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

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1

Introduction

Adult congenital heart disease-related heart failure

With an estimated birth prevalence of 9 per 1000 newborns and a global age-standardised prevalence rate of approximately 210 per 100.000, congenital heart disease (CHD) is one of the most common congenital anomalies.[1, 2] Between 1990 and 2021, the age-adjusted prevalence rate of CHD has remained stable, but CHD-related mortality and disability-adjusted life years have improved substantially due to advancements in care during early life.[1] As a result of these advancements, over 90% of paediatric CHD patients reach adulthood, and there are now more adults than children with CHD.[2] The clinical practice of CHD has thus shifted from childhood mortality towards chronic morbidity, as the progressively increasing adult congenital heart disease (ACHD) population is faced with the late sequelae of their congenital defects and initial repair.

Heart failure (HF) is the most frequently encountered late complication. It now represents the principal cause of morbidity and mortality in ACHD patients.[3] Although the burden of ACHD-related HF is increasing rapidly, it is not a new problem. CHD has long been recognised as the "original HF syndrome", characterised by a heterogeneous aetiology. Due to their structural cardiac abnormalities, with myocardial disarray and connective tissue malalignment already present from foetal development, ACHD patients appear destined to develop HF.[4-6] Their innate predisposition often culminates in the development of myocardial fibrosis and neurohormonal dysregulation, leading to systolic and/or diastolic ventricular dysfunction and often underrecognised symptoms such as exercise intolerance.[4, 7] HF complicates the clinical course of these younger patients with a lifelong condition, who are also increasingly affected by classical risk factors (such as coronary artery disease, hypertension, and degenerative valvular pathology) as they age.[8]

The impact of ACHD-related HF on the health care system is already substantial, and it is expected to increase further. From 1998 to 2011, the occurrence of HF hospitalisations increased by 91% in the ACHD population, compared to 21% in the "conventional HF population".[9] Moreover, ACHD patients who require hospitalisation for HF have a disproportionately longer hospitalisation duration and require more procedures.[9, 10] These disproportionate health care costs not only directly burden the health care system but also bring along an invisible financial burden to the patients and their families; a recent study from the United States found that the average lifetime costs of complex CHDs are 44 times that of "conventional HF patients".[11]

The impact of ACHD-related HF on quality of life (QOL) should also not be underestimated. In general, ACHD patients report a worse self-perceived health-related QOL compared to the

general population.[12] When these patients are diagnosed with HF, poor QOL is predictive of mortality, heart transplantation, mechanical circulatory support, and HF hospitalisations.[13] Ultimately, ACHD patients suffering from HF have an almost 5 times higher mortality rate than ACHD patients without HF.[14] A diagnosis of HF is a life-changing event in the course of the ACHD patient's life, and it warrants our full attention.

It is thus only logical that both the 2020 European Society of Cardiology (ESC) and the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of ACHD identify the underlying pathophysiology of HF and the indications for the application of conventional HF management strategies as key gaps in evidence that require solving through large-scale, collaborative, international registries and clinical trials on pharmacological and device therapy.[2, 15] Both guidelines identify these issues as most pressing in patients with a systemic right ventricles (sRV) and those with a single ventricle/Fontan circulation. This thesis sets out to bridge these gaps.

sRV failure

Complex congenital heart disease with a systemic right ventricle (sRV) is a distinct entity in ACHD where the morphological RV functions in the subaortic position and supports the systemic circulation. This occurs in a biventricular circulation in the setting of transposition of the great arteries (TGA) after the atrial switch procedure according to Mustard or Senning, or in congenitally corrected TGA (ccTGA).

The morphological and functional characteristics of the sRV, which is not equipped to chronically sustain the pressure of the systemic circulation, lead to a range of long-term complications, including arrhythmias and sRV failure. At 45 years of age, over 50% of TGA patients who underwent the atrial switch and up to 65% of ccTGA patients will have developed symptomatic HF.[17, 18] Not surprisingly, sRV patients report worse QOL than their peers with TGA and ccTGA who were palliated to a systemic left ventricle (sLV) circulation, and patients with milder complexity CHD.[19, 20] Their unfavourable anatomical characteristics ultimately result in a significantly diminished life expectancy, with adult survival rates ranging from 82-90% at 40 years in all sRV patients, to more recent data reporting cumulative survival of 61% at 48 years after surgical correction in atrial switch patients.[21-23]

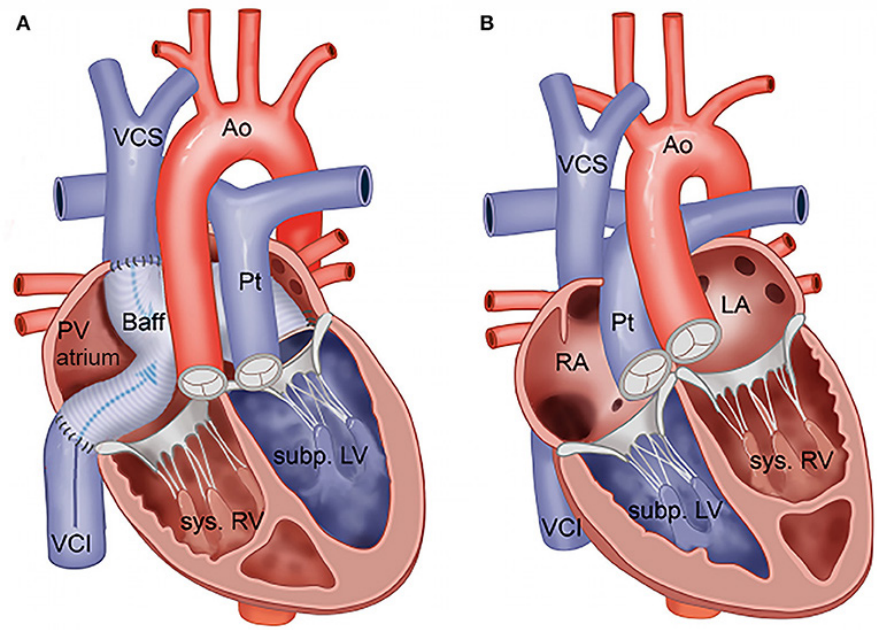

Figure 1. A) Transposition of the great arteries after the atrial switch procedure according to Mustard, with the surgical creation of an intra-atrial baffle rerouting the systemic venous circulation to the subpulmonary left ventricle and the pulmonary venous circulation to the systemic right ventricle. **B)** Congenitally corrected transposition of the great arteries, with a systemic right ventricle due to ventricular inversion. *Ao, aorta; Baff, baffle; LA, morphological left atrium; Pt, pulmonary trunk; PV atrium, pulmonary venous atrium; RA, morphological right atrium; Subp. LV, subpulmonary left ventricle; Sys. RV, systemic right ventricle; VCI, vena cava inferior; VCS, vena cava superior*. Derived from Zandstra et al. Front Cardiovasc Med 2021;8:644193, published under creative commons attribution license.[16] © 2021 Zandstra, Jongbloed, Widya, Ten Harkel, Holman, Mertens, Vliegen, Egorova, Schalij, and Kiès.

The role of baffle dysfunction in sRV failure

While HF and arrhythmias are well-known late sequelae in sRV patients, baffle-associated complications (stenosis and leaks) are a frequently underestimated complication in the subset of TGA atrial switch patients. Both baffle stenosis and leaks are often overlooked and reported in up to 50% of non-selected and asymptomatic patients.[24] Baffle stenosis obstructs the venous return to the sRV, reducing ventricular filling, worsening exercise capacity, and potentially increasing risk of sudden cardiac death.[25]

Although baffle leaks may not directly cause symptoms, they can complicate the fragile haemodynamic course and complex interplay between the sRV and the subpulmonary left ventricle (spLV). Consequently, baffle leaks are important to be aware of, in particular in the setting of reduced systolic sRV function. A left-to-right shunt (from the pulmonary

venous atrium (PVA) to the systemic venous atrium (SVA)) can lead to spLV volume-overload and pulmonary overflow, while a right-to-left shunt (from the SVA to the PVA) can result in cyanosis, sRV volume-overload, and paradoxical emboli. The diagnosis of baffle leaks is challenging due to the low sensitivity of transthoracic echocardiography, and might necessitate more advanced imaging techniques such as contrast echocardiography, cardiac magnetic resonance imaging (MRI), computed tomography (CT), and/or exercise testing.[2, 15] While the guidelines provide some support for baffle leak closure in symptomatic patients, patients with paradoxical emboli, and asymptomatic patients with substantial spLV volume-overload, the benefits of intervention remain unclear as there is a discrepancy between the high prevalence of baffle leaks and low prevalence of associated symptoms and related clinical deterioration.[25]

Single ventricle/Fontan circulatory failure

Patients with single ventricle physiology represent one of the most complicated haemodynamic subtypes within ACHD. In this heterogeneous group, two major types can be identified. The first type constitutes the majority of patients, who are able to undergo surgical palliation with the Fontan procedure, resulting in a circulation in which the single functional ventricle supports the systemic and pulmonary circulation 'in series'. A smaller proportion constitutes the second category of patients, who have a single functional ventricle physiology that is either intrinsically balanced or not amenable to Fontan palliation. In both groups, the mechanisms of circulatory failure are complex and multifactorial. Different underlying phenotypes have been proposed, including Fontan pathway obstruction, atrioventricular valve regurgitation, systolic ventricular dysfunction, high pulmonary vascular resistance, and restrictive physiology.[26] Of these, systolic ventricular dysfunction is the most prevalent underlying cause.[26, 27]

Fontan circulation

The Fontan operation, first introduced in 1968 for patients with tricuspid atresia, has given patients with a single functional ventricle a viable chance at survival without early transplant.[28] Over the last 50 years, the population of patients living with a Fontan circulation has grown substantially. In 2020, the estimated prevalence was 66 per million, with the majority (55%) being adults.[29] This monumental achievement in the management of patients with severe CHD has resulted in a rapidly expanding group of adult Fontan patients, who suffer long-term complications of an operative correction that is characterised by chronically elevated systemic venous pressure and reduced cardiac output. Chronic exposure to these physiologic stressors results in the majority of Fontan patients developing Fontan circulatory failure (FCF), with an estimated overall prevalence of 30%, approaching 100% in patients over 50

years of age.[14] HF is the principal cause of death in the Fontan population, and the overall adult survival rate is 90% at 30 years of age, 80% at 40, and 61% at 50.[30]

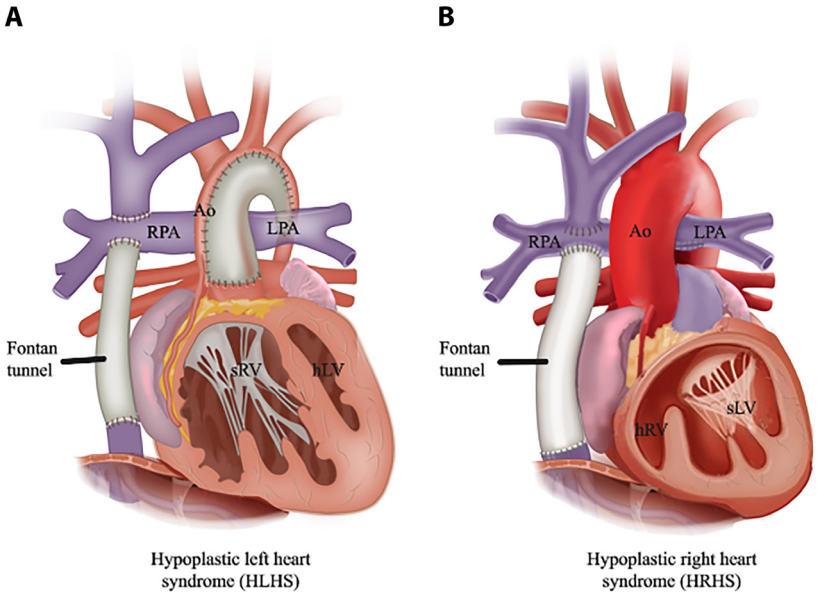

Figure 2. A) The left panel shows an extracardiac conduit-type Fontan circulation with a Fontan tunnel, and reconstructed neo-aortic root and arch, in HLHS. **B)** The right panel shows a similar extracardiac conduit-type Fontan circulation in HRHS. *Ao, aorta; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; hLV, hypoplastic left ventricle; hRV, hypoplastic right ventricle; LPA, left pulmonary artery; RPA, right pulmonary artery; sLV, systemic left ventricle; sRV, systemic right ventricle.* Adapted from Polyakova et al. Int J Cardiol Congenit Heart Dis 2025:100636, published under creative commons attribution license.[31]

Single functional ventricle circulation

Patients with a single ventricle physiology who do not undergo Fontan palliation but are also not amenable for biventricular repair may have an intrinsically 'balanced circulation', in which pulmonary blood flow is not too excessive nor too little. Alternatively, single ventricle patients may require systemic-to-pulmonary artery shunts that augment pulmonary blood flow, which in turn predisposes them to the development of pulmonary overcirculation and pulmonary vascular disease.[2] Ultimately, this challenging haemodynamic situation also leads to high rates of single ventricle circulatory failure.

Pharmacological therapies for ACHD-related HF

There have been major developments in the pharmacological treatment of "conventional HF" over the recent years, with the introduction of angiotensin receptor-neprilysin inhibitors (ARNI), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and the advent of the so called "fantastic four". The latest guidelines indicate that all patients with HF with a reduced ejection fraction (HFrEF, left ventricular ejection fraction (LVEF) ≤40%) should receive guideline-directed medical therapy (GDMT), consisting of a combination of four pharmacotherapy classes:

1. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor-neprilysin inhibitor (ARNI), or angiotensin receptor blockers (ARB)
2. Beta blockers
3. Mineralocorticoid receptor antagonists (MRA)
4. Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

In patients with HF with a mildly reduced (HFmrEF, LVEF 41–49%) and preserved ejection fraction (HFpEF, LVEF ≥50%), SGLT2i are currently the only medication with a class I recommendation.[32-34]

It is evident that solutions for ACHD-related HF, and sRV failure and single ventricle/Fontan circulatory failure specifically, are urgently needed. Unfortunately, ACHD patients have not been included in the randomised controlled trials forming the evidence for the establishment of GDMT. Although there have been some randomised studies investigating ACEi, ARB, beta blockers and MRA in the ACHD population, these were often too small and underpowered, and failed to show beneficial effects on clinically meaningful endpoints (35). Thus, there is currently no conclusive evidence on the efficacy of conventional HF pharmacotherapies in the ACHD population.

Due to the heterogeneous and complex pathophysiological mechanisms underlying ACHD-related HF, extrapolation of the guidelines for the management of conventional acquired HF is inappropriate, particularly for patients with sRV and single ventricle/Fontan failure.[2] Consequently, the current ACHD guidelines do not provide evidence-based recommendations to treat ACHD-related HF, and emphasise that discovering effective treatment strategies for ACHD-related HF should be one of the principal aims for the future.[2, 15] Perhaps part of the answer to ACHD-related HF lies in the new generation of pharmacological agents – SGLT2i and ARNI.

SGLT2i

The origins of SGLT2i can be traced back to 1835, when the naturally occurring compound phlorizin was first isolated from the bark of an apple tree.[36] Intriguingly, long before its purpose in modern medicine was uncovered, the apple tree has fascinated people and holds symbolic meaning across cultures. In Greek mythology, Gaia (mother earth) gifted an apple tree to Zeus and Hera on their wedding day, as a token of their love. The apples from the tree granted immortality when eaten, and thus the trees were heavily guarded in the Garden of the Hesperides.[37] The apple tree occupies an important symbolic position in Norse mythology and Christian theology too. The goddess Iðunn preserved the youth of the gods with her magical apples, and the forbidden fruit of the tree of the knowledge of good and evil in the garden of Eden is often thought to have been an apple.[38, 39] Even the birth of modern physics has been linked to the apple tree, as Isaac Newton reportedly formulated his Theory of Gravity after observing an apple falling from its tree.[40] A moment that transformed science. With such deep intercultural associations across eras, one cannot help but wonder what undiscovered secrets are still being held by the apple tree. After all, phlorizin was discovered in 1835, but it took nearly two centuries to appreciate the therapeutic potential of SGLT2i for managing diabetes mellitus, chronic kidney disease, and HF. SGLT2i have now become a cornerstone in the treatment of HF, reducing the risk of worsening HF, HF hospitalisation, and cardiovascular-related death across all ranges of ejection fraction in conventional HF patients.[32, 33]

Mechanisms of action

The exact underlying mechanisms of action of SGLT2i still largely remain to be elucidated, further adding to their mystery. SGLT2i appear to combat HF by targeting numerous pathways. They have a direct renal and haemodynamic effect, promoting diuresis and natriuresis, and leading to glucosuria though direct inhibition of the SGLT2 receptor, which is mainly present in the proximal tubules of the kidney and to a much lesser extent in the human heart.[41-43] SGLT2i are therefore hypothesised to have a range of pleiotropic "off-target effects", improving cardiac function by reducing sympathetic nervous system overactivation, decreasing pressure overload–induced myocardial fibrosis, decreasing inflammation, and improving overall myocardial energetics, leading to favourable cardiac remodelling.[44] The order and magnitude in which these different mechanisms contribute to the beneficial effects seen in HF patients, including the effects on cardiac remodelling and ventricular failure, still remains to be determined.[45]

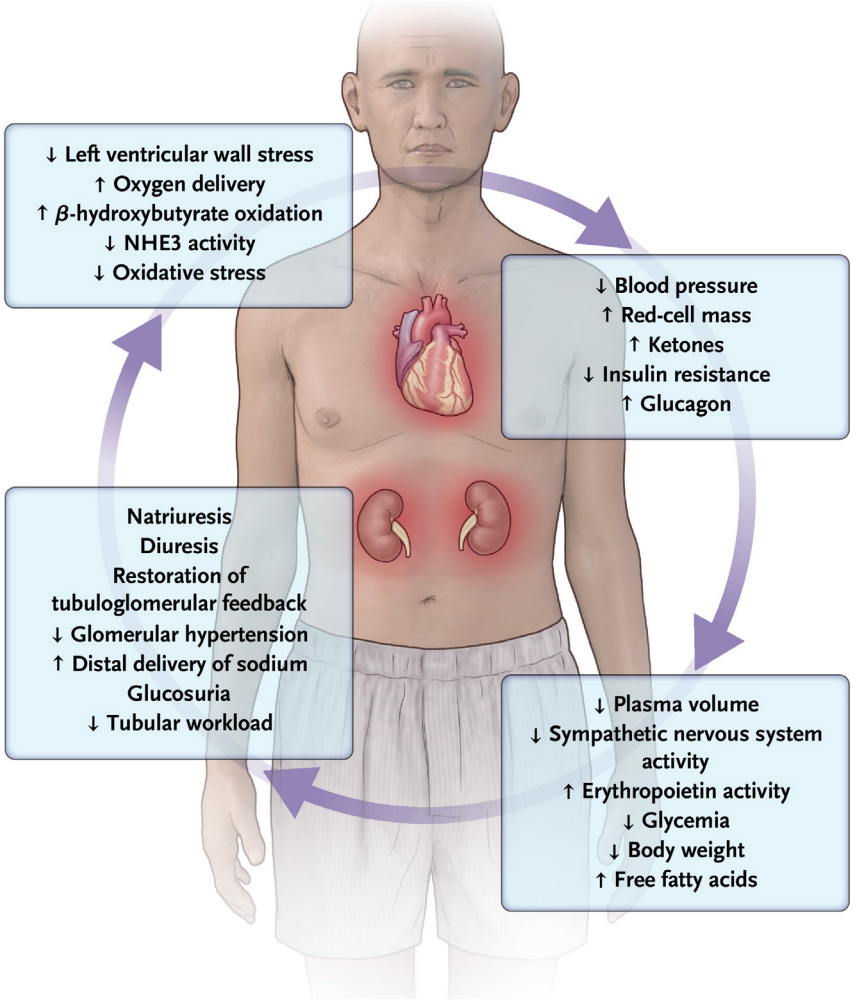

Figure 3. The kidney–heart connection for organ protection by sodium-glucose cotransporter 2 inhibitors. Reproduced with permission from Braunwald et al. N Engl J Med 2022;386:2024-2034,[43] Copyright Massachusetts Medical Society.

SGLT2i as a treatment for ACHD patients suffering from HF

Given the compelling evidence for the effectiveness of SGLT2i in conventional HF, the logical question is whether SGLT2i could also offer a solution to ACHD-related HF. The proposed pleiotropic mechanisms of action make it an especially promising option for ACHD patients due to the heterogeneous aetiology of HF in this young population.

In right ventricular failure for example, which is a lot more commonly seen in ACHD in the context of an sRV in a biventricular and single ventricle circulation, the hypothesised antifibrotic properties of SGLT2i are particularly interesting, as evidence suggests that the RV shows a stronger fibrotic response than the LV to volume and pressure overload.[46] Moreover, a recent meta-analysis demonstrated that SGLT2i therapy reduces pulmonary artery pressure and improves RV performance in conventional HF patients with RV dysfunction.[47] The proposed antifibrotic effects of SGLT2i might thus be one of the mechanisms by which the pathologic remodelling seen in the failing sRV could be ameliorated or potentially prevented when initiated at an early stage.[44] The reno-protective benefits of SGLT2i, slowing the progression of renal disease, offer an additional potential benefit, as renal dysfunction is present in more than 50% of ACHD patients and even mild renal dysfunction is associated with adverse outcomes.[48, 49]

SGLT2i have thus been prescribed "off-label" to ACHD patients as part of compassionate care. This was first demonstrated by *Egorova et al.*, who presented a patient with progressive sRV failure and insufficient response to other HF medication responding well to SGLT2i treatment.[50] This promising initial report laid the foundation for a large part of this thesis, exploring the potential benefits of SGLT2i in the ACHD population. As *Burchill et al.* stated in an editorial accompanying the study discussed in **Chapter 2**:

> *"Some solutions may come from the unlikeliest of places,*
> *including the bark of an apple tree"* [48]

ARNI

Preceding SGLT2i by a couple years, the ARNI sacubitril/valsartan is another relatively novel therapeutic option for the treatment of HF. Over the recent years, observational studies have evaluated sacubitril/valsartan in the sRV failure population, with promising results. Treatment with sacubitril/valsartan has been linked to consistent reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and improvement of systolic sRV function, 6-minute walk test (6MWT) distance, New York Heart Association (NYHA) class, and QOL.[51-53] There is evidence that the majority of these improvements are sustained up to 36 months after treatment initiation, although QOL has only been evaluated over the short-term.[53] These promising results suggest that HF in sRV patients may indeed be amendable to timely pharmacological intervention, although the medium-term QOL changes remain to be evaluated.

CRT as a treatment option for ACHD-related HF

Similar to the lack of evidence for the pharmacological therapies for ACHD-related HF, there is limited evidence for cardiac resynchronization therapy (CRT) in ACHD patients. With CRT, instead of conventional single-site pacing in the subpulmonary ventricle, an additional lead is positioned in the systemic ventricle through the coronary sinus to facilitate synchronised biventricular pacing. Doing so, CRT ameliorates electromechanical dyssynchrony in symptomatic HF patients without CHD, leading to improvement in functional status and reduction in HF-associated morbidity and mortality.[54-56] CRT has therefore become an integral part of the treatment of selected patients with acquired heart disease and HFrEF. Nonetheless, response to CRT remains heterogeneous, ranging from super-responders to stabilizers and non-responders, based on electrocardiographic, echocardiographic, and clinical criteria.[57] Several baseline characteristics have been associated with a higher likelihood of favourable CRT response, including non-ischemic HF aetiology, presence of left bundle branch block (LBBB), and female sex.[58]

For patients with ACHD with a systemic left ventricle (sLV), current guidelines recommend applying conventional CRT indications. However, these are based on studies in patients with anatomically normal hearts. In ACHD, complex anatomies, surgery-related scar tissue, and associated lesions may influence CRT response.[58] Unclear CRT criteria and doubts about efficacy in ACHD may lead to underutilisation, potentially resulting in suboptimal care for patients.[59]

Smaller studies have shown promising results for CRT in ACHD patients, although included patients often did not meet the classical guideline-based criteria for CRT.[60-63] Moreover, heterogeneity in patient selection and lack of a uniform definition of response complicate the interpretation of efficacy and limit comparability between studies.[64] Some studies used QRS narrowing to define response, while others focused on improvements in systemic ventricular function, NYHA class, or combinations of these.[60, 62, 63, 65, 66] Notably, no study has linked these CRT response definitions to hard clinical endpoints such as mortality, ventricular assist device implantation, heart transplantation, or clinical HF events. Given the unique anatomical and physiological characteristics of ACHD patients and the growing use of CRT in this population, an overview of the safety and efficacy of CRT, along with a clear and clinically meaningful definition of CRT response, is much-needed.

Thesis aim and outline

The aim of this thesis is to contribute to the unmet need for evidence-based treatment options for ACHD-related HF by focusing on evaluating novel pharmacological and device-based treatment options.

In ***Part I***, the safety and efficacy of two promising pharmacological treatments, SGLT2i and ARNI, are investigated across the entire ACHD population and in specific subgroups of patients with an sRV and a single ventricle/Fontan circulation. **Chapter 2** describes the first results of the ACHIEVE-SGLT2i registry (ClinicalTrials.gov NCT06932081), evaluating the real-world safety and efficacy of SGLT2i in a large cohort of ACHD patients. In **Chapter 3**, the first single-centre pilot study of patients with sRV failure treated with SGLT2i is presented. **Chapter 4** continues with the sRV failure population and evaluates the effect of SGLT2i on ventricular function as assessed with transthoracic echocardiography. In **Chapter 5**, there is a shift in focus from SGLT2i to ARNI, investigating the changes in quality of life in sRV failure patients after starting sacubitril/valsartan treatment. **Chapter 6** dives into the functional single ventricle/Fontan circulation population and evaluates the effects of SGLT2i on clinical and biomarker outcomes, while **Chapter 7** investigates the effects on ventricular function.

Part II focuses on device interventions for ACHD-related HF. **Chapter 8** is a case series discussing considerations for device closure of baffle leaks in sRV failure, illustrating the patient-tailored approach to the management of baffle leaks in the modern era. The real-world effects of CRT in the ACHD population are presented in **Chapter 9**.

The insights from these chapters culminate in ***Part III*** of this thesis. **Chapter 10** is an article published in the quarterly journal *Sinus* of the Dutch CHD patient association (Patiëntenvereniging Aangeboren Hartafwijkingen), which is co-authored by a lived experience expert with sRV failure who contributed to the studies presented in several chapters of this thesis.

This thesis concludes with a discussion of the findings in **Chapter 11**, providing context to the results and insights into the future perspectives for the treatment of ACHD-related HF. This is summarised in Dutch in **Chapter 12**.

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