Adult congenital heart disease-related heart failure: challenges and opportunities in pharmacological therapies and device interventions

Neijenhuis, R.M.L.

5

Sacubitril/Valsartan is Associated with Improvements in Quality of Life in Adult Congenital Heart Disease Patients with Systemic Right Ventricular Failure

Neijenhuis RML, Nederend M, Van Groningen AE, Jongbloed MRM, Vliegen HW, Jukema JW, Kiès P, Egorova AD

Open Heart. 2025 Jan 30;12(1):e003009.
DOI: 10.1136/openhrt-2024-003009.

Abstract

Background

Short-term improvements in quality of life (QOL) have been reported in adult congenital heart disease patients with systemic right ventricle (sRV) failure after treatment with sacubitril/valsartan. This study aimed to evaluate the medium-term QOL changes in sRV failure patients treated with sacubitril/valsartan.

Methods

In this single-centre, prospective cohort study, patients with symptomatic sRV failure completed the Netherlands Organisation for Applied Scientific Research/Academic Hospital Leiden Questionnaire for Adult's Health-Related Quality of Life (TAAQOL) at baseline and after starting treatment with sacubitril/valsartan. The TAAQOL was taken at structured outpatient follow-up moments after 6, 12, 24 and 36 months of treatment. Linear mixed effects models were used to evaluate the medium-term changes in 12 QOL domains.

Results

Of 40 sRV failure patients initiated on sacubitril/valsartan, 35 completed the titration phase, and 31 filled in a total of 98 TAAQOL questionnaires (response rate 77.5%). Significant improvements in gross motoric functioning ($p=0.008$), cognitive function ($p=0.002$), sleep ($p=0.041$), social functioning ($p<0.001$) and daily activities ($p=0.001$) were observed during follow-up. No significant changes were observed in fine motoric functioning, pain, sexuality, vitality, positive, depressive or aggressive emotions. Of interest, periods with restrictions relating to the COVID-19 pandemic did not significantly influence changes over time in any of the 12 QOL domains.

Conclusion

Sacubitril/valsartan treatment was associated with persistent medium-term QOL improvements in gross motoric functioning, cognitive function, sleep, social functioning and daily activities domains in sRV failure patients. Self-perceived QOL of sRV failure patients may be amenable to improvement with sacubitril/valsartan.

Introduction

Adults with congenital heart disease (ACHD) report a worse self-perceived health-related quality of life (QOL) when compared with the general population.[1] Patients with complex ACHD, such as systemic right ventricle (sRV), have a worse QOL than their peers with milder complexity CHD.[2] The sRV population consists predominantly of patients with transposition of the great arteries who underwent the atrial switch procedure and patients with congenitally corrected transposition of the great arteries. Due to the complex nature of their defect, with the sRV supporting the high-pressure systemic circulation, these patients frequently suffer from late sequelae, including heart failure and arrhythmias. At the same time, evidence-based treatment options are limited.[3]

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, is a contemporary therapeutic option for the treatment of heart failure that has recently been explored for sRV failure. Initial short-term evaluation by our centre demonstrated improvements in 6-minutes walk test distance, serum N-terminal-prohormone brain natriuretic peptide (NT-proBNP) levels, echocardiographic sRV function and QOL in the cognitive function, sleep and vitality domains.[4] The tolerability and functional improvements were sustained over the medium term (up to 36 months), although QOL was not evaluated.[5] Therefore, the current study aimed to assess the medium-term QOL changes in patients with sRV failure treated with sacubitril/valsartan.

Methods

Study design and population

In this single-centre, prospective cohort study, QOL was assessed in adult patients with sRV failure who were treated with sacubitril/valsartan at a tertiary ACHD care centre. All tests and procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki Declaration. Appropriate local scientific board approval was obtained, and the need for written informed consent was waived by the Medical Research Ethics Committee Leiden Den Haag Delft (reference: G21.187). All patients provided consent for registration, analysis and publication of their data.

QOL was assessed using the Netherlands Organisation for Applied Scientific Research/ Academic Hospital Leiden Questionnaire for Adult's Health-Related Quality of Life (TAAQOL). The TAAQOL has been validated in the ACHD population, includes 45 questions and evaluates 12 different domains of health-related QOL.[1] Patients with sRV failure were asked to complete the TAAQOL questionnaire at every outpatient clinic visit

as part of the smart technology-based clinical care pathway for sRV failure, as described previously.[4,6] Patients started sacubitril/valsartan after completing their first TAAQOL questionnaire, and follow-up was scheduled after 6, 12, 24 and 36 months. Patients were excluded from follow-up when a sodium-glucose cotransporter 2 inhibitor was started, as this could confound the QOL changes relating to sacubitril/valsartan. As the study duration coincided in part with the COVID-19 pandemic, the impact on QOL of periods with significant social restrictions was evaluated (February to May 2020, October 2020 to May 2021 and October 2021 to February 2022).

Statistical analysis

All statistical analyses were performed in SPSS V.25 (IBM Corp, Armonk, New York, USA) and R (R Foundation for Statistical Computing, packages 'nlme', 'lattice' and 'ggplot2'). For the descriptive baseline analyses, normally distributed continuous data were displayed as mean (±SD), non-normally distributed continuous data were presented as median (IQR) and categorical data were presented as numbers (%). Baseline characteristics were compared with an unpaired t-test, Mann-Whitney U-test, χ^2 test or Fisher's exact test, as appropriate. For the scoring of the different QOL domains, a proprietary SPSS syntax for the TAAQOL questionnaire was used to obtain an individual score between 0 and 100 for each of the 12 QOL domains, with a higher score indicating better QOL.

To evaluate the changes in the QOL domains over time, linear mixed effects models with time as a fixed effect and between-subject variability as a random effect with random intercepts and random slopes if appropriate were constructed. Multiple correlation matrices and variance functions were tested for each domain and the best fit was selected. Periods with significant COVID-19-related restrictions were included as fixed effect in the linear mixed models to evaluate if they contributed significantly to the QOL scores. A two-sided p value ≤ 0.05 was considered statistically significant.

Results

Of the 40 patients who were started on sacubitril/valsartan for sRV failure, 35 completed the titration phase. 31 patients completed a total of 98 TAAQOLs while on sacubitril/valsartan (response rate 77.5%). Of the nine patients who did not complete a TAAQOL, two deceased, two underwent ventricular assist device implantation, one stopped sacubitril/valsartan during the titration phase because of thirst and four patients did have follow-up visits but did not complete a TAAQOL for unknown reasons. 27 TAAQOLs were completed at baseline, 21 at 6 months, 17 at 12 months, 19 at 24 months and 14 at 36 months. Reasons for failing to complete the questionnaire at each follow-up moment remained unknown in the

majority of cases, except for one patient who deceased and five patients who were excluded because a sodium-glucose cotransporter 2 inhibitor was started. There were no differences in baseline characteristics between the group who completed the TAAQOL (n=31) and the overall sRV study cohort (n=40) (*Table 1*). The median follow-up duration was 30.9 (15.4–40.1) months.

Table 1. Baseline characteristics

	TAAQOL cohort (n=31)	**Overall sRV cohort (n=40)**	**P value**
Anatomy			0.592
ccTGA	7 (23%)	12 (30%)	
TGA atrial switch	24 (77%)	28 (70%)	
Age, years	47 (44–50)	48 (44–53)	0.629
Female	12 (39%)	16 (40%)	0.912
NYHA class			0.775
NYHA II	25 (81%)	30 (75%)	
NYHA III-IV	6 (19%)	10 (25%)	
CIED	16 (52%)	23 (58%)	0.621
sRV function (assessed with TTE)			0.643
Mildly reduced	5 (16%)	6 (15%)	
Moderately reduced	23 (74%)	27 (68%)	
Severely reduced	3 (10%)	7 (17%)	
6MWT, metres	570±83	560±91	0.670
VO_2max, mL/kg/min	17.3±4.0	17.5±4.8	0.895
NT-proBNP, ng/L	545 (267–1127)	623 (380–1247)	0.441

ccTGA, congenitally corrected transposition of the great arteries; CIED, cardiac implantable electronic device; 6MWT, 6-minute walk test; NT-proBNP, N-terminal-prohormone brain natriuretic peptide; NYHA, New York Heart Association; sRV, systemic right ventricle; TGA, transposition of the great arteries; TTE, transthoracic echocardiography; VO2max, maximal oxygen uptake.

Over time, significant improvements were observed in gross motoric functioning (p=0.008), cognitive function (p=0.002), sleep (p=0.041), social functioning (p<0.001) and daily activities (p=0.001). No significant changes were observed over time in fine motoric functioning, pain, sexuality, vitality, positive, depressive or aggressive emotions. The details of the mixed effects models are presented in *Table 2*, and the predicted fixed effects of the

mixed effects models for the QOL domains with significant changes over time are presented in *Figure 1*. COVID-19-related restriction periods did not significantly influence QOL in any of the 12 domains.

Table 2. Linear mixed effects models results for the 12 QOL domains

QOL domain	Baseline intercept score	Regression coefficient	95% CI	P value
Gross motoric functioning	75.03	0.25	0.07 to 0.43	0.008
Fine motoric functioning	98.88	<−0.01	−0.01 to 0.01	0.982
Cognitive function	73.68	2.69*	1.10 to 4.29	0.002
Sleep	65.24	0.24	0.02 to 0.47	0.041
Pain	77.93	0.04	−0.15 to 0.24	0.675
Social functioning	81.59	0.33	0.18 to 0.48	<0.001
Daily activities	73.61	0.41	0.18 to 0.65	0.001
Sexuality	84.57	0.09	−0.28 to 0.46	0.641
Vitality	60.45	0.07	−0.15 to 0.29	0.538
Positive emotions	71.62	0.10	−0.14 to 0.34	0.436
Depressive emotions	77.09	0.08	−0.25 to 0.41	0.663
Aggressive emotions	90.22	0.16	−0.01 to 0.34	0.071

*The linear mixed effects model for cognitive function has been constructed slightly differently, with follow-up duration as a consecutive integer instead of a continuous variable. The coefficient represents the change between each follow-up visit instead of the change per month. *CI, confidence interval; QOL, quality of life.*

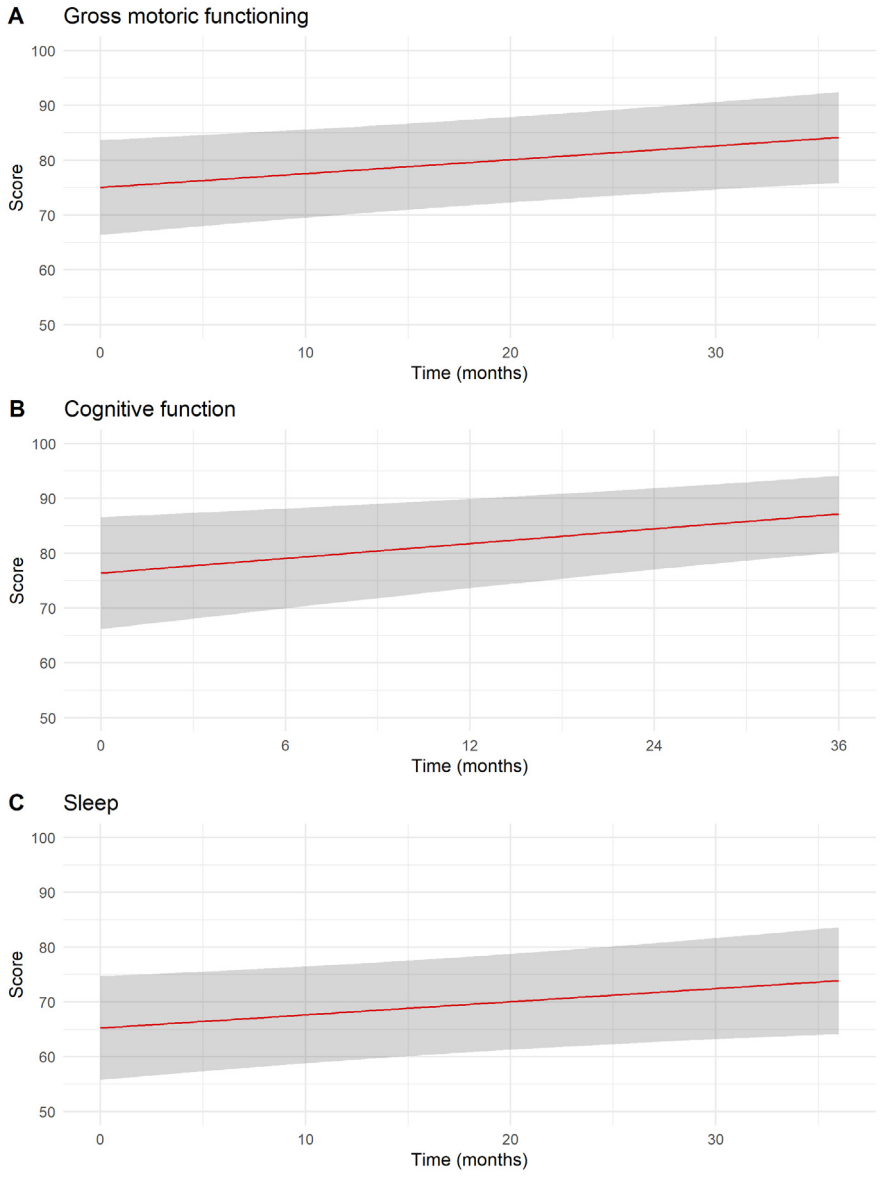

Figure 1. Predicted changes for the QOL domains with a significant change over time
The figure shows the predicted fixed effects of the linear mixed effects models (red line) with 95% CIs (grey band) for the five QOL domains that showed a significant improvement over time.

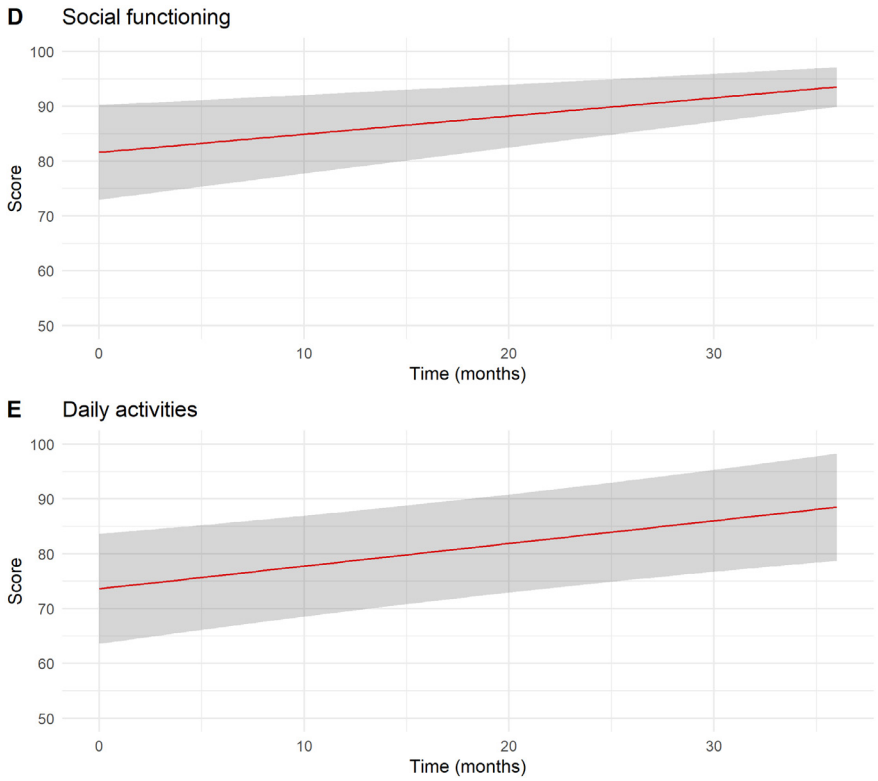

Figure 1. *Continued*

Discussion

This study demonstrates that treatment with sacubitril/valsartan was associated with significant improvements in QOL in sRV failure patients, specifically in the gross motoric function, cognitive function, sleep, social function and daily activities domains. These positive changes complement the previously reported improvements in 6-min walk test distance, NT-proBNP levels and echocardiographic sRV function, further strengthening the suggestion that sacubitril/valsartan may have a valuable role in the treatment of sRV failure.[4,5]

Awareness of the importance of QOL assessment has increased substantially over the recent years. Patients with complex CHD like sRV report lower QOL scores than the general population.[7] Before this study, the short-term changes in QOL after treatment with sacubitril/valsartan were evaluated at our centre in a smaller cohort.[4] 16 patients completed a TAAQOL questionnaire before starting sacubitril/valsartan and after 6 months. Significant

improvements in the cognitive function, sleep and vitality domains were observed. While these findings were promising, the follow-up duration was short and the numbers were small. In the current study, we demonstrate that the improvements in cognitive function and sleep were sustained over the medium-term follow-up period. Although the change in the vitality domain was no longer significant, improvements in additional domains were observed. These results are valuable, especially since heart failure is a progressive disease and worsening clinical status and QOL are observed if left unmanaged.

In line with our results, colleagues from Italy recently reported their 1-year experience with sacubitril/valsartan for sRV failure. They presented improvements in self-assessed physical functioning and pain, based on the Short Form-36 (SF-36) Health Survey.[8] While the SF-36 shows a satisfactory correlation with the TAAQOL in the ACHD population, the TAAQOL is regarded as more comprehensive, incorporating questions reflecting on the emotional reaction to health status problems when they are present.[7] Moreover, improvements in both physical and mental domains have been reported in the conventional heart failure population treated with sacubitril/valsartan in the landmark Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[9]

Recently, the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor vs. plAcebo in patients with Congenital sYStemic Right Ventricular heart failure (PARACYS-RV) trial was conducted. This randomised, double-blind, placebo-controlled, crossover trial aimed to compare sacubitril/valsartan to placebo in sRV failure patients but was terminated prematurely due to a high rate of worsening heart failure events after interruption of sacubitril/valsartan. Nonetheless, favourable trends in submaximal total exercise duration and NT-proBNP were reported after starting sacubitril/valsartan. While QOL evaluation with the Kansas City Cardiomyopathy Questionnaire was planned as a secondary outcome, these results were not reported.[10] Thus, the premature termination of this trial sustains the gap in prospective randomised evidence for the impact of pharmacological intervention on QOL in sRV patients.

Intrinsic to its nature, the current study is limited by the open-label, observational, single-arm design. The small patient numbers and decreasing number of patients completing the questionnaires during follow-up reflect the rarity of the condition and paucity of data on self-perceived QOL. Despite the seeming lack of differences between the patients who completed the TAAQOL questionnaire and the overall sRV failure cohort treated with sacubitril/valsartan, some degree of selection bias at baseline and during follow-up cannot

be excluded. Two patients who deceased after starting sacubitril/valsartan did not complete a TAAQOL, nor did two of the three patients who underwent ventricular assist device implantation during follow-up.

To conclude, this study provides the first medium-term evaluation of QOL in sRV failure patients treated with sacubitril/valsartan. Our findings suggest that the self-perceived QOL of sRV failure patients may be amenable to improvement with novel medical heart failure therapies like sacubitril/valsartan and that sacubitril/valsartan may have a valuable role in the treatment of both physical and psychosocial aspects of sRV failure.

References

1. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. Cardiol Young. 2013;23(4):473-85.
2. Kamphuis M, Zwinderman KH, Vogels T, Vliegen HW, Kamphuis RP, Ottenkamp J, et al. A cardiac-specific health-related quality of life module for young adults with congenital heart disease: development and validation. Qual Life Res. 2004;13(4):735-45.
3. Brida M, Diller GP, Gatzoulis MA. Systemic Right Ventricle in Adults With Congenital Heart Disease: Anatomic and Phenotypic Spectrum and Current Approach to Management. Circulation. 2018;137(5):508-18.
4. Zandstra TE, Nederend M, Jongbloed MRM, Kiès P, Vliegen HW, Bouma BJ, et al. Sacubitril/valsartan in the treatment of systemic right ventricular failure. Heart. 2021;107(21):1725-30.
5. Nederend M, Kiès P, Regeer MV, Vliegen HW, Mertens BJ, Robbers-Visser D, et al. Tolerability and beneficial effects of sacubitril/valsartan on systemic right ventricular failure. Heart. 2023.
6. Nederend M, Zandstra TE, Kiès P, Jongbloed MRM, Vliegen HW, Treskes RW, et al. Potential of eHealth smart technology in optimization and monitoring of heart failure treatment in adults with systemic right ventricular failure. European Heart Journal - Digital Health. 2021;2(2):215-23.
7. Kamphuis M, Ottenkamp J, Vliegen HW, Vogels T, Zwinderman KH, Kamphuis RP, et al. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. Heart. 2002;87(4):356-62.
8. Fusco F, Scognamiglio G, Merola A, Iannuzzi A, Palma M, Grimaldi N, et al. Safety and Efficacy of Sacubitril/Valsartan in Patients With a Failing Systemic Right Ventricle: A Prospective Single-Center Study. Circ Heart Fail. 2023;16(2):e009848.
9. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, et al. Health-Related Quality of Life Outcomes in PARADIGM-HF. Circ Heart Fail. 2017;10(8).
10. Chaix M-A, Dore A, Mondésert B, Mongeon F-P, Roy V, Desrosiers-Gagnon C, et al. Angiotensin receptor-neprilysin inhibitor vs. placebo in congenital systemic right ventricular heart failure: the PARACYS-RV trial. European Heart Journal. 2024;45(16):1481-3.