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

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Discussion

Summary

This thesis set out to address the unmet need for evidence-based treatment options for adult congenital heart disease (ACHD)-related heart failure (HF) by evaluating novel pharmacological and device-based treatment options. **Chapter 1** provides a general overview of the impact of ACHD-related HF and introduces the potential treatment options that are explored in this thesis.

Pharmacological therapies

The objective of this thesis was, in large part, realized by the foundation of the Adult Congenital Heart Disease International EValuation of the Effectiveness of SGLT2i (ACHIEVE-SGLT2i) registry (ClinicalTrials.gov NCT06932081), which aims to evaluate the real-world experience with SGLT2i in the ACHD population. At the end of 2025, over 400 patients have been enrolled from 10 participating centres. In **Chapter 2**, the first evidence for the use of SGLT2i resulting from this international collaboration is provided.[1] In the absence of guideline-directed therapy for ACHD-related HF, the increasing prescription of SGLT2i reported in this study reflects a substantial unmet therapeutic need in this population. Given the historical exclusion of the heterogeneous ACHD cohort from the landmark HF trials, ACHD clinicians appear compelled to extrapolate from non-ACHD guideline recommendations despite the lack of supporting evidence. Fortunately, the study concluded that SGLT2i were safe and generally well-tolerated in 174 ACHD patients, with a side effect rate comparable to the conventional HF trials. Moreover, SGLT2i use was associated with a decrease in 6-month HF hospitalization rate, indicating the first signs of a possible prognostic benefit for ACHD patients with HF.

As explained in Chapter 1, the burden of HF appears most pressing in patients with a systemic right ventricle (sRV) and a single ventricle/Fontan circulation. Starting with the former, **Chapter 3** presents the first single-centre experience with SGLT2i in 10 adults with sRV failure.[2] The study showed that dapagliflozin was well-tolerated; no patients discontinued treatment, and blood pressure, glucose, and electrolytes remained stable. Although a subtle decline in renal function was observed, it recovered to baseline during follow-up. While such a finding might prompt caution, this concern is mitigated by the now well-established reno-protective effects of SGLT2i.[3, 4] Furthermore, significant improvements in NT-proBNP and New York Heart Association (NYHA) class were observed. Only one HF hospitalization occurred during follow-up, which was substantially fewer than in the preceding months for that specific patient, supporting the notion of a potential benefit described in Chapter 2. Echocardiographic systolic function was evaluated in only eight patients and remained unchanged, which might be attributed to the small sample size and inherent variability in sRV imaging.

Following this study, **Chapter 4** therefore set out to systematically analyse more comprehensive transthoracic echocardiography data to evaluate the effects of SGLT2i on ventricular function.[5] Echocardiographic data of 39 sRV failure patients included in the ACHIEVE-SGLT2i registry were re-assessed, and linear mixed models were utilised to effectively analyse unbalanced repeated measurements data obtained during longitudinal follow-up. SGLT2i therapy was associated with significant early improvements in sRV global longitudinal strain (GLS) and fractional area change (FAC), two validated parameters of systolic sRV function.[6] Moreover, covariate analyses revealed that chronic subpulmonary left ventricular (spLV) pacing attenuated longer-term improvement in sRV FAC, while age negatively influenced overall sRV GLS but did not alter the treatment response. Improvements were also observed in tricuspid annular plane systolic excursion (TAPSE) and spLV free-wall strain (FWS), further suggesting a potential reverse remodelling effect of SGLT2i. Taken together, this study provides data supporting that SGLT2i therapy may improve systolic sRV function, while highlighting the importance of patient-specific factors in modulating treatment response.

With **Chapter 5**, the focus remained on the sRV failure population but shifted from evaluating SGLT2i to angiotensin receptor-neprilysin inhibitors (ARNI).[7] This study investigated the impact of the ARNI sacubitril/valsartan on medium-term changes in quality of life (QOL) in a prospective, on-treatment analysis, and found that sacubitril/valsartan was associated with meaningful and sustained improvements. Thirty-one patients completed 98 QOL questionnaires, and linear mixed models revealed significant and coherent improvements in multiple domains. These findings confirm and extend previously reported short-term improvements in QOL after starting sacubitril/valsartan, strengthening the evidence for its therapeutic role beyond functional and biomarker-based benefits, and supporting the hypothesis that sRV failure may be amenable to targeted pharmacological therapy.[8]

Moving on to the single ventricle/Fontan circulation population, **Chapter 6** aimed to investigate the safety and efficacy of SGLT2i in 33 patients with Fontan circulatory failure (FCF) included in the ACHIEVE-SGLT2i registry.[9] This study demonstrated that SGLT2i therapy was also safe and well-tolerated in this highly specific population. As an attempt to explore different pathophysiological mechanisms of FCF and deepen our understanding of the complex underlying haemodynamics of FCF, differences in treatment response between patients with reduced and preserved ventricular function phenotypes were explored. SGLT2i treatment was associated with a significant reduction in NT-proBNP in FCF patients, regardless of FCF phenotype.

In **Chapter 7**, longitudinal changes in transthoracic echocardiography parameters of single ventricle function were subsequently assessed in 13 single ventricle circulatory failure patients.[10] The majority had a Fontan circulation, and all longitudinal echocardiograms were re-assessed. The study found that SGLT2i therapy was associated with a significant reduction in end-systolic area, improvements in systemic ventricle FWS and basal lateral strain, and an early improvement in isovolumic acceleration. Patients with reduced systolic ventricular function experienced an early improvement in FAC, while patients with preserved function did not. These findings suggest that SGLT2i therapy may indeed improve ventricular function in single ventricle circulation patients, although this may in part be a phenotype-specific response. These preliminary insights are limited by the small sample size and inherent heterogeneity associated with this complex congenital heart disease. Nonetheless, this study provided the first structured evidence that SGLT2i was associated with improved systolic functional improvements in single ventricle failure.

Device interventions

Second to these pharmacological therapies, two specific device interventions for ACHD-related HF were investigated in this thesis. In **Chapter 8**, the complex patient-tailored decision-making process surrounding the management of baffle leaks in adults with sRV failure late after the atrial switch procedure is discussed.[11] Three cases with divergent hemodynamic profiles and illustrative management strategies are presented. Two patients experienced exercise-induced cyanosis due to functional right-to-left shunting and underwent successful percutaneous device closure, resolving their cyanosis. The third case involved spLV volume overload caused by significant left-to-right shunting. This patient was managed conservatively to avoid further deterioration of sRV function, because the left-to-right shunt was deemed haemodynamically beneficial as it effectively "unloaded" the failing sRV with its elevated end-diastolic pressure. Together, these cases underscore the importance of individualised, patient-centred decision-making, informed by multimodality imaging and invasive haemodynamic assessment.

Chapter 9 set out to investigate the effects of cardiac resynchronization therapy (CRT), an integral part of the treatment of selected patients with "conventional HF", in a multicentre retrospective cohort of 101 ACHD patients.[12] This study showed that CRT, when performed in expert centres and when technically feasible, was associated with significant improvements in QRS duration, systemic ventricular function, and NYHA class in the first year after implantation. While QRS duration reduction was more pronounced in patients who underwent an upgrade procedure (i.e., patients who already had a cardiac implantable electronic device and underwent an upgrade to a CRT device), the observed improvements extended to patients with an sRV and with a non-left bundle branch block (LBBB) QRS

morphology, the latter of which has typically been associated with worse response to CRT in the "conventional HF" population.[13] Overall, this study supports CRT as a safe and effective therapy in selected ACHD patients, with a favourable response observed in over 70% of patients at 12 months.

Patient involvement

Finally, the findings from this thesis culminate in **Chapter 10**. This chapter was co-authored with a lived experience expert with sRV failure who participated in multiple studies included in this thesis. The article was published in the quarterly journal Sinus of the Dutch congenital heart disease patient association (Patiëntenvereniging Aangeboren Hartafwijkingen).[14] It aims to translate recent advancements in the management of ACHD-related HF into accessible, patient-centred language, and emphasises the importance of patient involvement in ACHD research and care. Strengthening patient involvement is paramount for the future of ACHD care, particularly in an era of abundant, yet increasingly complex, medical information and possibilities. Ultimately, our scientific endeavours should be guided by the needs of our patients.

Context and future perspectives

Over the recent years, substantial efforts have been made to evaluate potential pharmacological therapies and device interventions to reduce the burden of HF in the ACHD population. Evidence supporting these treatment options has increased steadily, and the studies presented in this thesis contribute meaningfully to this dynamic field. Alongside the work presented in this thesis, several important studies were published by other research groups, providing context to the presented findings.

The use of SGLT2i in the ACHD population has been summarised in a systematic review by *Marshall et al*. (2024) and a meta-analysis by *Das et al*. (2025). Both studies confirmed that SGLT2i are safe and well-tolerated in ACHD patients with HF.[15, 16] Although direct comparisons regarding safety and tolerability between these studies and the landmark SGLT2i trials in "conventional HF" are not feasible, the reported proportion of patients experiencing side effects and the side effect profile appear comparable.[17] Combining the results of 8 studies including a total of 287 patients, the analysis by *Das et al*. showed that SGLT2i also seemed to improve clinical symptoms and NT-proBNP levels, findings that are in line with the results reported in Chapters 3 and 6. It is important to note that Chapter 2 of this thesis provides the majority of the underlying data analysed in the meta-analysis, although notable reference should also be made to the DAPA-SERVE trial, forming the only open-label, randomised study on the subject to date. Investigating 50 sRV failure patients, 25 of whom were treated with SGLT2i, the authors concluded that SGLT2i was safe and

associated with improvements in systolic sRV function.[18] Further strengthening support for the use of SGLT2i in sRV failure, the prospective DAPA-SRV study found improvements in 6-minute walk test distance, QOL, and echocardiographic sRV function after starting SGLT2i in 32 patients.[19] Evidence supporting the use of ARNI has also emerged over recent years. Observational studies predominantly focused on sRV failure and generally showed satisfactory safety and tolerability. Promising improvements in clinical outcomes, imaging parameters, and natriuretic peptides are described, although there also appears to be a risk of hypotension and renal function decline, requiring careful monitoring.[8, 20-23]

Thus, while the evidence for the effectiveness of novel pharmacological agents in treating ACHD-related HF remains limited and is based on small, mostly observational studies, both SGLT2i and ARNI appear safe, are well-tolerated, and show promising signs of early efficacy. Nonetheless, disease- and phenotype-specific treatment responses across relevant subgroups, such as sRV or single ventricle/Fontan circulation patients and HF with reduced versus preserved ejection fraction, remain possible and require further evaluation.

Parallels can be drawn between the state of evidence for SGLT2i, ARNI, and CRT. To date, there is only one systematic review summarising the evidence for CRT in the sRV population, which has only included retrospective, observational studies. The authors concluded that CRT can be an effective treatment for sRV failure, with varying CRT response rates and definitions.[24] More recently, a propensity-matched analysis of 105 sRV patients who underwent CRT implantation suggested that CRT is not associated with improved survival, questioning the effectiveness of this treatment for sRV failure.[25] Other observational studies have shown promising results in the general ACHD population, although consensus on accurate responder definitions, studies including data on hard clinical endpoints, and systematic reviews are currently lacking.[26] To continue to advance the knowledge on this topic, the Real-World Data on the Effects of Cardiac Resynchronization Therapy in Adult Patients With Congenital Heart Disease (RECORD-CHD) registry (NCT06969924) has been established by our group.

From the evidence provided in this thesis and the studies published in recent years, an overarching limitation becomes apparent. ACHD research is structurally hindered by limited sample sizes involving heterogeneous populations, observational and often single-centre study designs, and a general absence of adequately powered prospective trials. While the early benefits observed for these novel treatment options are encouraging, evidence is far from definitive and, in its current form, unlikely to result in strong recommendations in ACHD or HF-specific guidelines. This thesis therefore provides a strong rationale for large, multicentre, prospective, randomised trials aimed at elucidating the effectiveness of

these novel treatment options in the ACHD population. Nonetheless, the substantial costs associated with conducting clinical trials remain a major limiting factor in ACHD research. Previous experience has demonstrated that conducting trials in ACHD is not an easy feat, as illustrated by the recent premature termination of the PARACYS-RV trial due to safety concerns. PARACYS-RV aimed to evaluate the effects of sacubitril/valsartan in the sRV failure population through a randomised, placebo-controlled, double-blind, crossover trial design. It was terminated because an increase in worsening HF events was observed, associated with interruption of sacubitril/valsartan after the run-in phase and during the planned washout period. Whilst improvements in submaximal exercise duration and NT-proBNP were observed in the patients treated with sacubitril/valsartan, the premature termination precluded definitive conclusions regarding efficacy. This experience shows that observational findings can differ from randomised trial outcomes, and emphasises the complexity of robust trial design in ACHD. The safety concerns with PARACYS-RV are particularly unfortunate, as crossover designs are methodologically attractive in ACHD research due to their efficiency, allowing for reduced sample size requirements and controlling for inter-subject variability.[27]

A more straightforward single-centre trial randomising ACHD patients to sacubitril/valsartan or placebo is currently recruiting and expected to provide valuable insights in the future (NCT06693674). Two randomised clinical trials evaluating the effects of SGLT2i in patients with Fontan circulatory failure (NCT06955260) and tetralogy of Fallot (NCT06668389), and one evaluating the effects of CRT in the general ACHD population (NCT05524324) can be identified in the ClinicalTrials.gov database. The results of these trials are eagerly awaited by the ACHD community, although concerns persist regarding population heterogeneity, the balance between reaching adequate statistical power and feasible recruitment timelines, and the choice of the optimal (surrogate) endpoints.

To navigate these concerns and provide a complementary strategy to advance the knowledge on ACHD-related HF, this thesis set out to leverage real-world data through the foundation of the ACHIEVE-SGLT2i and RECORD-CHD registries. Although these registries remain limited in scope, only facilitating multicentre observational data collection, part of the answers we seek may ultimately be derived from large, prospective, registry-based clinical trials.[28, 29] Real-world follow-up studies could provide insights into long-term safety and be used to perform dedicated neurohumoral biomarker and imaging studies. Moreover, real-world registries and registry-based trials are a powerful tool to measure hard clinical endpoints, potentially improving patient selection, guiding decision making, and altering guideline recommendations.

To establish this infrastructure, the ACHD community could draw inspiration from successful initiatives like the Swedish national HF registry (SwedeHF) and data-linkage between this disease-specific registry and national mortality and hospitalisation databases.[30] Specific to the Dutch situation, this could be achieved through the Dutch database for congenital heart disease (CONCOR), which has in part been joined with the Dutch Heart Registration (Nederlandse Hart Registratie, NHR) and provides a platform for data-linkage studies. Two components are essential to harness the full potential of this real-world evidence approach.

First, strong national and international collaboration is imperative to achieve the scale required. This can be achieved nationally through networks such as the "Deltaplan Hartfalen" of the Dutch CardioVascular Alliance (DCVA), of which the work in this thesis is already part. Internationally, the Working Group on Adult Congenital Heart Disease of the European Society of Cardiology (ESC), the International Society for Adult Congenital Heart Disease (ISACHD), and the Alliance for Adult Research in Congenital Cardiology (AARCC) can play a key role in fulfilling this ambition.

Second, methodological advancements in ACHD research are required for robust analysis of this real-world data. As highlighted in this thesis, mixed-effects modelling provides a rigorous statistical framework for unbalanced repeated measurements data, which is required to reliably assess longitudinal changes in complex datasets. Beyond this, target trial emulation is an emerging approach to designing observational studies that has significantly improved observational study quality and allows for the estimation of the causal effect of interventions.[31]

Together, strong (inter-)national collaboration and methodological advancements can mitigate some of the practical obstacles known to conventional randomised-controlled trials, providing a realistically attainable strategy to work towards answering the many gaps in evidence that remain in ACHD-related HF.

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