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Original research

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ABSTRACT

Objective Patients with a systemic right ventricle (sRV) in the context of transposition of the great arteries (TGA) after atrial switch or congenitally corrected TGA (ccTGA) are prone to sRV dysfunction. Pharmacological options for sRV failure remain poorly defined. This study aims to investigate the tolerability and effects of sacubitril/valsartan on sRV failure in adult patients with sRV.

Methods In this two-centre, prospective cohort study, all consecutive adult patients with symptomatic heart failure and at least moderately reduced sRV systolic function were initiated on sacubitril/valsartan and underwent structured follow-up.

Results Data of 40 patients were included (40% female, 30% ccTGA, median age 48 (44–53) years). Five patients discontinued therapy during titration. Median follow-up was 24 (12–36) months. The maximal dose was tolerated by 49% of patients. No episodes of hyperkalaemia or renal function decline occurred. Six-minute walking distance increased significantly after 6 months of treatment (569±16 to 597±16 m, p=0.016). Serum N-terminal-prohormone brain natriuretic peptide (NT-proBNP) levels decreased significantly after 3 months (567 (374–1134) to 404 (226–633) ng/L, p<0.001). Small, yet consistent echocardiographic improvements in sRV function were observed after 6 months (sRV global longitudinal strain: −11.1±0.5% to −12.6±0.7%, p<0.001, and fractional area change: 20% (16%–24%) to 26% (19%–30%), p<0.001). The linear mixed-effects model illustrated that after first follow-up moment, no time effect was present for the parameters.

Conclusions Treatment with sacubitril/valsartan was associated with a low rate of adverse effects in this adult sRV cohort. Persisting improvement in 6-minute walking test distance, NT-proBNP levels and echocardiographic parameters of sRV function was observed in an on-treatment analysis and showed no differential response based on sex or anatomy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Congenital heart disease (CHD) patients with a systemic right ventricle (sRV) are prone to systolic sRV dysfunction and heart failure, with over 50% having a reduced systolic sRV function and symptoms by the age of 40 years. To date, pharmacological options for sRV patients are poorly defined.

WHAT THIS STUDY ADDS

⇒ This study explores tolerability and medium-term effects of sacubitril/valsartan treatment in sRV failure and reflects on 64 patient-years. Sacubitril/valsartan was reasonably tolerated with a low rate of significant adverse effects and associated with an improvement in 6-minute walking test performance, decrease in NT-proBNP levels, and echocardiographic systolic sRV function. These positive effects persist during a median follow-up of 24 [12-36] months and show no differential response based on sex or underlying anatomy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ One of the main gaps in knowledge identified by the recent guidelines on adult CHD management is the lack of evidence for the application of standard heart failure treatment in sRV patients. The results of this study suggest that sacubitril/valsartan is reasonably safe with a low rate of significant adverse effects in sRV patients and might have a role in halting the progression of heart failure in this patient group and substantiates a future randomized controlled trial.

INTRODUCTION

Patients with transposition of the great arteries (TGA) after the atrial switch operation and patients with congenitally corrected TGA (ccTGA) form a group of patients with congenital heart disease (CHD) with a systemic right ventricle (sRV) in a biventricular circulation. The morphological RV in a subaortic position sustaining the systemic circulation is not equipped for this state of chronic pressure overload, leading to a myriad of late sequelae.[1]

Heart failure (HF) is currently the major cause of morbidity and mortality in this ageing group of patients.[1–4] The course of HF in patients with sRV is characterised by subclinical periods of 5–10 years during which signs of sRV dysfunction are already present, providing a potential window of opportunity to halt the progression to clinically overt HF through timely intervention.

Over the past years, a great deal of knowledge has been gained on the management of left ventricular (LV) failure in patients without CHD.[5] However, the specific anatomical and haemodynamic

characteristics of the RV limit our ability to extrapolate this to sRV failure. Pharmacological options for the sRV are not well defined and the most recent European (European Society of Cardiology) and American (American Heart Association) guidelines refrain from recommendations regarding specific therapy for systolic sRV dysfunction.[1 6] Follow-up analysis of the valsartan in failing sRV trial showed that in symptomatic patients in the placebo group, the sRV function deteriorated significantly, whereas the ejection fraction remained stable over 3 years in the valsartan group.[7 8] Longer follow-up also showed fewer clinical events in symptomatic patients treated with valsartan, suggesting that pharmacological therapy targeting the renin–angiotensin–aldosterone system can impact long-term outcomes.[7 8] The first short-term experiences with sacubitril/valsartan in adult CHD (ACHD) have been optimistic.[9–14] The aim of this study is to investigate the medium-term effects of sacubitril/valsartan treatment on a cohort of patients with sRV failure in a prospective setting.

METHODS

Design and inclusion/exclusion criteria

This two-centre, prospective observational cohort study was performed at the Departments of Cardiology of the Leiden and Amsterdam University Medical Centers. Data of all consecutive adult patients with a failing sRV in a biventricular circulation treated with sacubitril/valsartan are reported. Symptomatic patients with an estimated sRV ejection fraction of ≤40% (defined as at least moderately reduced systolic echocardiographic sRV function, or mildly reduced sRV function with moderate-severe tricuspid regurgitation (TR)), who were initiated on sacubitril/valsartan in an ambulant setting on top of their current medical therapy in the period between January 2019 and March 2022, were included for analysis.[5] Where appropriate, ACE inhibitor/angiotensin II receptor blocker was replaced. A subgroup of this cohort has previously been described.[13]

Treatment and follow-up

All investigations and outpatient clinic visits were performed as part of a standardised clinical pathway at both participating centres.[15] Data were collected from the electronic patient records and included medical history, complaints (a.o. New York Heart Association (NYHA) classification), pharmacological therapy, physical examination, 12-lead ECG recording, bicycle ergometry with VO_2max, 6-minute walking test (6MWT), transthoracic echocardiography, laboratory investigations and cardiac implantable electronic device interrogation when applicable. Data were collected at the outpatient clinic visit and/or telephone consultation prior to treatment initiation (baseline), during titration and at 3, 6, 12, 24 and 36 months of follow-up after the highest tolerated dose was initiated. The closing date for follow-up was February 2023, or at the last outpatient clinic visit prior to escalation to a sodium-glucose cotransporter 2 inhibitor (SGLT2i) and/or severe valvular heart disease necessitating intervention and/or heart transplantation/ventricular assist device (VAD) eligibility listing or death.

Serial echocardiograms were performed with commercially available ultrasound systems and were analysed offline in EchoPAC (GE Medical Systems, USA) independently by at least two imagers with expertise in CHD and blinded to the patient status. The methodology was at large previously described (online supplemental material 1).[13 16]

Outcomes

The primary endpoint was the temporal change from baseline to 6, 12, 24 and 36 months in the 6MWT distance. The key secondary endpoint was the temporal change from baseline to 3, 6, 12, 24 and 36 months in serum N-terminal-prohormone brain natriuretic peptide (NT-proBNP) levels. Further, secondary endpoints included the serial changes in systolic sRV function, laboratory values (including renal function and haematocrit), NYHA class and performance at bicycle ergometry. An explorative subgroup analysis was performed to differentiate for sex, anatomy, maximal tolerated sacubitril/valsartan dose and for the subgroup who required treatment escalation during follow-up.

Statistical analysis

All statistical analyses were performed in IBM SPSS V.25. Normally distributed continuous data are displayed as mean±SE and non-normally distributed continuous data are displayed as median with the IQR (Q1–Q3). Proportions are displayed as numbers (percentages). Normality was graphically assessed and additionally tested with the use of the Shapiro-Wilk test.

For the comparison of continuous data, a paired samples t-test was used. For categorical data, the McNemar test or Wilcoxon signed-rank test was used, as appropriate. In case of substantial right skew in the outcomes, the natural log transformation was first applied.

A linear mixed-effects model was used to adjust for the trend in repeated measures from first follow-up moment after baseline. The models were adjusted for within-patient observations with random intercept per patient and linear time effect, and baseline values as fixed effects. Time was used as a categorical variable to get estimated means at each follow-up time. In the case of categorical variables with a binary outcome, a generalised linear logistic model was used.

The interobserver and intraobserver agreement between individual measurements for sRV global longitudinal strain (GLS) and sRV fractional area change (FAC) was statistically assessed by calculating the intraclass correlation coefficient (ICC) using a two-way mixed model. ICC values of <0.5, 0.5–0.75, 0.75–0.9 and >0.9 indicated poor, moderate, good and excellent reliability, respectively.[17]

For the subgroup analyses, baseline characteristics and initial treatment response (change from baseline to first follow-up moment in terms of primary and key secondary outcomes) were assessed by unpaired t-tests, one-way analysis of variance or X^2 tests as appropriate.

A p value of <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

Treatment with sacubitril/valsartan was initiated in 40 patients (40% female, 30% ccTGA, 58% had concomitant defects; table 1). The median age was 48 (44–53) years. The median follow-up period was 24 (12–36) months and entailed 64 patient-years. A total of 35 patients completed the 3-month follow-up, and 34, 29, 20 and 12 patients completed the 6, 12, 24 and 36 months of follow-up, respectively (figure 1). Twenty-eight patients (70%) were in NYHA class II at treatment initiation. All patients were on at least one HF medication prior to the initiation of sacubitril/valsartan, 25% were on at least two HF medications, and 45% used three or more. Five patients (12%) had primarily HF-related hospitalisation in the year prior to initiation of sacubitril/valsartan.

Treatment

Five patients discontinued therapy during the titration phase (one patient had an HF-related death, two underwent a VAD

Table 1 Patient characteristics at baseline differentiated for anatomy

Patient characteristics at baseline	All patients initiated on sacubitril/valsartan (n=40)	ccTGA (n=12)	TGA atrial switch (n=28)	P value for comparison between ccTGA and TGA atrial switch
Anatomy				
ccTGA	12 (30%)			
TGA atrial switch	28 (70%)			
Age, years (median (Q1–Q3))	48 (44–53)	51 (39–61)	47 (44–50)	0.879
Female	16 (40%)	6 (50%)	10 (36%)	0.398
General				
NYHA functional class				**0.017**
NYHA II	30 (75%)	6 (50%)	24 (86%)	
NYHA III–IV	10 (25%)	6 (50%)	4 (14%)	
History of atrial arrhythmia	22 (55%)	6 (50%)	16 (57%)	0.677
History of TV surgery	11 (27%)	5 (42%)	6 (21%)	0.189
HF-related hospitalisation in past year	5 (12%)	3 (25%)	2 (7%)	0.118
CIED	23 (58%)	6 (50%)	17 (61%)	0.530
AAI-PM	2 (5%)	0 (0%)	2 (7%)	
DDD-PM	7 (17%)	1 (8.5%)	6 (21%)	
DDD-ICD	7 (17%)	1 (8.5%)	6 (21%)	
CRT-P	1 (2%)	0 (0%)	1 (4%)	
CRT-D	6 (15%)	4 (33%)	2 (7%)	
Pharmacological therapy				
Beta-blocker	18 (45%)	4 (33%)	14 (50%)	0.332
ACEi/ARB	39 (98%)	12 (100%)	27 (96%)	0.507
MRA	16 (40%)	7 (58%)	9 (32%)	0.121
Diuretics (loop and/or thiazide)	19 (47%)	7 (58%)	12 (43%)	0.369
Antiarrhythmic	11 (27%)	5 (42%)	6 (21%)	0.189
Functional parameters				
Weight, kg (mean±SE)	81±3	83±6	80±3	0.630
BMI, kg/m^2 (median (Q1–Q3))	25 (23–28)	28 (22–28)	25 (23–28)	0.715
Systolic blood pressure, mm Hg (median (Q1–Q3))	110 (104–119)	109 (103–114)	110 (104–133)	0.060
6MWT, metres (mean±SE)	560±16	542±36	567±17	0.480
Exercise capacity (watt), % of predicted (mean±SE)	85±4	85±9	85±4	0.997
VO_2max, mL/kg/min (mean±SE)	17.5±0.8	15.9±1.7	18.0±1.0	0.269
Laboratory findings				
eGFR, mL/min/1.73 m^2 (mean±SE)	84±3	76±8	87±3	0.207
NT-proBNP, ng/L (median (Q1–Q3))	623 (380–1247)	1602 (417–4329)	558 (371–1083)	**0.045**
Echocardiography				
sRV function				0.195
Mildly reduced	6 (15%)	2 (17%)	4 (14%)	
Moderately reduced	27 (68%)	6 (50%)	21 (75%)	
Severely reduced	7 (17%)	4 (33%)	3 (11%)	
Tricuspid regurgitation				0.197
Grade 1 or less	16 (40%)	4 (33%)	12 (43%)	
Grade 2	20 (50%)	5 (52%)	15 (54%)	
Grades 3–4	4 (10%)	3 (25%)	1 (4%)	

Data are expressed as number (percentage) unless otherwise indicated.
Bold data: statistically significant (p <0.05)
ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; ccTGA, congenitally corrected transposition of the great arteries; CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy with a pacemaker and an implantable cardioverter defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator ; MRA, mineralocorticoid receptor antagonist; 6MWT, 6-minute walking test; NT-proBNP, N-terminal-prohormone brain natriuretic peptide; NYHA, New York Heart Association functional classification; PM, pacemaker; Q, quartile; sRV, systemic right ventricle; TGA, transposition of the great arteries; TV, tricuspid valve.

implantation, one had a strong personal preference to cease pharmacological treatment and one experienced uncontrollable thirst after drug initiation) (figure 1). No HF-related hospitalisation occurred during follow-up. Of the five patients with previous HF-related hospitalisation, three (60%) underwent VAD implantation, heart transplantation or died within a year after initial treatment initiation. Of these three, two (66%) discontinued treatment during titration. Further analyses on treatment were performed on the remaining 35 patients who completed the titration phase.

The maximal dose of 97/103 mg sacubitril/valsartan two times per day was tolerated by 49% of the patients and no episodes of

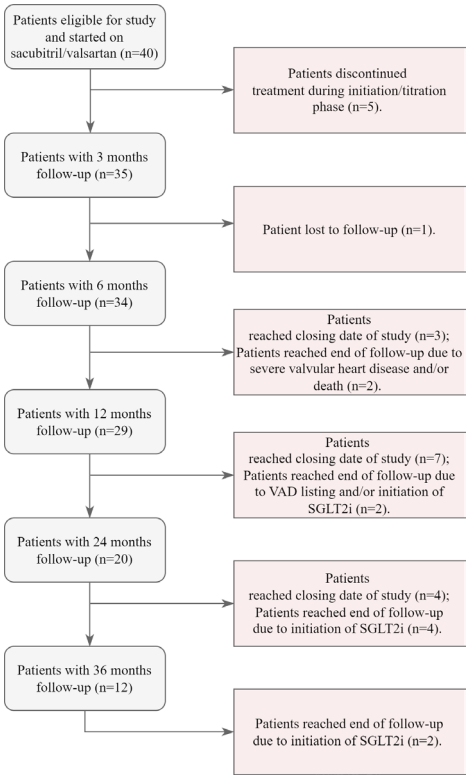

Figure 1 Study flow chart illustrating a schematic overview of patient inclusion and treatment or follow-up discontinuation. SGLT2i, sodium-glucose cotransporter 2 inhibitor; VAD, ventricular assist device.

renal function decline or hyperkalaemia were observed (table 2). The main reason for not reaching the highest dose was (orthostatic) hypotension (89%). Systolic blood pressure remained unchanged during follow-up.

Clinical outcomes

The clinical and echocardiographic outcomes per follow-up moment are shown in tables 3 and 4.

Primary endpoint

The 6MWT distance increased significantly from baseline to 6 months of treatment from 569±16 to 597±13 m (p=0.016) (figure 2). The linear mixed-effects model illustrated that thereafter, no time effect was present, that is, the effects of treatment with sacubitril/valsartan on the 6MWT performance remained unchanged from 6 months to 12, 24 and 36 months of follow-up.

Key secondary endpoint

Serum NT-proBNP levels decreased significantly from baseline to 3 months of treatment from 567 (374–1134) to 404 (226–633) ng/L, p<0.001, and remained stable from 3 months onwards (figure 3).

Secondary endpoints

Global sRV systolic function remained stable from baseline to 6 months of treatment (p=0.058) and no time effect was present throughout follow-up. sRV GLS and FAC improved significantly from baseline to 6 months of treatment (−11.1±0.5% to −12.6±0.7%, p<0.001 and 20% (16%–24%) to 26% (19%–30%), p<0.001, respectively). Tricuspid annular plane systolic excursion also improved from 13±0.5 to 14±0.6 mm (p=0.030). Free-wall LV GLS improved slightly from −20.3±1 to −22.7±1 (p=0.019). The linear mixed-effects model illustrated that from 6 months onwards, no time effect was present for the majority of the echocardiographic parameters.

There was no significant renal function decline from baseline to 3 months (estimated glomerular filtration rate 85±3 to 82±4 mL/min/1.73 m^2, p=0.188), and it remained stable during follow-up. Haematocrit also remained unchanged. The NYHA functional class and exercise capacity as measured by bicycle ergometry remained unchanged from baseline to 3 and 6 months, respectively, which persisted during follow-up.

Interobserver and intraobserver agreement

The ICC for interobservant and intraobservant for sRV GLS was good (0.889; 95% CI 0.731 to 0.955, p<0.001 and 0.844; 95% CI 0.341 to 0.962, p=0.007, respectively). The ICC for interobservant variability was poor for sRV FAC (0.409; 95% CI 0.235 to 0.741, p<0.078), and good for intraobservant (0.827; 95% CI 0.357 to 0.956, p=0.005).

Subgroup analyses

No significant differences between the ccTGA or the atrial switch group with regard to demographic characteristics, 6MWT or bicycle ergometry performance, history of tricuspid valve surgery, pharmacotherapy, echocardiographic findings or renal function at baseline were found (table 1). NYHA class and levels of the NT-proBNP were significantly higher in patients with ccTGA compared with TGA after atrial switch (50% NYHA III–IV vs 14%, p=0.017 and 1602 (417–3429) vs 558 (371–1083) ng/L, p=0.045). No differential response of the primary and key secondary endpoint stratified by anatomy was observed (ccTGA vs TGA after atrial switch: change in 6MWT distance: 34±20 vs 25±13 m, p=0.726, and change in NT-proBNP: −42±7% vs −30±5%, p=0.250).

Table 2 Maximal tolerated dose of sacubitril/valsartan, differentiated for anatomy and sex

Maximal tolerated dose of sacubitril/valsartan	All patients who completed the titration phase (n=35)	ccTGA (n=9)	TGA atrial switch (n=26)		Female (n=14)	Male (n=21)	
24/26 mg two times per day	7 (20%)	3 (33%)	4 (25%)	p=0.485	5 (36%)	2 (10%)	**p=0.004**
49/51 mg two times per day	11 (31%)	2 (22%)	9 (35%)		7 (50%)	4 (19%)	
97/103 mg two times per day	17 (49%)	4 (45%)	13 (50%)		2 (14%)	15 (71%)	

Data are expressed as number (percentage).
Bold data: statistically significant (p <0.05)
ccTGA, congenitally corrected transposition of the great arteries; TGA, transposition of the great arteries.

Table 3 Clinical outcomes at baseline (patients who have completed titration) and at the follow-up moments

	Baseline (n=35)	3 months (n=35)	6 months (n=34)	Paired t-test p value from baseline to first FU moment*	12 months (n=29)	24 months (n=20)	36 months (n=12)	Model-based p value trend in time from first FU moment onwards
General, n (%)								
NYHA functional class				0.125				0.927
NYHA II	28 (80)	29 (94)	33 (97)		25 (93)	18 (90)	11 (92)	
NYHA III–IV	7 (20)	2 (7)	1 (3)		2 (7)	2 (10)	1 (8)	
HF-related hospitalisation in past year or time since previous follow-up	3 (9)	0 (0)	0 (0)	na	0 (0)	0 (0)	0 (0)	na
Functional findings								
Weight, kg	81±3	81±3	80±3	0.326	80±4	81±4	84±5	0.200
BMI, kg/m^2 (median (Q1–Q3))	25 (23–28)	26 (22–28)	26 (23–27)	0.321	26 (22–28)	25 (23–28)	25 (22–28)	0.334
Systolic blood pressure, mm Hg (median (Q1–Q3))	110 (102–120)	105 (95–122)	105 (100–120)	0.082	108 (100–124)	106 (97–123)	108 (98–127)	0.289
6MWT, metres	569±16	na	597±13	**0.016**	598±14	604±21	621±19	0.694
Exercise capacity, watt	138±8	na	136±9	0.887	137±10	134±13	147±14	0.522
Exercise capacity (watt), % of predicted (mean±SE)	88±4	na	87±3	0.397	87±3	86±5	85±5	0.063
VO_2max, mL/kg/min	17.9±0.8	na	17.8±0.6	0.749	18.5±1.0	17.6±0.9	18.9±1.2	0.213
Per cent of predicted VO_2max, %	62±3	na	60±2	0.807	63±3	62±3	63±3	0.152
Heart rate, % of predicted	78±3	na	78±3	0.610	77±3	77±3	78±4	0.513
Heart rate reserve, bpm	68±5	na	69±5	0.466	69±5	67±7	73±8	0.929
RER	1.18±0.02	na	1.19±0.01	0.618	1.18±0.02	1.16±0.02	1.21±0.02	0.753
Laboratory findings								
Hb, mmol/L	9.0±0.2	8.8±0.2	8.9±0.1	0.222	8.9±0.2	8.9±0.2	9.1±0.3	0.325
Ht, L/L	0.432±0.007	0.422±0.008	0.432±0.005	0.189	0.426±0.007	0.478±0.05	0.431±0.01	0.268
Sodium, mmol/L	140±0.3	141±0.3	141±0.4	0.064	140±0.4	140±0.6	140±0.6	**0.036**
Potassium, mmol/L	4.4±0.06	4.4±0.08	4.5±0.06	0.363	4.5±0.08	4.4±0.07	4.3±0.07	0.218
Creatinine, mmol/L (median (Q1–Q3))	84 (73–91)	86 (78–99)	93 (76–101)	0.057	84 (76–99)	82 (73–94)	85 (73–96)	0.119
eGFR, mL/min/1.73 m^2	85±3	82±4	81±3	0.188	82±4	84±4	90±6	0.370
ASAT, U/L (median (Q1–Q3))	30 (25–34)	25 (21–29)	25 (23–30)	0.213	26 (22–33)	27 (23–30)	24 (21–27)	0.297
ALAT, U/L (median (Q1–Q3))	32 (23–38)	22 (19–34)	24 (20–34)	0.058	26 (20–35)	28 (22–32)	24 (18–35)	0.794
Gamma GT, U/L (median (Q1–Q3))	42 (27–82)	55 (33–77)	44 (28–57)	0.793	51 (30–64)	43 (30–69)	47 (27–85)	0.542
NT-proBNP, ng/L (median (Q1–Q3))	567 (374–1134)	404 (226–633)	373 (206–661)	**<0.001**	464 (234–657)	342 (241–765)	298 (226–665)	0.200

Data are expressed as mean±SE unless otherwise indicated. Statistical comparison is shown between baseline and first follow-up moment available.
Bold: statistically significant (p <0.05)
*For categorical data, the McNemar test or Wilcoxon signed-rank test was used, as appropriate, and this p value is shown.
ALAT, alanine transaminase; ASAT, aspartase aminotransferase; BMI, body mass index; bpm, beats per minute; eGFR, estimated glomerular filtration rate; FU, follow-up; Gamma GT, gamma glutamyltransferase; Hb, haemoglobin; HF, heart failure; Ht, haematocrit; 6MWT, 6-minute walking test; na, not applicable; NT-proBNP, N-terminal-prohormone brain natriuretic peptide; NYHA, New York Heart Association functional classification; Q, quartile; RER, respiratory exchange ratio.

The comparison of patient characteristics at baseline between women and men can be found in online supplemental table 1. Women were lighter (74±5 vs 85±3 kg,p=0.044), more symptomatic (44% in NYHA III–IV vs 13% of males, p=0.025), had lower 6MWT distance and VO_2max (523±27 vs 588±17 m, p=0.038 and 15.3±1.4 vs 19.3±0.8 mL/kg/min, p=0.014) at baseline and tolerated a lower maximal dose of sacubitril/valsartan (p=0.004, table 2). However, no difference was observed in the change of 6MWT (44±17 vs 14±13 m, p=0.166) or NT-proBNP (−24±6% vs −38±6%, p=0.107) during follow-up.

Additionally, no differential response based on the maximal tolerated sacubitril/valsartan dose was observed in the change in 6MWT (14±30 vs 46±24 vs 22±12 m, p=0.514) or NT-proBNP (−16±8% vs −28±6% vs −41±6%, p=0.101).

The comparison of patient characteristics at baseline between patients requiring further escalation of treatment and without escalation can be found in online supplemental tables 2 and 3. Patients who required treatment escalation had a higher NYHA class, had more diuretic use and higher NT-proBNP levels at baseline. They more often had a history of tricuspid valve surgery and tolerated lower doses of sacubitril/valsartan. They initially responded well to treatment in terms of 6MWT distance improvement and had a comparable good response in terms of decline of NT-proBNP.

DISCUSSION

The main findings of this study are that treatment of patients with sRV failure with sacubitril/valsartan is (1) reasonably tolerated with a low rate of significant adverse effects; and is associated

Table 4 Echocardiographic outcomes at baseline (patients who have completed titration) and at the follow-up moments

	Baseline (n=35)	3 months (n=35)	6 months (n=34)	Paired t-test p value from baseline to first FU moment*	12 months (n=29)	24 months (n=20)	36 months (n=12)	Model-based p value trend in time from first FU moment onwards
sRV function (n, %)				0.058				
Mildly reduced	6 (17)	na	10 (32)		11 (42)	7 (35)	2 (17)	
Moderately reduced	23 (66)	na	17 (55)		14 (54)	12 (60)	10 (83)	
Severely reduced	6 (17)	na	4 (13)		1 (4)	1 (5)	0 (0)	
≥1 grade of sRV function improvement	na	na	8 (24%)		3 (11%)	2 (10%)	0 (0%)	
≥1 grade of sRV function decline	na	na	2 (6%)		0 (%)	2 (11%)	1 (7%)	
sRVEDD, mm	54±2	na	55±1	0.476	55±2	55±2	55±2	0.101
sRV GLS, %	−11.1±0.5	na	−12.6±0.7	**<0.001**	−13.2±0.6	−12.8±0.6	−12.8±0.8	0.298
sRV FAC, % (median (Q1–Q3))	20 (16–24)	na	26 (19–30)	**<0.001**	27 (22–33)	27 (22–32)	27 (24–34)	**0.023**
sRV s', cm/s	6±0.4	na	6±0.3	0.540	7±0.6	6±0.4	6±0.3	0.107
TAPSE, mm	13±0.5	na	14±0.6	**0.030**	14±0.5	13±0.6	13±0.6	0.152
Tricuspid regurgitation (n,%)				0.317				
Grade 1 or less	13 (37)	na	14 (45)		13 (50)	9 (45)	6 (50)	
Grade 2	20 (57)	na	16 (52)		13 (50)	11 (55)	6 (50)	
Grades 3–4	2 (6)	na	1 (3)		0 (0)	0 (0)	0 ()	
≥1 grade of improvement of TR	na	na	1 (3%)		2 (6%)	1 (5%)	1 (9%)	
≥1 grade of worsening of TR	na	na	0 (%)		0 (0%)	1 (5%)	0 (0%)	
spLV function (n, %)				0.564				
Good	23 (66)	na	21 (68)		20 (77)	14 (70)	10 (91)	
Mildly reduced	11 (31)	na	10 (32)		6 (23)	6 (30)	1 (9)	
Moderately reduced	1 (3)	na	0 (0)		0 (0)	0 (0)	0 (0)	
spLVEDD, mm	41±1	na	40±1	0.326	41±2	42±2	41±2	0.323
spLV GLS, %	−20.3±1	na	−22.7±1	0.019	−22.6±1	−22.0±2	−22.8±2	0.733
MAPSE, mm	21±0.7	na	20±0.9	0.278	20±0.9	19±1	20±0.7	0.895
Mitral regurgitation (n, %)				0.317				
Grade 1 or less	29 (85)	na	26 (84)		21 (80)	16 (80)	11 (92)	
Grade 2	4 (12)	na	3 (10)		2 (8)	4 (20)	1 (8)	
Grades 3–4	1 (3)	na	2 (6)		3 (12)	0 (0)	0 (0)	
≥1 grade of improvement of MR	na	na	0 (0%)		0 (0%)	1 (5%)	0 (0%)	
≥1 grade of worsening of MR	na	na	1 (3%)		2 (8%)	1 (5%)	0 (0%)	

Data are expressed as mean±SE unless otherwise indicated. Statistical comparison is shown between baseline and first follow-up moment available.
Bold: statistically significant (p <0.05)
*For categorical data, the McNemar test or Wilcoxon signed-rank test was used, as appropriate, and this p value is shown.
FAC, fractional area change; FU, follow-up; GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion; MR, mitral regurgitation; na, not applicable; Q, quartile; s', lateral tricuspid annulus peak systolic velocity; spLV, subpulmonary left ventricle; spLVEDD, subpulmonary left ventricular end-diastolic diameter; sRV, systemic right ventricle; sRVEDD, systemic right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

with (2) an improvement in functional capacity as assessed using 6MWT; (3) a reduction of the serum levels of the HF biomarker NT-proBNP; and (4) consistent small improvements in the systolic sRV function as assessed by echocardiography. These effects persist during a median follow-up of 24 (12–36) months in an on-treatment analysis and show no differential response based on sex or underlying anatomy.

Current study in light of previous studies

Sacubitril/valsartan has a marked role in the treatment of LV HF with reduced ejection fraction.[5 18] The current study is, to date, the largest in terms of duration of follow-up with 64 patient-years addressing the effects of treatment with sacubitril/valsartan on sRV failure. Our first smaller sRV patient single-centre study on sacubitril/valsartan reported the treatment to be feasible, with improvements in NT-proBNP and sRV echocardiographic function.[13] This two-centre study confirms these findings in a larger cohort with longer follow-up and is in line with the recent publication of Fusco *et al* reporting beneficial effects in a cohort of 50 patients with sRV during a 1-year period.[14] Sacubitril/valsartan use was associated with improved sRV systolic function and reverse remodelling, and a comparable improvement in 6MWT distance. Of interest, Fusco *et al* did not see a persistent decline in the NT-proBNP levels, potentially reflecting a higher burden of haemodynamically important TR in their cohort.

Despite a significant and consistent increase in the 6MWT distance, the performance at bicycle ergometry with VO_2max remained stable throughout follow-up. In patients with sRV, the exercise capacity is often limited by the cardiac output, due to combination of chronotropic incompetence, reduced preload and increased sRV afterload combined with systolic sRV dysfunction.[1] Although 6MWT is typically reflective of the submaximal exercise activity, in patients with severe ventricular dysfunction, it is suggested that the 6MWT might best be perceived as a maximal exercise activity.[19] In patients with ACHD, the 6MWT

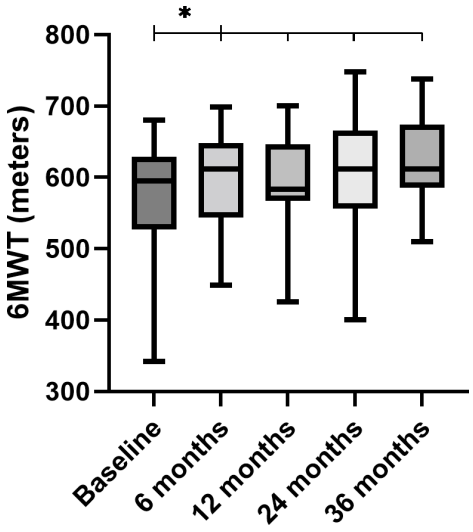

Figure 2 Box and whisker plot showing the absolute median 6-minute walking test (6MWT) distance in metres (horizontal line) with 25th and 75th percentiles (box) and lower and upper extremes (whiskers) per follow-up moment. *Statistically significant between baseline and 6 months of follow-up. The temporal changes during the follow-up period were not significant.

is a validated cardiopulmonary functional assessment tool and correlates well with levels of prognostic HF biomarkers.[20]

NT-proBNP is a surrogate and prognostic marker for HF and has been reported to correlate well with sRV dysfunction, as well as to have a robust predictive value for clinical endpoints and mortality in adult patients with sRV.[21] Present cohort showed a mean reduction of 33% in NT-proBNP levels, comparable with the 28% reduction after 8–10 weeks of treatment reported in the post-hoc analysis of Paradigm-HF.[22] Of interest, of the patients who did not show a response to sacubitril/valsartan treatment in terms of serum NT-proBNP levels after 3 months, all but one did show a significant decline in NT-proBNP levels after 6 months of

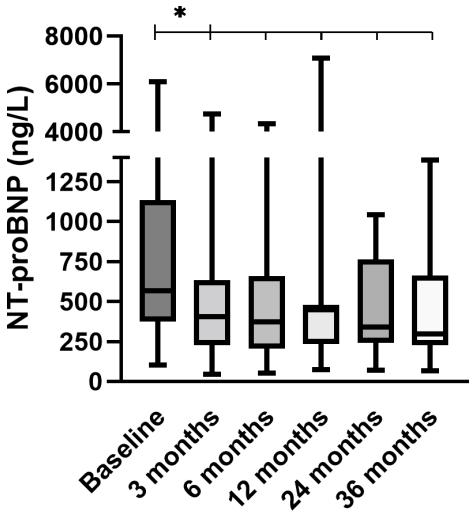

Figure 3 Box and whisker plot showing the absolute median values of N-terminal-prohormone brain natriuretic peptide (NT-proBNP) levels in ng/L (horizontal line) with 25th and 75th percentiles (box) and lower and upper extremes (whiskers) per follow-up moment. *Statistically significant between baseline and 3 months of follow-up. The temporal changes during the follow-up period were not significant.

treatment. This suggests that some patients might experience a delayed onset of beneficial effects of the treatment.

Of interest, patients with TGA after atrial switch had significantly lower NT-proBNP levels at baseline than patients with ccTGA with comparable clinical characteristics. This might be explained by the atrial wall stress-triggered NT-proBNP release in the setting of congestive HF and the reduced amount of native atrial tissue in patients with extensive baffles.[23] However, this did not have any differential effect on the benefit of treatment with sacubitril/valsartan. Looking at sex-driven effects, female patients were initially more symptomatic and performed worse at functional testing, and tolerated a lower maximal dose of sacubitril/valsartan despite having similar body mass index as men. In conventional HF, women have also been reported to present with more severe symptoms and have a different response to and tolerability of pharmacological therapy.[24] Despite these differences, there was no differential response to sacubitril/valsartan treatment in terms of 6MWT distance and NT-proBNP levels. It is important to elucidate sex-specific effects in patients with ACHD and further studies should focus on this.

After an initial beneficial response with improvement and stabilisation of sRV dysfunction and complaints, a small number of patients did show a clinical decline. These patients were started on an SGLT2i or listed for heart transplantation/VAD. Interestingly, these patients were more symptomatic at baseline, yet did show a good and comparable initial treatment response in terms of NT-proBNP, and even a superior response in terms of 6MWT distance. It might be speculated that the window of opportunity to halt the progression to clinically overt HF lies even earlier in the course of sRV dysfunction. Pharmacological intervention should therefore not be considered to be a cure for the sRV failure and at best be regarded as supportive measures to halt progression of HF. Although the current cohort used less medication than could be expected from a non-congenital HF cohort, the present study population used more pharmacotherapy than reported in the recent study on the Dutch national cohort.[25] HF is associated with a particularly poor prognosis in patients with ACHD, with a 20% 1-year mortality after primarily HF-related hospitalisation. This is considerably higher compared with conventional LV HF, underlining the unmet need for timely pharmacological intervention in patients with ACHD.[26]

Future perspectives

To date, pharmacological options for the sRV are not well defined and randomised controlled trials are scarce. A number of ongoing research initiatives deserve a specific mention. First, an international registry for sacubitril/valsartan in patients with ACHD with HF (ENTRUST ACHD HF) is ongoing, including a multicentre analysis focusing on adult patients with sRV.[27] Montreal Heart Institute is conducting a randomised, double-blind, placebo-controlled, crossover clinical trial for sacubitril/valsartan in patients with sRV failure (PARACYS-RV, ClinicalTrials.gov: NCT05117736). On the horizon are SGLT2is, a new group of drugs that have been demonstrated to reduce the risk of worsening HF and cardiovascular-related death in patients with chronic LV failure, and which certainly deserve further exploration in the pharmacological treatment of sRV failure.[5 28 29]

Study limitations

The results of this study should be interpreted in light of the relatively small study population, and the open-label, single-arm, observational design. The study design inherently results in differential follow-up time and limits the number of patients in

the longer follow-up window. The cohort consists of TGA after the atrial switch operation and patients with ccTGA, which, although not reflected by any differential effects in the analysis, does generate a somewhat heterogeneous population. Limited by a substantial number of patients with epicardial and/or abandoned leads, temporal MRI assessment could not be performed. Despite this, the results do provide a foundation for evidence-based recommendations for addressing sRV failure in patients with ACHD.

CONCLUSION

Treatment with sacubitril/valsartan was reasonably tolerated, with a low rate of adverse effects in this adult sRV cohort. A persisting improvement in 6-minute walking test distance, NT-proBNP levels and echocardiographic parameters of sRV function was observed in an on-treatment analysis. These effects showed no differential response based on sex or underlying anatomy.

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