ≤35%. During a 6-week run-in period, all patients received valsartan therapy, which was up-titrated to the highest tolerated dose level (80 mg bid or 160 mg bid) and then randomized to either valsartan or sacubitril/valsartan. Myocardial oxygen consumption, energetic efficiency of cardiac work, cardiac and systemic haemodynamics were quantified using echocardiography and ^{11}C-acetate positron emission tomography before and after 6 weeks of therapy (on stable dose) in 55 patients (ARNI group: $n = 27$, mean age 63 ± 10 years, LVEF 29.2 ± 10.4%; and valsartan-only control group: $n = 28$, mean age 64 ± 8 years, LVEF 29.0 ± 7.3%; all p = NS). The energetic efficiency of cardiac work remained unchanged in both treatment arms. However, both diastolic (−4.5 mmHg; $p = 0.026$) and systolic blood pressure (−9.8 mmHg; $p = 0.0007$), myocardial perfusion (−0.054 ml/g/min; $p = 0.045$), and left ventricular mechanical work (−296; $p = 0.038$) decreased significantly in the ARNI group compared to the control group. Although myocardial oxygen consumption decreased in the ARNI group (−5.4%) compared with the run-in period and remained unchanged in the control group (+0.5%), the between-treatment group difference was not significant ($p = 0.088$).

Conclusions We found no differences in the energetic efficiency of cardiac work between ARNI and valsartan-only groups in HFrEF patients. However, ARNI appears to have haemodynamic and cardiac mechanical effects over valsartan in heart failure patients.

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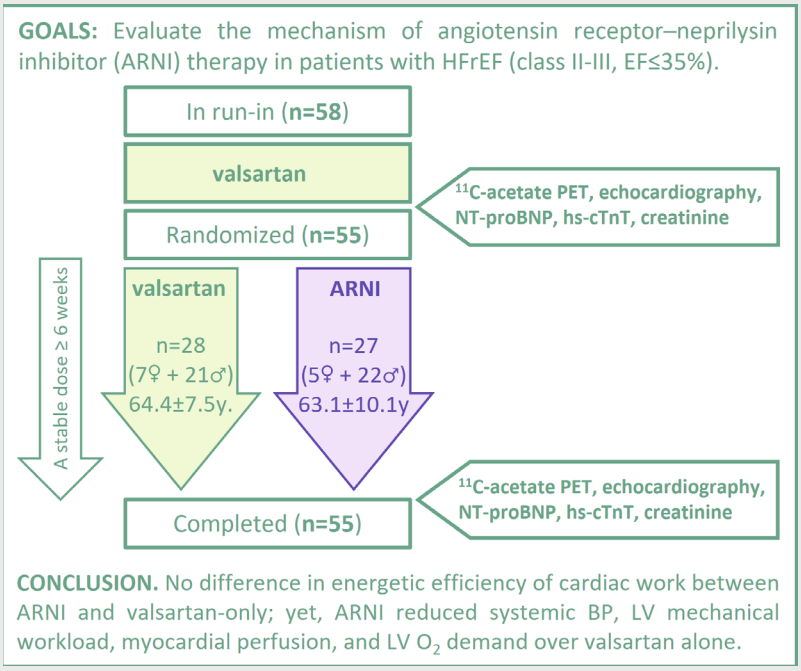
Graphical Abstract



This randomized, prospective, double-blind, parallel group study investigated short-term effects of sacubitril/valsartan therapy on myocardial oxygen consumption and energetic efficiency of cardiac work in patients with heart failure and reduced ejection fraction. Myocardial oxygen consumption, energetic efficiency of cardiac work, cardiac and systemic hemodynamics were quantified using echocardiography and ^{11}C-acetate positron emission tomography imaging before and after 6 weeks of therapy. Energetic efficiency of cardiac work remained unchanged in both treatment arms. However, there were reduction in blood pressure, myocardial perfusion and LV mechanical work as compared with the control group. BP - blood pressure; HFrEF - heart failure with reduced ejection fraction; hs-cTnT - High-sensitivity cardiac troponinT; LV - left ventricle; NT-proBNP - N-terminal prohormone brain natriureticpeptide.

Keywords Heart failure • Positron emission tomography • Echocardiography • Oxygen consumption • Perfusion • Ventricular function

Introduction

Heart failure is a severe medical condition that affects about 26 million people worldwide. It is a major cause of morbidity and mortality, with an estimated 1 million hospitalizations annually in the United States. Early detection, lifestyle modifications, and appropriate medical therapy can improve outcomes and reduce the burden of heart failure on patients.[1–3]

Combinations of disease-modifying medical therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 inhibitors effectively improve outcomes in chronic heart failure with reduced ejection fraction (HFrEF).[4,5] The PARADIGM-HF trial demonstrated that treatment with sacubitril/valsartan – the only existing ARNI – reduced the risk of cardiovascular death or heart failure hospitalization by 20% compared with enalapril in patients with New York Heart Association (NYHA) class II to IV heart failure with a left ventricular ejection fraction (LVEF) ≤35%.[6] Since then, several other clinical trials have investigated the safety and efficacy of ARNI in various subgroups of patients with or at risk of heart failure.[7–12]

The aim of ARNI therapy is to increase vasodilator natriuretic peptides and prevent counter-regulatory activation of the renin–angiotensin system in heart failure.[13] Despite the proven clinical benefits of ARNI therapy in HFrEF, its underlying mechanistic effects are largely unknown.[6,12] This study aimed to advance the understanding of these effects on haemodynamics, left ventricular (LV) function, myocardial oxygen consumption, and energetic efficiency of cardiac work as quantified by ^{11}C-acetate positron emission tomography (PET) and echocardiography. We compared the effects of ARNI with valsartan-only

therapy in a double-blind randomized study in patients with chronic HFrEF.

Methods

Study design and population

This study was a phase IV, prospective, randomized, double-blind, double-dummy, parallel-group single-centre trial performed in patients with HFrEF at Turku University Hospital, Turku, Finland. Differences in systemic haemodynamics, LV function, myocardial oxygen consumption, and energetic efficiency of cardiac work were evaluated by comparing the measures obtained after 6 weeks of treatment to those obtained at baseline.

Main inclusion criteria were: (i) age 40–80 years, (ii) documented chronic heart failure with LVEF 25–35% determined by echocardiography and NYHA class II–III symptoms, (iii) systolic blood pressure 110–160 mmHg at the time of randomization, (iv) optimal standard heart failure therapy according to the European Society of Cardiology (ESC) guidelines including at a minimum beta-blocker and valsartan treatment tolerated dose of 80 mg or 160 mg bid for at least 4 weeks during the screening/run-in period.

The main exclusion criteria were (i) current acute or subacute decompensated heart failure, (ii) acute coronary syndrome, stroke, transient ischaemic attack, or other major cardiovascular event or cardiovascular procedure within 3 months before screening, (iii) estimated glomerular filtration rate (eGFR) <45 ml/min, (iv) serum potassium >5.2 mmol/L, (v) serum creatinine >1.5 x upper limit of normal (ULN) at any time during the screening/run-in period that persists even after modification of concomitant medication(s), and (vi) contraindication to neprilysin inhibitor or angiotensin receptor blockers.

Eligible subjects were enrolled at a single site, the Heart Center of Turku University Hospital, from July 2018 to December 2021. Patients were included after providing verbal and written information on the study, its risks, and its benefits, and they signed an informed consent form. The competent authority (The Finnish Medicines Agency, Fimea) authorized the study before its commencement.

Fifty-five subjects were randomized in a 1:1 ratio to receive either ARNI or valsartan only, and all the randomized subjects completed the treatment phase. Stratified randomization was used to obtain matched groups in terms of renal insufficiency (eGFR <60 ml/min), diabetes, and tolerated dose of valsartan during the run-in period. The randomization was generated by an independent statistician at TFS HealthScience using SAS®. For details of randomization see *Appendix A*.

The study was conducted according to the International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), so the investigation conforms with the principles outlined in the Declaration of Helsinki. The data that provide the basis for the study findings are available from the corresponding author upon reasonable request.

Visit schedule and study treatment

We planned the total duration of the study to be 14 weeks for each subject. Still, it could be longer if required for scheduling purposes (e.g. availability of imaging slots, subject's schedule). During the study (*Figure 1A*), the subjects had 5–6 study visits – the safety visit 2 (*Figure 1A*, V) was not mandatory in the absence of titration of study medication. Two of the visits – the screening visit 2 (*Figure 1A*, II) and the safety visit 2 (*Figure 1A*, V) – could be performed remotely (i.e. telephone contact) if considered sufficient by the investigator. In addition, unscheduled visits could be scheduled at any time if deemed necessary for subject safety. Blood pressure, heart rate, and safety blood samples, including serum potassium and creatinine, were obtained at all visits.

After the screening evaluations, the patients entered a run-in period of up to 6 weeks, during which they received valsartan therapy with the maximum tolerated dose of 80 mg bid or 160 mg bid for a minimum of 4 weeks. After randomization (*Figure 1B*, III), the patients received the study drugs (for details of blinding see *Appendix B*). The starting dose for each patient in the sacubitril/valsartan arm was 100 mg bid, and in the valsartan arm was 80 mg bid or 160 mg bid, depending on the valsartan dose during the run-in phase. During the following visit (*Figure 1B*, IV), treatment tolerability was evaluated, and an attempt to up-titrate to the next dose level (sacubitril/valsartan 200 mg in the ARNI arm; or valsartan 160 mg in the valsartan arm) was made, if clinically possible.

Patient-reported symptomatic hypotension, systolic blood pressure <90 mmHg, serum potassium >5.2 mmol/L, eGFR <45 ml/min or serum creatinine >1.5 ULN resulted in deferring up-titration or down-titration of medication. The treatment period lasted, on average, for 9 weeks for each subject, with a stable dose for at least 6 weeks before the second set of assessments and imaging. Optimal standard heart failure therapy and other concomitant medications needed to treat concurrent diseases were allowed but kept stable during the study. The most common concomitant therapies were beta-blocking agents (93%), anti-thrombotic agents (78%), diuretics (64%), lipid-modifying agents (56%), and potassium-sparing agents (46%), with similar distributions between treatment groups.

Imaging assessments

Positron emission tomography imaging with ^{11}C-acetate and echocardiography were performed at the baseline visit after the valsartan run-in period and before randomization (*Figure 1A*, III). Blood pressure and heart rate were measured using a validated and reproducible stress test blood pressure monitor (Tango M2 Stress Test Monitor, Suntech, Morrisville, NC, USA) during both echocardiography and PET imaging at several time points. The mean value was used to represent the blood pressure during imaging. Procedures were repeated after 6 weeks on a stable dose of the study drug in each arm. All staff and the experts who performed the imaging tests were blinded to study groups.

^{11}C-acetate positron emission tomography

Positron emission tomography imaging was performed with a PET/computed tomography scanner (GE Discovery 690 PET/CT) at Turku PET Centre. Resting myocardial perfusion and oxygen consumption were quantified by ^{11}C-acetate PET as the tracer uptake (k_1) and mono-exponential clearance rate of ^{11}C-acetate (k_{mono}), respectively. Resting perfusion (k_1) was also used to calculate myocardial vascular resistance. The energetic efficiency of LV mechanical work was calculated as follows: Efficiency = (LV work/g of tissue)/k_{mono}.

In addition, the viable myocardium energetic efficiency was derived using vk_{mono} in the equation. The vk_{mono} was calculated similarly to k_{mono} but only from viable myocardium segments based on echocardiography. This parameter was included to rule out possible bias related to scar tissue in subjects with ischaemic cardiomyopathy.

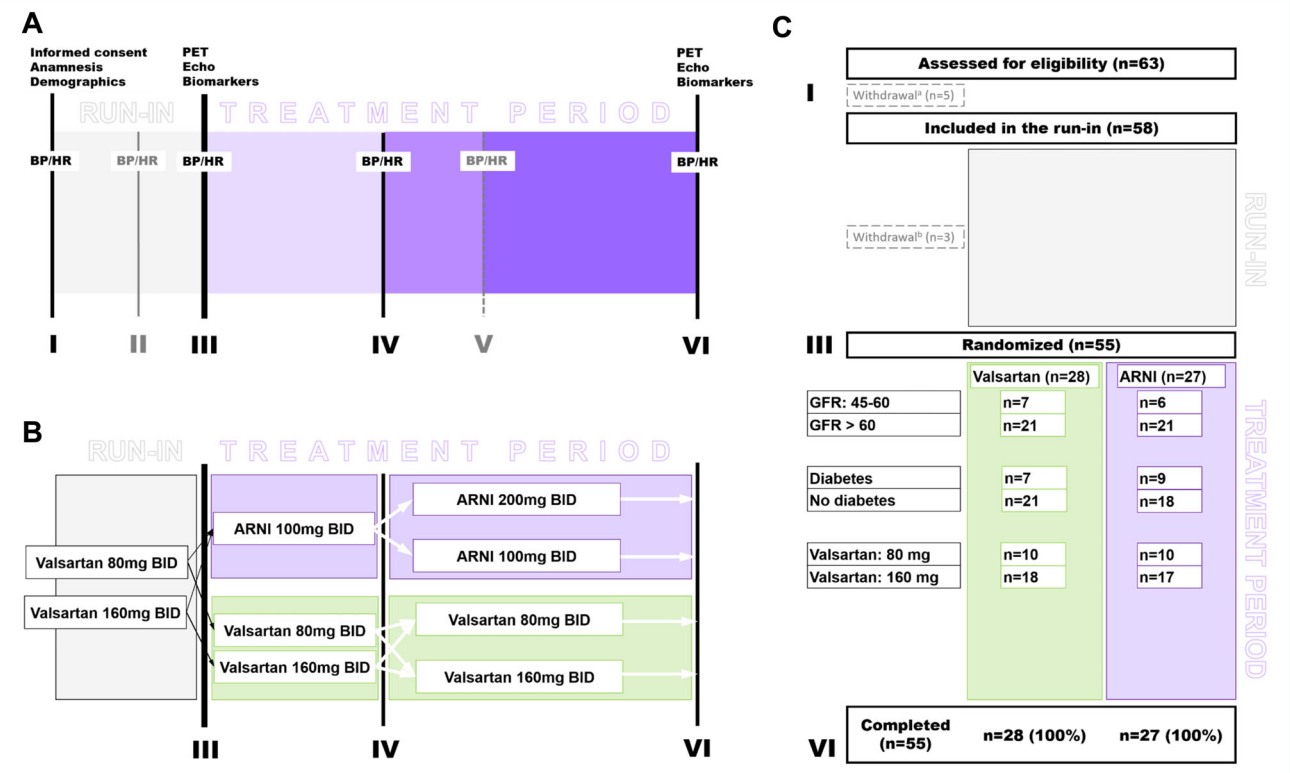


Figure 1 (*A*) Subject visit schedule. (*B*) Study treatments. (*C*) Subjects' dispositions and characteristics. I – screening visit 1, also the informed consent day; II – screening visit 2; III – the randomization visit, also the baseline imaging (positron emission tomography [PET], echocardiography) and the treatment start date; IV – safety visit 1; V – safety visit 2 (was not mandatory); VI – the follow-up imaging and also the end of treatment. I–III – the run-in (screening) period, 7 weeks on average; III–VI – the treatment period, 9 weeks on average. ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; GFR, glomerular filtration rate; HR, heart rate

Echocardiography

Echocardiography was performed with a GE Vivid E9 device (GE Vingmed Ultrasound, Horten, Norway) equipped with the MS5 matrix cardiac probe, according to standardized imaging protocol. All images were digitally stored for offline analysis (EchoPAC PC version 203; GE Vingmed, Horten, Norway).

The LVEF was measured using the biplane Simpson's method from the apical two- and four-chamber views. Segments with akinesia and wall thinning (≤4 mm) were defined as non-viable. The diameter of the LV outflow tract (LVOT) and LV mass (linear method) were measured in parasternal long-axis views. From apical five-chamber and three-chamber views, velocity time integral in the LVOT was measured using pulsed-wave Doppler as an average of at least three cardiac cycles in sinus rhythm and at least five cardiac cycles in atrial fibrillation for calculation of LV stroke volume.

Left ventricular work was calculated with the equation:

LV work = systolic blood pressure × stroke volume × heart rate.

Biomarkers

N-terminal prohormone brain natriuretic peptide (NT-proBNP), high-sensitivity troponin, and creatinine were measured to study mechanisms of changes in cardiac efficiency.

Statistics

Sample size

In earlier studies using biventricular pacing techniques in previously medicated subjects, the cardiac efficiency improved by 20%,[14] so we assumed that the clinically significant change in cardiac efficiency would be about the same 20%. In our previous studies in subjects with heart failure,[15,16] we studied the same patients twice in 3 months, and the coefficient of variation (CV%) of k_{mono} in the placebo group was 18.4%, and in the efficiency 19.7%. Based on sample size calculations, to detect a 15% change in cardiac efficiency, 27 subjects must be included in each treatment arm (assuming $\alpha = 0.05$ and $\beta = 0.2$). Due to potential dropout during the study, the target was to enrol 30 subjects for each treatment arm.

Endpoints and statistical analysis

The primary endpoint was the change in cardiac efficiency from baseline to end of treatment after 6 weeks on stable sacubitril/valsartan or valsartan therapy, which was analysed with ANCOVA. It included treatment group and stratification as independent factors and covariate adjustment for baseline cardiac efficiency. This model estimated the within-treatment group (ARNI-valsartan) changes by least-square means. The corresponding treatment difference was calculated with a 95% confidence interval and a *p*-value. In addition, treatment

by stratification interaction analyses were performed for the primary efficacy parameters to estimate within-stratification group differences. In addition to the primary endpoint, we analysed several echocardiography- and PET imaging-derived parameters using ANCOVA.

The results were summarized by the treatment arm using descriptive statistics at the baseline visit and the end of treatment, including change from the baseline to the end of treatment.

Results

Patient demographics

Sixty-three subjects were considered eligible, of whom 55 were ultimately randomized (*Figure 1C*). All the randomized subjects completed the treatment phase. Reasons for eight screening failures were: not fulfilling the inclusion criteria for heart failure ($n = 1$), hypotension ($n = 2$), renal dysfunction ($n = 1$), drug-induced rash during the run-in period ($n = 1$), consent withdrawal by subject ($n = 1$), lost to follow-up ($n = 2$). Overall, the treatment groups were matched at baseline (*Table 1*). The mean age was 63.1 ± 10.1 years in the ARNI group and 64.4 ± 7.5 years in the valsartan group. Atrial fibrillation was found in 41.8% and coronary artery disease in 29.1% of patients, with similar prevalence between treatment groups.

Changes in cardiac energetic efficiency

The study primary hypothesis was that short-term therapy with ARNI, versus valsartan-only, would improve the efficiency of cardiac work in subjects with systolic heart failure. There was no significant improvement in cardiac energetic efficiency after ARNI treatment compared with valsartan-only treatment. The absence of improvement was evident for both the full-analysis set ($p = 0.7$) and per-protocol set ($p = 0.8$) analysis populations (*Figure 2A*).

The energetic efficiency of viable myocardium was evaluated as a sensitivity analysis to exclude possible bias related to scar tissue (*Table 2*). In line with the primary analysis results, the sensitivity analysis showed no significant difference between the treatment groups for full-analysis set ($p = 0.8$) or per-protocol set ($p = 0.8$) (*Figure 2B*).

Changes in other measured parameters

The changes in the other cardiac and systemic haemodynamic parameters are summarized in *Tables 3* and *4*. Both diastolic (−4.5 mmHg; $p = 0.026$) and systolic blood pressure (−9.8 mmHg; $p = 0.0007$) were significantly lower in the ARNI group compared with the valsartan group at the end of treatment. In addition, resting myocardial perfusion (−0.054 mL/g/min; $p = 0.045$) and LV mechanical work (−296; $p = 0.038$) decreased significantly in the ARNI group compared with the valsartan group. Myocardial oxygen consumption similarly decreased in the ARNI group at the end of treatment (−5.4%, $p = 0.031$) compared with that at the run-in period, but remained unchanged in the valsartan group (+0.5%, $p = 0.8$). However, the difference was not statistically significant between the two groups at the end of treatment ($p = 0.088$). There were no changes in the other predefined measurements between groups.

Discussion

The PARADIGM-HF trial demonstrated that treatment with ARNI reduced the risk of cardiovascular death or heart failure hospitalization compared with enalapril in symptomatic patients with heart failure and LVEF ≤35%.This resulted in the incorporation of ARNI in the ESC guidelines for the management of heart failure as a class I recommendation (level of evidence B) for the treatment of patients with HFrEF.[17,18] Several other trials evaluated ARNI in patients with HFrEF, showing its safety[19] and beneficial effects in terms of reduced NT-proBNP, quality of life, and LV remodelling.[7–12,20,21] Despite the clinical benefits of ARNI, the underlying functional cardiac effects are largely unknown.[6,12] This study aimed at improving our understanding of the mechanisms of action of ARNI therapy, especially its effects on haemodynamics, LV function, myocardial oxygen consumption, and the energetic efficiency of cardiac work. We included patients that are similar to those in the PARADIGM-HF trial and in whom ARNI is clinically indicated.

We found that ARNI did not improve the energetic efficiency of cardiac work compared with valsartan only. However, it significantly reduced systemic blood pressure, LV mechanical work, and resting myocardial perfusion versus valsartan. In parallel with reduced LV mechanical work, ARNI reduced myocardial oxygen consumption compared with baseline; no such change was observed in the valsartan group. Since the energetic efficiency of cardiac work is a ratio between LV mechanical work and myocardial oxygen consumption, it remained therefore unchanged in the ARNI group. Yet, the change in myocardial oxygen consumption was not significantly different between the two groups at the end of treatment ($p = 0.08$). Based on our findings, ARNI therapy reduces afterload and LV work, possibly leading to reduced myocardial perfusion and myocardial oxygen demands and consumption. Thus, these findings support the myocardial oxygen-sparing effects of ARNI (*Graphical Abstract*).

The effects of heart failure and its therapies on myocardial oxygen consumption is a fascinating topic. The current understanding is that in the early phase of heart failure, myocardial oxygen consumption is preserved, but the reduction of the produced cardiac work leads to decreased work efficiency – oxygen is wasted. With progressing heart failure and deteriorating myocardium, oxygen consumption starts to decline, along with further reduced work efficiency.[22–24]

The effects of heart failure therapies on myocardial oxygen consumption and efficiency of work have been studied in several trials. Beta-blockers have been shown to reduce myocardial oxygen consumption and increase the efficiency of LV work.[25] On the other hand, some therapies, such as dobutamine infusion, improve LV work and increase myocardial oxygen consumption but do not change efficiency.[22] Other vasodilating therapies with afterload-reducing effect, such levosimendan, are neutral towards efficiency and myocardial oxygen consumption.[26,27] Cardiac resynchronization therapy[28] appears to improve LV function without

Table 1 Subjects' characteristics and clinical history beyond heart failure[a]

	ARNI	Valsartan	Total
Patient characteristics			
Age, years, mean ± SD	63.1 ± 10.1	64.4 ± 7.5	63.8 ± 8.8
Female sex, *n* (%)	5 (18.5)	7 (25.0)	12 (21.8)
Male sex, *n* (%)	22 (81.5)	21 (75.0)	43 (78.2)
Clinical history of subjects beyond heart failure, *n* (%)			
Dyslipidaemia	13 (48.1)	16 (57.1)	29 (52.7)
Type 1 diabetes mellitus	1 (3.7)	0	1 (1.8)
Type 2 diabetes mellitus	8 (29.6)	7 (25.0)	15 (27.3)
Hypertension	15 (55.6)	14 (50.0)	29 (52.7)
Atrial fibrillation	14 (51.9)	9 (32.1)	23 (41.8)
Coronary artery disease	8 (29.6)	8 (28.6)	16 (29.1)
Previous myocardial infarction	1 (3.7)	3 (10.7)	4 (7.3)
Coronary artery bypass	4 (14.8)	0	4 (7.3)
Cardiac pacemaker	3 (11.1)	2 (7.1)	5 (9.1)
Physiological parameters at baseline, median (Q1–Q3)			
Heart rate, bpm	62.0 (59.0–78.0)	60.5 (56.2–71.0)	61.0 (57.0–73.0)
Systolic BP, mmHg	109.0 (99.0–126.0)	114.5 (101.8–125.5)	113.0 (100.0–126.0)
Diastolic BP, mmHg	66.0 (61.0–74.0)	65.5 (58.0–74.5)	66.0 (59.0–74.0)
NT-proBNP, pg/ml	574.0 (389.0–1720.0)	681.0 (336.0–1190.0)	605.5 (355.0–1380.0)

ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; Q, quartile; SD, standard deviation.
[a]None of the variables were significantly different between groups.

Table 2 Viable myocardial energetic efficiency (full-analysis set)

	ARNI	Valsartan
Baseline		
Number of observations	27	28
Mean (SD)	48 163 (16720)	49 576 (18256)
Median	43 416	44 226
Q1–Q3	37 874–60 800	37 833–60 041
Min–max	23 530–83 926	19 063–98 933
End of therapy		
Number of observations	27	28
Mean (SD)	49 914 (20821)	52 250 (19586)
Median	41 309.4	49 241
Q1–Q3	36 541–56 993	38 958–65 052
Min–Max	20 828–95 843	23 956–104 298

ARNI, angiotensin receptor–neprilysin inhibitor; Q, quartile; SD, standard deviation.

increasing global LV oxidative metabolism, resulting in improved myocardial efficiency. The results of these studies suggest that the known beneficial long-term therapies for heart failure typically are neutral or reducing myocardial oxygen consumption but should not increase oxygen demands. The findings with myocardial energetic efficiency suggest that these therapies typically either improve efficiency or are neutral to it, whereas they may increase LV performance. None of the known beneficial therapies appear to reduce the efficiency of work. The observed differences in effects between these therapies likely depend on the mechanism of action and the severity of heart failure in the studied population.

The results of the present study suggest that ARNI, when compared with valsartan only, does not change the efficiency of myocardial work but leads to reduced systemic blood pressure, LV mechanical work, myocardial perfusion, and oxygen consumption. Interestingly, ARNI did not change many other measured parameters, including LVEF, cardiac output, systemic vascular resistance, and biomarkers such as NT-proBNP. The earlier larger trials demonstrated a decrease in NT-proBNP.[29,30] Our study was not powered to detect changes in such parameters as ejection fraction or NT-proBNP. The endpoints were the specific haemodynamic parameters, oxygen consumption, and efficiency of myocardial work, aiming to understand the mechanisms of the therapy and explain the detected clinical findings in previous larger trials. Of note, all patients were receiving valsartan therapy during the run-in period, as well as the control group during the study. Therefore, our results do not tell what kind of changes ARNI would generally induce in drug-naïve patients. Still, they tell more about the effects of the combination of sacubitril and valsartan over valsartan only.

The effect of neprilysin inhibitors is not straightforward or unidirectional. In the cardiovascular system, neprilysin, a versatile enzyme, degrades numerous vasoactive peptides. The affinities differ, and this also interferes with the end effect. Neprilysin displays the highest affinity for atrial natriuretic peptide, C-type natriuretic peptide, and angiotensin I and II. The affinity towards B-type natriuretic peptide, endothelin-1, and bradykinin is lower. Inhibition of neprilysin activity elevates plasma concentrations of natriuretic peptides, which induce vasodilatation and have both

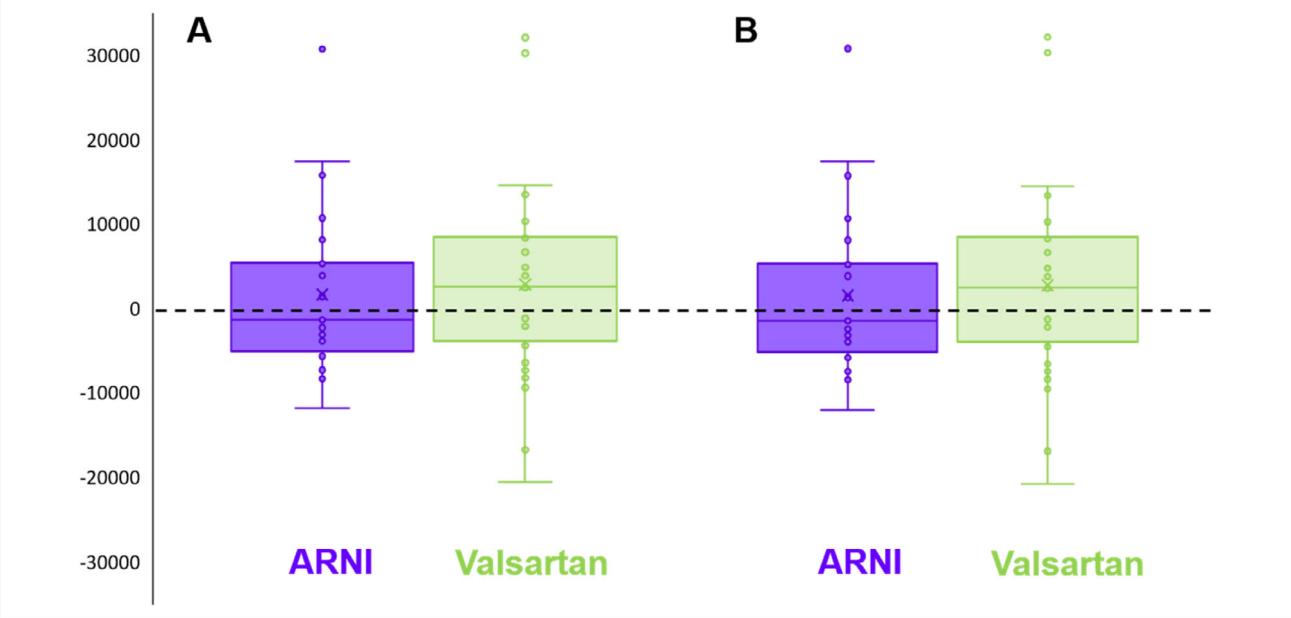


Figure 2 Changes from baseline in myocardial efficiency. (*A*) Changes in myocardial energetic efficiency. (*B*) Changes in viable myocardial energetic efficiency. Dotted line (at y = 0) is 'no changes'. The angiotensin receptor–neprilysin inhibitor (ARNI) arm included 27 subjects; the valsartan arm included 28 subjects.

Table 3 Changes in systemic blood pressure during echocardiography and positron emission tomography imaging (full-analysis set)

	Treatment	*n*	LS mean change	LS mean EoT	Estimated difference	95% CI	*p*-value
Echocardiography							
Diastolic BP	ARNI	27	−4.3	61.8	−5.5	−10.4; −0.5	0.031
	Valsartan	28	1.2	67.3			
Systolic BP	ARNI	27	−4.2	108.7	−7.8	−15.4; −0.3	0.043
	Valsartan	28	3.7	116.5			
PET scan							
Diastolic BP	ARNI	27	−4.3	62.7	−4.5	−8.4; −0.6	0.026
	Valsartan	28	0.2	67.1			
Systolic BP	ARNI	27	−7.2	108.1	−9.8	−15.2; −4.4	0.0007
	Valsartan	28	2.6	117.9			

ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure (mmHg); CI, confidence interval; EoT, end of treatment; LS, least square; PET, positron emission tomography.
Based on the ANCOVA model for change from baseline after 6 weeks, including treatment group and strata as factors and baseline level as a covariate.

systemic and local cardioprotective effects.[13] Yet, neprilysin also degrades vasoconstrictor peptides – e.g. angiotensin I and II and endothelin-1 – and thus, can simultaneously have an opposite effect, which is counteracted by its combination with valsartan.

Study limitations

Only patients with HFrEF were included in the study, and the results may not be extrapolated to other groups of heart failure. The power of the study was based on an estimated 15% change in the main parameters. Therefore, smaller changes could not be detected. However, clinically meaningful changes in such surrogate markers should be in this range. As the duration of ARNI therapy was only 6 weeks, it was not possible to investigate long-term effects such as LV reverse remodelling.[31,32] Despite the appropriate randomization, some imbalances occurred between the groups. For instance, the ARNI group had 14 patients (51.9%) with a history of atrial fibrillation, while valsartan had 9 (32.1%); in the ARNI group, 4 (14.8%) patients had a coronary artery bypass, while the valsartan group did not have such patients (0, 0.0%).

Conclusion

We found no difference in the energetic efficiency of cardiac work between ARNI and valsartan-only groups in HFrEF patients. However, ARNI reduces systemic blood pressure, LV mechanical workload, myocardial perfusion, and LV oxygen demands over run-in period valsartan alone. These findings suggest a myocardial

Table 4 Echocardiography, positron emission tomography and laboratory parameters and their changes in each arm (full-analysis set)

Parameter	ARNI				Valsartan				Estimated difference ARNI vs. valsartan	*p*-value
	Baseline	End of therapy	Change	LS mean change	Baseline	End of therapy	Change	LS mean change		
Echocardiography										
Stroke volume	76.8 (20.8)	76.9 (19.8)	0.1 (5.6)	−0.1163	83.7 (15.3)	86.2 (15.1)	2.5 (7.2)	2.7193	−2.8356	0.12
Cardiac output	5132 (1316)	5176 (1167)	44.8 (649.4)	32.2	5293 (1128)	5457 (955)	163.4 (794.1)	175.6	−143.3	0.43
LV mechanical work	2715 (1004)	2610 (932)	−105 (453.2)	−106.1	2790 (941.5)	2979 (1136)	189.2 (542.4)	190.2	−296.3	**0.038**
Ejection fraction	29.2 (10.4)	30.2 (10.8)	1.0 (5.3)	1	29.0 (7.3)	31.6 (9.9)	2.6 (6.8)	2.6	−1.6	0.36
Resistance										
Systemic vascular	0.0230 (0.0071)	0.0217 (0.0063)	−0.0013 (0.0041)	−0.0012	0.0228 (0.0066)	0.0222 (0.0055)	−0.0005 (0.0050)	−0.0006	−0.0006	0.57
Coronary vascular	183.3 (56.5)	181.0 (46.3)	−2.3 (30.3)	−1.1	174.1 (51.0)	174.8 (42.6)	0.7 (32.2)	−0.5	−0.6	0.93
PET										
Resting perfusion	0.676 (0.202)	0.629 (0.167)	−0.047 (0.080)	−0.05	0.710 (0.207)	0.710 (0.200)	0 (0.117)	0.003	−0.054	**0.045**
k_{mono}	0.0571 (0.0149)	0.0541 (0.0133)	−0.0031 (0.0087)	−0.0031	0.0573 (0.0140)	0.0576 (0.0123)	0.0003 (0.0082)	0.0003	−0.0034	0.088
NT-proBNP	1360.3 (1862.7)	1118.3 (1769.2)	−242.0 (736.7)	−234.5	1176.3 (1971.3)	1093.8 (1790.3)	−125.33 (331.1)	−132.8	−101.7	0.48

Based on the ANCOVA model for change from baseline after 6 weeks, including treatment group and strata as factors and baseline level as a covariate.
ARNI, angiotensin receptor–neprilysin inhibitor; k_{mono}, mono-exponential clearance rate of ^{11}C-acetate; LS, least square; LV, left ventricular; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PET, positron emission tomography.

oxygen-sparing effect of ARNI over valsartan in patients with heart failure.

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Appendix

Randomization

Sealed envelopes containing the individual treatment codes (randomization number and the corresponding treatment) were stored adjacent to the investigational medicinal products until the end of the trial. In case of emergency requiring immediate knowledge of the treatment administered, the code of an individual subject may be opened. The reasons for opening the code have to be documented and the subject was to be discontinued from the study. The study monitor and the sponsor should be immediately informed about breaking treatment code.

Blinding

Study drug packages were provided from Novartis with removable labels stating the treatment. Treatment allocation was done by an unblinded member of the study team who removed the labels stating the treatment before distributing the study drug packages to the subjects. The study was conducted in a double-blind fashion. Since the sacubitril/valsartan and valsartan tablets differ in appearance, the study was performed in a double-dummy manner with the subjects taking one active tablet and one placebo tablet bid. The different strengths of the two study drugs were not identical in appearance so the possible dose modification(s) during the treatment period could be performed in a blinded manner. However, the up-titration step was aligned in both treatment arms – the subjects will start on valsartan (80 mg bid or 160 mg bid) or sacubitril/valsartan (100 mg bid) and there will be only one scheduled up-titration visit after the randomization. The subjects who started with valsartan 160 mg bid had similar scheduled visit but they stayed on the same dose.

Valsartan used in the screening/run-in period was taken from local commercial stock and was labelled by Tamro. Study drugs for

the treatment period of the study were manufactured by Novartis, in accordance with Good Manufacturing Practice (GMP) guidelines. Supplies for the study were packed and labelled in compliance with GMP regulations, then released at Novartis. The different strengths of the study drugs and the corresponding placebo tablets were packed in separate study drug packages and an appropriate number of these study drug packages were provided to the study site. The study drug packages containing the different strengths of the specific treatment (i.e. sacubitril/valsartan or valsartan) and placebo were labelled in a way that does not reveal the treatment arm; the removable label stating the treatment was removed before dispensing the packages to the subjects. The possible up-titration of the study drug dose was decided by the investigator based on the clinical status of the subject and safety assessments.

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