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

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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]

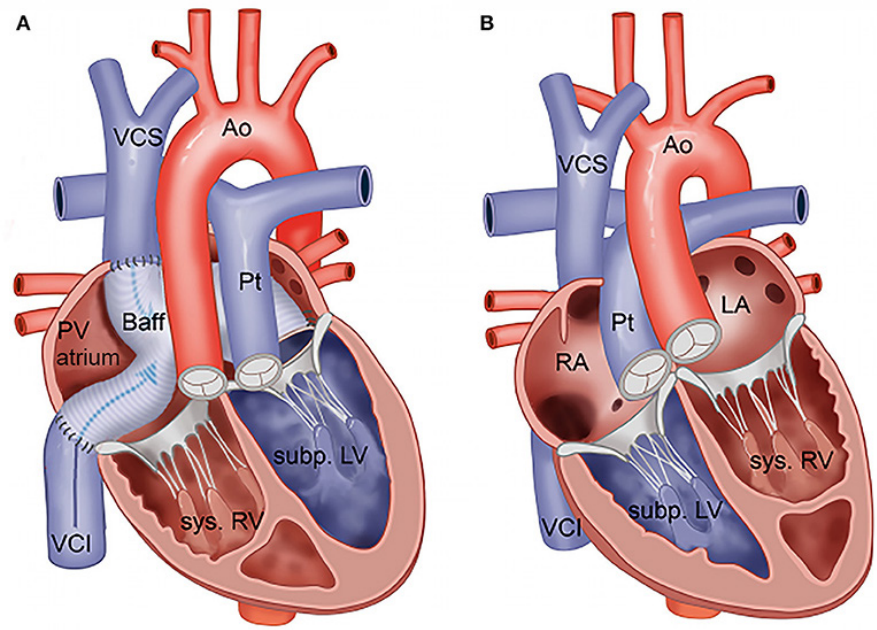

Figure 1. A) Transposition of the great arteries after the atrial switch procedure according to Mustard, with the surgical creation of an intra-atrial baffle rerouting the systemic venous circulation to the subpulmonary left ventricle and the pulmonary venous circulation to the systemic right ventricle. **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]

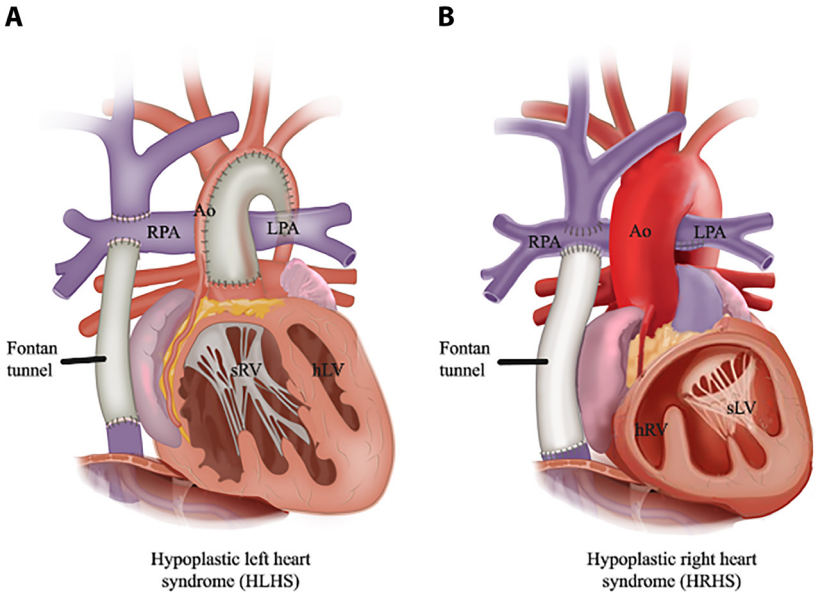

Figure 2. A) The left panel shows an extracardiac conduit-type Fontan circulation with a Fontan tunnel, and reconstructed neo-aortic root and arch, in HLHS. **B)** The right panel shows a similar extracardiac conduit-type Fontan circulation in HRHS. *Ao, aorta; HLHS, hypoplastic left heart syndrome; 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]

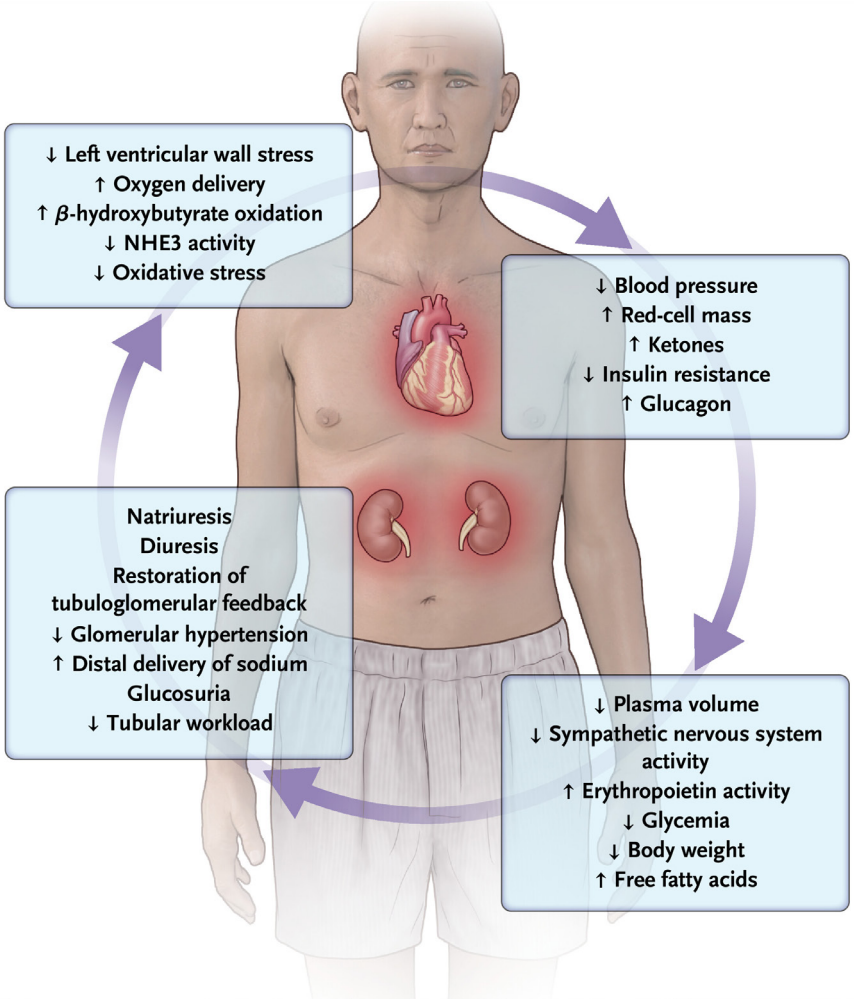

Figure 3. The kidney–heart connection for organ protection by sodium-glucose cotransporter 2 inhibitors. Reproduced with permission from Braunwald et al. N Engl J Med 2022;386:2024-2034,[43] Copyright Massachusetts Medical Society.

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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PHARMACOLOGICAL THERAPIES FOR ACHD-RELATED HF

PART 1

2

Effect of Sodium-Glucose Cotransporter 2 Inhibitors in Adults with Congenital Heart Disease

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Abstract

Background

Heart failure (HF) is the principal cause of morbidity and mortality in adults with congenital heart disease (ACHD). Robust evidence-based treatment options are lacking.

Objectives

This study aims to evaluate the safety, tolerability, and short-term HF-related effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in a real-world ACHD population.

Methods

All patients with ACHD treated with SGLT2i in 4 European ACHD centers were included in this retrospective study. Data were collected from 1 year before starting SGLT2i to the most recent follow-up. Data on side effects, discontinuation, mortality, and hospitalizations were collected.

Results

In total, 174 patients with ACHD were treated with SGLT2i from April 2016 to July 2023. The mean age was 48.7 ± 15.3 years, 72 (41.4%) were female, and 29 (16.7%) had type 2 diabetes mellitus. Ten (5.7%) patients had mild, 75 (43.1%) moderate, and 89 (51.1%) severe congenital heart disease. HF was the most frequent starting indication (n=162, 93.1%), followed by type 2 diabetes (n=11, 6.3%) and chronic kidney disease (n = 1, 0.6%). At median follow-up of 7.7 months (Q1-Q3: 3.9–13.2 months), 18 patients (10.3%) reported side effects, 12 (6.9%) permanently discontinued SGLT2i, and 4 (2.3%) died of SGLT2i-unrelated causes. A significant reduction in the HF hospitalization rate was observed from 6 months before to 6 months after starting SGLT2i (relative rate = 0.30; 95% CI: 0.14–0.62; P = 0.001).

Conclusions

SGLT2i generally seem safe, well-tolerated, and potentially beneficial in patients with ACHD. SGLT2i was associated with a 3-fold reduction in the 6-month HF hospitalization rate. These results warrant prospective randomized investigation of the potential benefits of SGLT2i for patients with ACHD.

Introduction

In adults with congenital heart disease (ACHD), heart failure (HF) represents the principal cause of morbidity and mortality.[1] Compared to patients with ACHD without HF, patients with HF have an almost 5 times higher mortality rate.[2] Contrary to the "conventional" left ventricular HF population, the etiology of HF in patients with ACHD is heterogeneous. 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, or degenerative valvular pathology. There is limited evidence on the efficacy of conventional HF pharmacotherapies, and the existing evidence remains largely empirical based on relatively small studies with heterogeneous populations.[3] Consequently, the current ACHD guidelines do not provide evidence-based recommendations to address ACHD-related HF.[4,5]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a relatively new class of drugs shown to reduce the risk of worsening HF and cardiovascular-related death in patients with conventional HF. They have rapidly become a pillar in the treatment of HF.[6,7] Although the exact mechanisms of action are still largely to be elucidated, SGLT2i appear to combat HF by targeting numerous pathways. SGLT2i have a direct hemodynamic effect, promoting diuresis and natriuresis. Moreover, SGLT2i seem to improve cardiac function by reducing sympathetic nervous system overactivation, decreasing pressure overload–induced myocardial fibrosis, decreasing inflammation, and improving overall myocardial energetics, thereby leading to favorable cardiac remodeling.[8]

Despite the compelling evidence on the effectiveness of SGLT2i over a broad range of cardiac dysfunction, robust data supporting the use of SGLT2i in the treatment of ACHD-related HF is lacking to date. The growing burden of ACHD-related HF has nonetheless led to an "off-label" prescription of SGLT2i as part of compassionate care for selected patients with ACHD worldwide.[9-13] The current study aims to evaluate prescription patterns, safety and tolerability, and short-term HF-related efficacy of SGLT2i in a contemporary, real-world ACHD population.

Methods

Study design and participants

This international, multicenter, retrospective cohort study was conducted at the Center for Congenital Heart Disease Amsterdam-Leiden, location Leiden University Medical Center (LUMC, Leiden, the Netherlands), Scottish Adult Congenital Cardiac Service at the Golden Jubilee University National Hospital (Glasgow, United Kingdom), Barts Heart Centre (St

Bartholomew's Hospital, London, United Kingdom), and University Hospital of Wales (Cardiff, United Kingdom). All tests and procedures were performed as part of standard clinical care. The study was conducted in accordance with the ethical standards of the institutional and/or national research committees and with the 2013 Helsinki Declaration or comparable ethical standards. Appropriate approval with a waiver for written informed consent was obtained from the institutional medical ethical boards/clinical governance divisions of all participating centers (LUMC Medical Research Involving Human Subjects Act [WMO] committee division 1, protocol reference 2022-068). All patients with ACHD (≥18 years of age) who were initiated on an SGLT2i in the period between April 2016 to July 2023 were included.

Data collection and follow-up

Data were collected retrospectively from the electronic health records and included anatomical characteristics, medical history, complaints, hospitalization data, pharmacologic therapy, physical examination, 12-lead electrocardiogram recordings, exercise testing, transthoracic echocardiography, laboratory investigations, intervention data, and cardiac implantable electronic device interrogation when applicable. Systolic systemic and subpulmonary ventricular function were classified into 4 categories based on transthoracic echocardiography examination, including biplane (or 3-dimensional when available) assessment of the ejection fraction, global longitudinal strain analysis, fractional area change, and qualitative visual function assessment. Data were collected from 1 year before the initiation of the SGLT2i and at each subsequent outpatient visit and/or admission until the most recent follow-up. The closing date for follow-up was July 2023, the date of discontinuation of SGLT2i therapy, last outpatient visit, death, or admission for any catheter or surgical intervention influencing the hemodynamic status of the patient (ie, implantation or an upgrade to a cardiac resynchronization therapy device, severe valvular heart disease necessitating intervention, and heart transplantation).

Primary outcome measures

The primary outcome measures were the safety and tolerability of SGLT2i in the contemporary ACHD population. This was evaluated by assessing side effects, discontinuation of SGLT2i therapy, mortality, and short-term effects on safety indices from 2 weeks to 3 months after starting SGLT2i including weight, systolic and diastolic blood pressure, serum sodium, potassium, glucose, and creatinine.

Secondary outcome measures

The secondary outcome measures focused on HF-related efficacy of SGLT2i in patients who started SGLT2i due to HF. A diagnosis of HF was defined as a clinical syndrome with symptoms and/or signs of HF, combined with elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) and/or objective evidence of pulmonic or systemic congestion, in accordance with the universal definition of HF.[14] The principal secondary outcomes were the occurrence of HF hospitalizations and a comparison of HF hospitalization rates before and after starting SGLT2i. An HF hospitalization was defined as an unscheduled admission with a primary diagnosis of HF, with a duration of at least 24 hours or crossing a calendar day, in accordance with the Clinical Data Interchange Standards Consortium.[15]

Additional secondary outcome measures included clinical data on admissions for arrhythmia and (changes in) concomitant HF pharmacotherapy. HF pharmacotherapy (other than SGLT2i) was divided into 4 categories: 1) beta-blockers; 2) angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI); 3) mineralocorticoid receptor antagonists (MRA); and 4) diuretics.

Statistical analysis

All statistical analyses were performed and figures were created in SPSS version 25 (IBM Corp), R (R Foundation for Statistical Computing), and GraphPad Prism version 9.3.1 (GraphPad Software). For the descriptive analyses at baseline, normally distributed continuous data were displayed as mean ± SD and compared between systemic ventricle groups using a one-way analysis of variance. Non-normally distributed continuous data were presented as median (Q1–Q3) and compared using a Kruskal-Wallis test. Categorical data were presented as counts and percentages and compared using the chi-square test or Fisher exact test as appropriate. Paired Student's t-tests or Wilcoxon signed-rank tests were performed to assess the safety and tolerability effects of SGLT2i therapy on continuous variables from baseline to the short-term visit.

Kaplan-Meier survival analysis and log-rank tests were used to evaluate the occurrence of hospitalizations. Hospitalization rates before and after SGLT2i initiation were compared with a Poisson regression with random effect to account for within-person correlation. McNemar's tests were used to evaluate changes in HF pharmacotherapy categories. A 2-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and follow-up

In total, 174 patients with ACHD were treated with an SGLT2i and included at the 4 participating ACHD centers (*Supplemental Figure 1*). The mean age was 48.7 ± 15.3 years, 72 (41.4%) were female, and 29 (16.7%) had type 2 diabetes mellitus. At inclusion, the median systolic and diastolic blood pressures were 113 mm Hg (Q1–Q3: 104–126 mm Hg) and 68 mm Hg (Q1–Q3: 61–75 mm Hg), respectively. The median estimated glomerular filtration rate was 60 mL/min/1.73 m2 (Q1–Q3: 59–76 mL/min/1.73 m2). According to the European Society of Cardiology classification of congenital heart disease (CHD) complexity, 10 (5.7%) participants had mild, 75 (43.1%) had moderate, and 89 (51.1%) had severe CHD (4). The majority (n=162, 93.1%) had a biventricular circulation, and 12 (6.9%) participants had univentricular circulations. Seven cyanotic patients (4.0%) with a baseline oxygen saturation <90% were included (*Table 1, Supplemental Table 1*).

Table 1. Patient Characteristics at Baseline (N=174)

Female	72 (41.4)
Age, y	48.7 ± 15.3
Systemic ventricle	
Systemic LV	102 (58.6)
Systemic RV	60 (34.5)
Univentricular circulation	12 (6.9)
CHD complexity[a]	
Mild	10 (5.7)
Moderate	75 (43.1)
Severe	89 (51.1)
No. of cardiac surgeries	1 (1–2)
CIED	84 (48.3)
Pacemaker	37 (21.3)
Transvenous ICD (single and dual chamber)	18 (10.3)
S-ICD	5 (2.9)
CRT-P	7 (4.0)
CRT-D	17 (9.8)
Type 2 diabetes mellitus	29 (16.7)
On oral therapy	26 (14.9)
On insulin therapy	3 (1.7)
Physical examination findings	
Systolic blood pressure, mmHg (n=123)	113 (104–126)
Diastolic blood pressure, mmHg (n=122)	68 (61–75)

Table 1. *Continued*

Heart rate, beats per minute (n=137)	69 (60–80)
Weight, kg (n=115)	72 (60–89)
BMI, kg/m^2 (n=110)	26.6 (22.5–30.8)
Laboratory parameters	
Hemoglobin, mmol/L (n=147)	8.7 ± 1.3
Hematocrit, L/L (n=146)	0.419 ± 0.060
Creatinine, µmol/L (n=165)	85 (73–106)
eGFR, mL/min/1.73m^2 (n=163)	60 (59–76)
Renal function (n=161)	
Normal (eGFR ≥60 mL/min/1.73m^2)	118 (73.3)
Moderately reduced (30 – 59 mL/min/1.73m^2)	38 (23.6)
Severely reduced (15 – 29 mL/min/1.73m^2)	5 (3.1)
Renal failure (<15 mL/min/1.73m^2)	0 (0)
Serum glucose, mmol/L (n=43)	5.6 (5.0–7.2)
HbA1c, mmol/mol (n=43)	43.9 (39.0–54.4)

[a]CHD complexity categorization adapted from the ESC classification (4).
Values are n (%), mean ± SD, or median (Q1-Q3).
BMI = body mass index; CHD = congenital heart disease; CIED = cardiac implantable electronic device; CRT(-P/D) = cardiac resynchronization therapy (-pacemaker/defibrillator); eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; HbA1c = hemoglobin A1c; ICD = implantable cardioverter-defibrillator; LV = left ventricle; RV = right ventricle; S-ICD = subcutaneous implantable cardioverter-defibrillator.

The median follow-up duration was 7.7 months (Q1–Q3: 3.9–13.2 months). One patient was lost to follow-up (99.4% complete), and 4 patients (2.3%) died during follow-up. Causes of death were progressive congestive cardiac failure (n=1), sudden cardiac death (n=1), respiratory tract infection (n=1), and chronic gastrointestinal bleeding secondary to warfarin use for mechanical valve prostheses (n=1).

Prescription patterns

A clear temporal increase in SGLT2i prescription was observed in the ACHD population with a notable progression in the past 2 years (*Figure 1*). Most patients were started on dapagliflozin (n=137, 78.7%) or empagliflozin (n=36, 20.7%) at the standard dose of 10 mg once per day (n=171, 98.3%). In 31 patients (17.8%), SGLT2i was initiated during a clinical admission. The most common starting indication was HF (n=162, 93.1%) (*Table 2*).

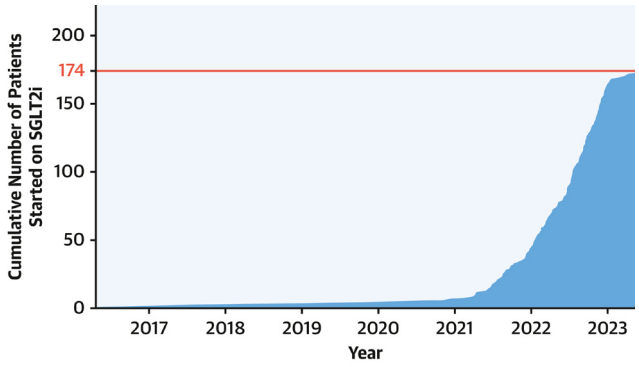


Figure 1. Increasing Prescription of SGLT2i in the ACHD Population
Cumulative number of patients who started a sodium-glucose cotransporter 2 inhibitor (SGLT2i) throughout the years, showing a sharp increase in SGLT2i prescription in the adults congenital heart disease (ACHD) population from 2021 onwards. The horizontal red line indicates the total number of patients included in the study (n=174).

Table 2. SGLT2i Prescription Details (N=174)

SGLT2i types	
Dapagliflozin	137 (78.7)
Empagliflozin	36 (20.7)
Canagliflozin	1 (0.6)
SGLT2i dose at start, OD	
10mg	171 (98.3)
5mg (dapagliflozin reduced dose)	1 (0.6)
25mg (empagliflozin increased dose)	1 (0.6)
100mg (canagliflozin standard dose)	1 (0.6)
SGLT2i starting indication	
Heart failure	162 (93.1)
HFrEF	159 (91.4)
Systemic RV failure	59 (33.9)
Systemic LV failure	49 (28.2)
Biventricular failure	25 (14.4)
Subpulmonary RV failure	15 (8.6)
Univentricular circulation failure	11 (6.3)
HFpEF	3 (1.7)
Type 2 diabetes mellitus	11 (6.3)
Chronic kidney disease	1 (0.6)

Values are n (%). Data were available for all 174 patients.
HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; OD = once daily; SGLT2i = sodium-glucose cotransporter 2 inhibitor; other abbreviations as in *Table 1*.

Safety and tolerability

Side effects were observed in 18 patients (10.3%), 9 of whom discontinued SGLT2i therapy. Overall, SGLT2i was permanently discontinued in 12 patients (6.9%). The side effects and reasons for discontinuing SGLT2i therapy are presented in *Table 3*. After 3 years, 1 patient developed Fournier's gangrene (necrotizing fasciitis) requiring surgical debridement and discontinuation of SGLT2i. The patient had a history of a perineal abscess, noninsulin dependent type 2 diabetes mellitus with persistent high-serum glucose, and obesity. The patient survived and was doing well 10 months after surgery. Three patients (1.7%) experienced recurrent urinary tract infections which were treated successfully with oral antibiotics. In 2 patients, these recurrent urinary tract infections were associated with episodes of atrial fibrillation requiring electrical cardioversions. Of these 2 patients, 1 discontinued SGLT2i therapy. A rash developed after starting dapagliflozin in 3 patients (1.7%). One patient was switched to empagliflozin, after which the rash was resolved. The other 2 patients discontinued SGLT2i therapy. The side effects and reasons for discontinuing SGLT2i in the remaining patients resolved without issues.

Table 3. Side Effects and Discontinuation of SGLT2i Therapy (N=174)

Side effects	18 (10.3)
Symptomatic (orthostatic) hypotension	6 (3.4)
Urinary tract infections	5 (2.9)
Rash	3 (1.7)
Fatigue	2 (1.1)
Dysuria	1 (0.6)
Fournier's gangrene	1 (0.6)
Permanent discontinuation of SGLT2i	12 (6.9)
Fatigue	2 (1.1)
Rash	2 (1.1)
Symptomatic (orthostatic) hypotension	2 (1.1)
Dysuria	1 (0.6)
Fournier's gangrene	1 (0.6)
No beneficial effects noticed	1 (0.6)
Precautionary due to weight loss	1 (0.6)
Significant increase in serum creatinine (started SGLT2i simultaneously with intravenous furosemide)	1 (0.6)
Urinary tract infections	1 (0.6)

Values are n (%) experiencing the respective side effects or discontinuing SGLT2i for the mentioned reasons.
Data were available for all 174 patients.
Abbreviation as in Table 2.

In the first 3 months, no significant changes were observed in weight (73.7 ± 19.7 kg to 73.3 ± 20.1 kg, P=0.525), serum sodium (139 mmol/L [Q1–Q3: 137–141 mmol/L] to 139 mmol/L [Q1–Q3: 137–140 mmol/L]; P=0.765), potassium (4.4 mmol/L [Q1–Q3: 4.0–4.6 mmol/L] to 4.4 mmol/L [Q1–Q3: 4.1–4.6 mmol/L]; P=0.974), and glucose (5.5 mmol/L [Q1–Q3: 5.0–7.1 mmol/L] to 5.2 mmol/L [Q1–Q3: 4.5–6.6 mmol/L]; P=0.755). Although diastolic blood pressure did not change significantly (68 mm Hg [Q1–Q3: 61–75 mm Hg] to 67 mm Hg [Q1–Q3: 58–72 mm Hg]; P=0.420), there was a significant decrease in systolic blood pressure from 113 mm Hg (Q1–Q3: 104–126 mm Hg) to 108 mm Hg (Q1–Q3: 100–121 mm Hg) (P=0.004). A statistically significant creatinine increase (84 μmol/L [Q1–Q3: 73–106 μmol/L] to 93 μmol/L [Q1–Q3: 78–115 μmol/L]; P<0.001) was observed compared to baseline, and SGLT2i was discontinued for this reason in 1 patient.

SGLT2i in ACHD-related HF

HF was the indication for initiation of SGLT2i in 162 patients (93.1%); 93 patients had a systemic left ventricle (LV), 58 a systemic right ventricle (RV), and 11 a univentricular circulation. Systemic ventricular function was at least moderately reduced in 69.5%, and subpulmonary ventricular function was at least mildly reduced in 52.1%. In the year preceding SGLT2i therapy, 20.4% experienced at least 1 HF hospitalization, and the majority of patients were in NYHA functional class II (45.2%). Baseline HF-related characteristics are shown in *Table 4*.

At baseline, there were significant differences in: 1) systemic ventricular function between circulation types, with more severe dysfunction in patients with a systemic RV or univentricular circulation compared to a systemic LV (P<0.001); 2) subpulmonary ventricular function, with more systemic LV patients with at least moderately reduced function (P<0.001); 3) systemic atrioventricular valve regurgitation, with at least moderate regurgitation being more prevalent in the systemic RV group (P=0.045); and 4) subpulmonary atrioventricular valve regurgitation, with more systemic LV patients with at least mild regurgitation (P<0.001).

Most patients were on at least 3 HF drugs at baseline (68.8%). An ACEI, ARB, or ARNI was prescribed for 83.1% of patients. Details on baseline pharmacotherapy are shown in Figure 2. There were no significant changes in concomitant HF pharmacotherapy during follow-up (*Supplemental Table 2*). After a median follow-up of 7.5 months (Q1–Q3: 3.7–12.6 months) in the HF cohort, 28 (17.3%) patients reached end of follow-up due to having undergone an intervention with significant hemodynamic impact (n=15, 9.3%), permanent discontinuation of SGLT2i (n=11, 6.8%), or heart transplantation (n=2, 1.2%).

Table 4. HF-Related Baseline Characteristics

	Total (n=162)	Systemic LV (n=93)	Systemic RV (n=58)	Univentricular (n=11)	P Value
No. of HF hospitalizations in year preceding SGLT2i	33 (20.4)	18 (19.8)	11 (18.3)	4 (36.4)	0.287
1	27 (16.7)	14 (15.4)	10 (16.7)	3 (27.3)	
2	4 (2.5)	3 (3.3)	0 (0)	1 (9.1)	
≥3	2 (1.2)	1 (1.1)	1 (1.7)	0 (0)	
NYHA functional class (n=62)					0.658
I	5 (8.1)	4 (10.3)	1 (4.5)	0	
II	28 (45.2)	19 (48.7)	8 (36.4)	1 (100)	
III	24 (38.7)	13 (33.3)	11 (50)	0	
IV	5 (8.1)	3 (7.7)	2 (9.1)	0	
NT-proBNP, ng/L (n=112)	924.1 (477.5–2,317.8)	1,170 (479–2,748.5)	858 (518.7–1,184.8)	647.9 (220.8–2,259)	0.306
Exercise capacity (n=33)					
VO_2 max, mL/kg/min	15.4 ± 4.2	16.2 ± 3.5	14.6 ± 4.3	17.5 ± 5.6	0.396
% predicted VO_2 max	53.4 ± 15.9	53.6 ± 21.9	53.6 ± 12.4	51.3 ± 16.0	0.974
Transthoracic echocardiography (n=146)					
Systemic ventricular function					<0.001
Good	18 (12.8)	18 (21.7)	0 (0)	0 (0)	
Mildly reduced	25 (17.7)	16 (19.3)	6 (12)	3 (37.5)	
Moderately reduced	33 (23.4)	17 (20.5)	15 (30)	1 (12.5)	
Severely reduced	65 (46.1)	32 (38.6)	29 (58)	4 (50)	

Table 4. *Continued*

	Total (n=162)	Systemic LV (n=93)	Systemic RV (n=58)	Univentricular (n=11)	P Value
Subpulmonary ventricular function					<0.001
Good	56 (47.9)	20 (27.8)	36 (80)	—	
Mildly reduced	31 (26.5)	23 (31.9)	8 (17.8)	—	
Moderately reduced	11 (9.4)	11 (15.3)	0 (0)	—	
Severely reduced	19 (16.2)	18 (25)	1 (2.2)	—	
Systemic AV valve regurgitation					0.045
No	20 (14.8)	15 (19.5)	5 (10.4)	0 (0)	
Mild (grade 1-2)	95 (70.4)	55 (71.4)	30 (62.5)	10 (100)	
Moderate (grade 3)	8 (5.9)	4 (5.2)	4 (8.3)	0 (0)	
Severe (grade 4)	12 (8.9)	3 (4)	9 (18.8)	0 (0)	
Subpulmonary AV valve regurgitation					<0.001
No	24 (19.8)	5 (6.3)	19 (46.3)	—	
Mild (grade 1-2)	75 (62)	55 (68.8)	20 (48.8)	—	
Moderate (grade 3)	9 (7.4)	8 (10)	1 (2.4)	—	
Severe (grade 4)	13 (10.7)	12 (15)	1 (2.4)	—	

Values are n (%), median (Q1–Q3), or mean ± SD. Data were available for the 162 patients who started SGLT2i for heart failure, unless otherwise specified. For the comparison of categorical variables across systemic ventricle groups, the Fisher exact test was used. For the comparison of continuous variables, 1-way analysis of variance was used (Levene's test for equal variance $P > 0.05$ in all cases).

AV = atrioventricular; HF = heart failure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; other abbreviations as in *Tables 1* and *2*.

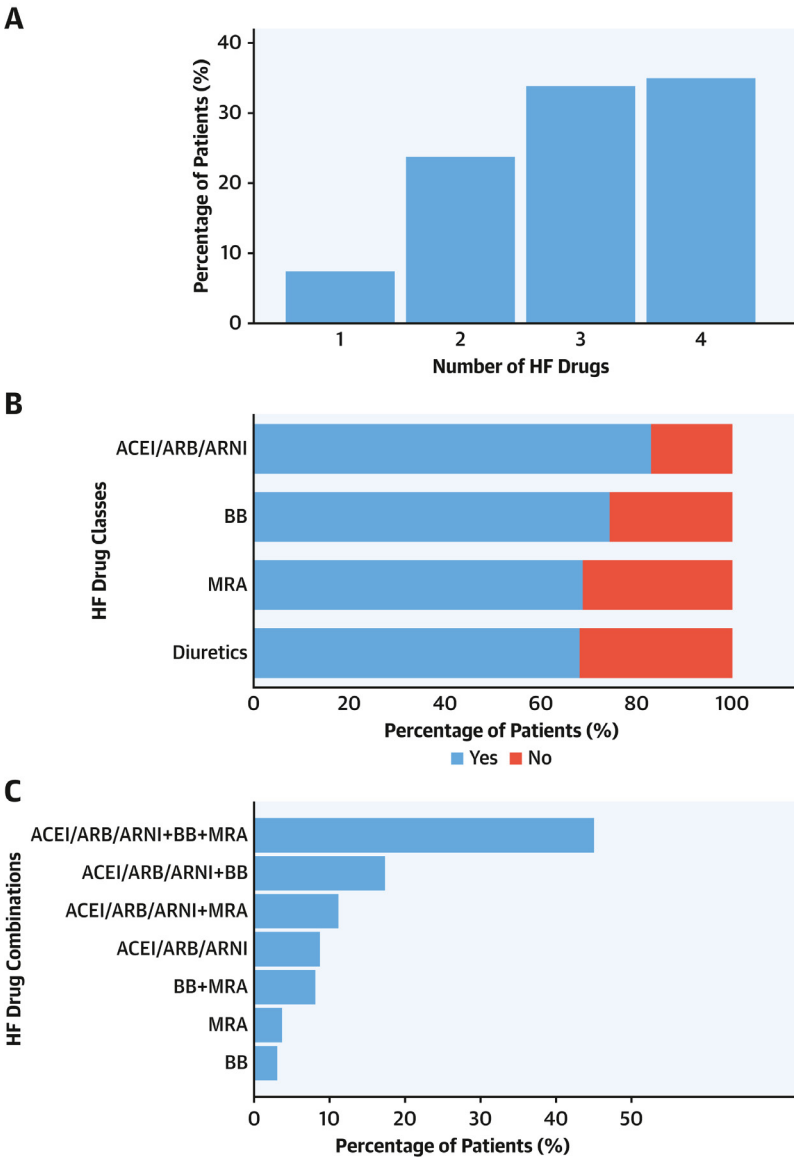


Figure 2. HF Pharmacotherapy at Baseline

Details on heart failure (HF) pharmacotherapy at baseline in patients who were started on SGLT2i due to HF. Data were available for 160 of 162 patients (98.8%). (**A**) The number of HF drugs used at baseline. Most patients were on ≥3 HF drugs (68.8%), consisting of the following categories: 1) beta-blockers (BB); 2) angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI); 3) mineralocorticoid receptor antagonist (MRA); and 4) diuretics. (**B**) Percentage (%) of patients using specific classes of HF drugs at baseline. (**C**) The most frequently encountered combinations of HF drugs at baseline, excluding diuretics use.

HF hospitalizations and arrhythmia admissions

In total, 60 HF hospitalizations occurred in 38 patients (23.5%); 42 (70%) in the 12 months preceding initiation of SGLT2i therapy, and 18 (30%) during follow-up. There was a significantly higher risk of HF hospitalization in patients with an HF hospitalization in the 12 months before SGLT2i initiation (n=33) compared to patients without HF hospitalization in the previous year (n=129) (log-rank P=0.0024) (*Figure 3*). Of the 11 individuals who experienced HF hospitalization(s) during follow-up, 6 had an HF hospitalization in the 12 months before start. There were no differences in HF hospitalizations when stratified for systemic ventricular morphology or CHD complexity subgroups (log-rank P=0.43 and P=0.84, respectively) (*Supplemental Figures 2 and 3*). A significant reduction in HF hospitalization rate was observed during the 6 months after starting (n=9) compared to the 6 months before starting SGLT2i (n=36) (relative hospitalization rate=0.30; 95% CI: 0.14–0.62; P=0.001) (*Central Illustration*).

Sixty-eight arrhythmia admissions were observed in 33 patients (20.4%); 41 (60.3%) in the 12 months preceding SGLT2i initiation, and 27 (39.7%) during follow-up. There was no significant difference in arrhythmia admission rate in the 6 months before (n=21) and after (n=12) SGLT2i initiation (relative admission rate=0.68; 95% CI: 0.33–1.39; P = 0.289) (*Central Illustration*).

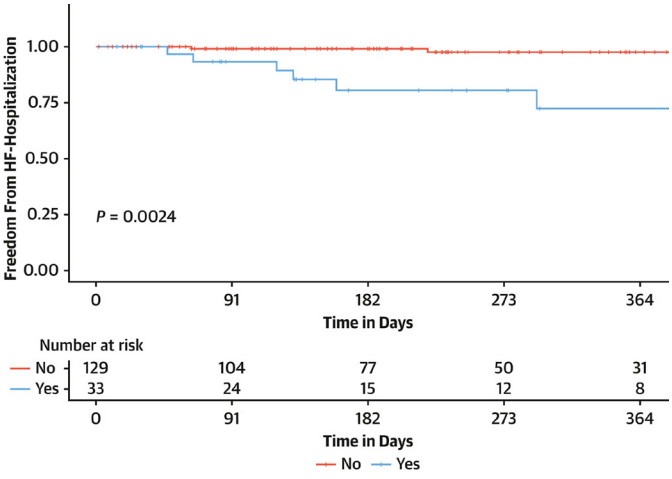
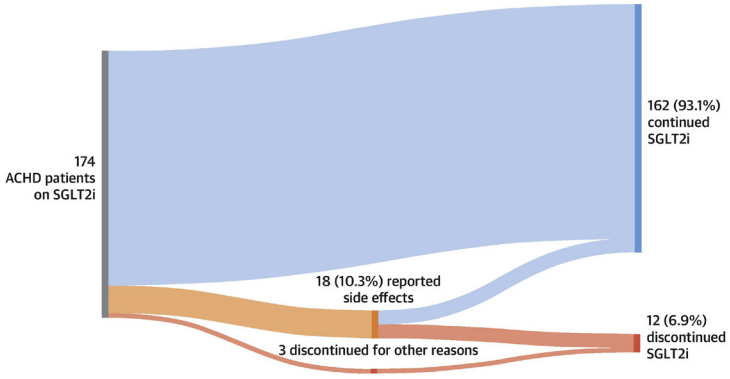
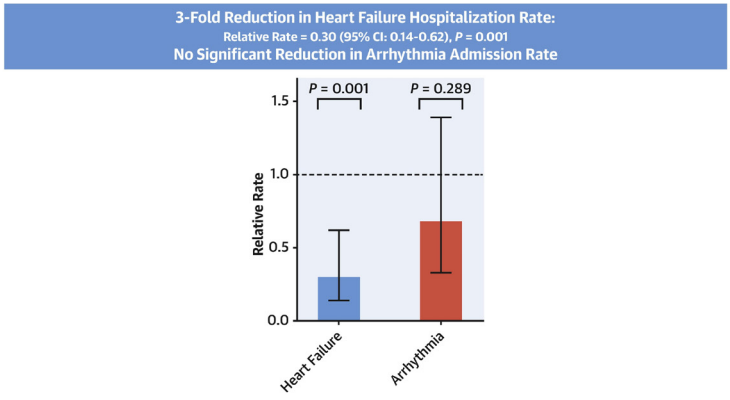


Figure 3. Freedom From HF Hospitalization

Kaplan-Meier curves show freedom from HF hospitalization in the year after starting SGLT2i in the HF cohort (n=162). The 2 Kaplan-Meier curves represent patients with an HF hospitalization in the 12 months before starting SGLT2i (yes, blue) and the patients without (no, red). Patients with an HF hospitalization in the year before SGLT2i initiation had a higher risk of (re-)hospitalization (log-rank P=0.0024). Abbreviations as in *Figures 1* and *2*.

CENTRAL ILLUSTRATION: Sodium-Glucose Cotransporter 2 Inhibitors in Adults With Congenital Heart Disease





Neijenhuis RML., et al. J Am Coll Cardiol. 2024;83(15):1403-1414.

Central Illustration.

In this multicenter retrospective cohort study, SGLT2i were safe, well-tolerated and potentially beneficial in 174 ACHD patients. Side effects were observed in 18 patients (10.3%), 9 of whom discontinued SGLT2i therapy. Overall, SGLT2i was permanently discontinued in 12 patients (6.9%). In a subset of 162 ACHD patients with heart failure, a 3-fold reduction in heart failure-hospitalization rate from the 6 months before to the 6 months after starting SGLT2i was observed (P=0.001). There was no significant reduction in arrhythmia admission rate (P=0.289). *ACHD = adult congenital heart disease; SGLT2i = sodium-glucose cotransporter 2 inhibitor*.

Discussion

The main findings of this study are that: 1) despite limited evidence, SGLT2i are prescribed with increased frequency in the heterogeneous ACHD population, with HF as the most frequently encountered indication; 2) SGLT2i are safe and generally well-tolerated, with comparable occurrence of side effects to the landmark trials in conventional HF patients; and 3) SGLT2i use was associated with a decreased 6-month HF-related hospitalization rate, suggesting a potential prognostic benefit for patients with ACHD with HF.

SGLT2i prescription patterns and real-world treatment of ACHD-related HF

The study reports on a heterogeneous ACHD cohort with varied anatomy and frequent concomitant defects including pulmonary hypertension and tricuspid regurgitation, in whom SGLT2i therapy was most frequently initiated for HF with a reduced ejection fraction. HF with a preserved ejection fraction was the indication for starting SGLT2i in only 3 patients (1.7%). This might partly be explained by underdiagnosis of HF with a preserved ejection fraction in the ACHD population but also reflects that SGLT2i were only recently included as a Class 1 treatment for HF with a preserved ejection fraction in the updated European Society of Cardiology HF guidelines.[7]

In this contemporary, real-world ACHD setting, a steady increase in SGLT2i prescriptions was observed over time. This indicates a more prevalent prescription of SGLT2i for HF in patients with ACHD than the recently reported observational experience of 35 patients with ACHD treated with SGLT2i at a single center in the United States, where only 40.6% of patients had HF as the starting indication. More than 65% of the cohort reported in *Saef et al*. had diabetes mellitus, whereas this was only 16.7% in the current cohort.[11] These differences might reflect the early prescription indications of SGLT2i as a treatment for diabetes regardless of the cardiorenal status, the higher prevalence of diabetes in the United States compared to Northern European countries, and the proactive treatment of ACHD-related HF by the centers participating in this study.

The proactive HF management strategy in our population is reflected by more than 80% of patients using an ACEI/ARB/ARNI, and 45% a combination of beta-blockers, ACEI/ARB/ARNI, and MRA. To show the disparity between centers when it comes to HF management in the ACHD population, pharmacotherapy has been evaluated in systemic RV patients—who make up more than one-third of our cohort—in the German National Register for Congenital Heart Defects. No patients used SGLT2i, and in patients with systemic RV dysfunction, a combination of beta-blockers, ACEI/ARB/ARNI, and MRA was prescribed in 26.7% whereas 13.6% did not use any cardiovascular drugs. The investigators concluded

that there were signs of beneficial effects of pharmacotherapy for systemic RV failure.[16] In a recent Dutch evaluation of systemic RV patients, 52% used renin-angiotensin-aldosterone system inhibitors and 29% did not use any cardiovascular drugs. Symptomatic patients had a lower risk of mortality when using renin-angiotensin-aldosterone system inhibitors and beta-blockers. These findings indicate a potential beneficial effect of HF pharmacotherapy for systemic RV failure.[17] Patients with ACHD have a higher use of cardiovascular and noncardiovascular drugs, and a higher prevalence of polypharmacy (≥5 drugs) compared to age- and sex-matched controls from the general population.[18] This highlights the demographic differences between the non-ACHD and the ACHD patient, who is burdened with the consequences of a chronic condition from a much younger age.

Safety and tolerability

In the current study, 10.3% reported side effects and 6.9% discontinued SGLT2i. In the landmark SGLT2i trials, discontinuation of SGLT2i therapy ranged from 10.5% to 23.2% and did not differ significantly from placebo.[19-22] Although direct comparison of side effect profiles is not possible due to different study designs, adverse event definitions and observation periods, no novel side effects were observed, and the occurrence of reported side effects seems comparable to the literature.[23] This suggests that SGLT2i are generally well-tolerated and safe in patients with ACHD. During follow-up, 1 patient nonetheless developed Fournier's gangrene (necrotizing fasciitis) requiring surgical debridement. Retrospectively, this patient had several risk factors for developing Fournier's gangrene in addition to the SGLT2i therapy. This devastating side effect is very rare but, given the rapid progression and high associated morbidity and mortality, early recognition and action is imperative.[24]

Short-term effects on safety indices were evaluated from baseline to the first routine check within 2 weeks to 3 months after starting SGLT2i. Although most parameters remained unchanged, a statistically significant decrease in systolic blood pressure and an increase in creatinine were observed. Although these changes were statistically significant, their clinical relevance might be limited and related to the mechanisms of action of SGLT2i. During follow-up, 6 patients (3.4%) reported symptomatic (orthostatic) hypotension (of whom only 2 discontinued treatment), and SGLT2i was discontinued in 1 patient due to an increase in creatinine. An initial "dip" in renal function after starting SGLT2i has now been widely reported in the literature and may be associated with renal protection in the long term.[25]

Value of NT-proBNP in ACHD-related HF

NT-proBNP is a surrogate marker of clinical status in ACHD-related HF and provides prognostic information on the risk of cardiovascular events, including mortality and HF

course.[26,27] Although a pilot study evaluating 10 patients with systemic RV failure on SGLT2i has shown a reduction in NT-proBNP after 6 months, longitudinal changes in NT-proBNP were not formally evaluated in this study.[9] While significant reductions in NT-proBNP have also been reported in the majority of the large SGLT2i trials,[19,20,22] the risk of HF events is reduced independently of baseline NT-proBNP levels.[28] Moreover, the observed reduction in NT-proBNP after SGLT2i initiation seems modest compared to other established HF therapies and not in line with the large clinical improvements. Thus, the role of NT-proBNP as a surrogate marker of the efficacy of SGLT2i remains to be investigated.[29]

Hospitalizations

In the ACHD population, HF hospitalizations have increased dramatically over the years, and are more complex and costly than in the non-ACHD HF population.[30] HF hospitalizations severely impact prognosis and are associated with a substantially higher risk of death in ACHD patients, and it is imperative to closely monitor these patients.[31,32] Patients in our study with an HF hospitalization in the 12 months before SGLT2i initiation were at a higher risk of HF hospitalization during follow-up compared to patients without HF hospitalization in the year preceding SGLT2i initiation. This emphasizes the need for intensified follow-up regimens in high-risk ACHD HF patients who may be identified by recent HF hospitalization. Studies have shown that SGLT2i therapy consistently reduces HF hospitalizations in the conventional HF population, regardless of ejection fraction, hospitalization duration, or severity.[33] This study found no differences in HF hospitalizations after stratifying for systemic ventricular morphology or CHD complexity, despite markedly different ventricular function profiles at baseline. The 3-fold reduction in HF hospitalization rate that was observed from 6 months before to 6 months after SGLT2i initiation is a promising signal. Investigating a potential confounder of these results, no significant changes in the use of other HF drugs were observed from baseline to 6 months or most recent follow-up.

Finally, we observed no differences in the occurrence of arrhythmia admissions. We did not expect SGLT2i to have a direct effect on these admissions, nor do we see this as a robust marker for HF status. Supraventricular arrhythmias are common in ACHD-related HF and often related to scar tissue, especially in complex cohorts such as systemic RV patients.

Study limitations

The decision to start SGLT2i therapy was at the discretion of the physician, introducing potential selection bias. There were no standardized follow-up protocols across the participating centers, which resulted in variable follow-up assessments. The heterogeneity

of the ACHD population and relative overrepresentation of complex ACHD patients in the current study should be noted, as should the relatively limited follow-up duration. Although the study was not powered for "hard endpoints" such as mortality and HF hospitalizations, a promising reduction in HF hospitalization rate was observed. Keeping these limitations in mind, this study design allowed a real-world evaluation of SGLT2i in the ACHD population.

Future directions

The positive results presented in this study provide a strong foundation to justify a prospective randomized trial to further elucidate the effects of SGLT2i on ACHD-related HF. Moreover, further follow-up is required to perform dedicated neurohormonal biomarker and imaging studies to evaluate the mechanistic effects of SGLT2i in the larger ACHD-related HF subgroups such as tetralogy of Fallot, univentricular circulation/Fontan, and systemic RV patients.

Conclusions

This study is the largest to date to evaluate the use of SGLT2i in the ACHD population. SGLT2i were well-tolerated and safe in 174 patients with ACHD, with similar side effects and treatment discontinuation rates to the SGLT2i trials in conventional HF patients. In 162 patients who received SGLT2i for HF, SGLT2i therapy was associated with a 3-fold reduction in HF hospitalization rate during follow-up compared to before treatment. These positive results might indicate a prognostic benefit and warrant further prospective randomized investigation of the potential benefits of SGLT2i for ACHD-related HF.

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3

The Potential of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Systemic Right Ventricular Failure in Adults with Congenital Heart Disease

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Abstract

Aims

Given the compelling evidence on the effectiveness of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in the conventional heart failure population, SGLT2i deserve exploration in systemic right ventricular (sRV) failure. The initial experience with dapagliflozin in sRV failure patients is described, with a focus on tolerability and short-term effects on clinical outcomes.

Methods and results

Ten patients (70% female, median age 50 years [46.5–52]) with symptomatic sRV failure who received dapagliflozin 10 mg per day on top of optimal medical therapy between 04–2021 and 01–2023 were included. Within 4 weeks, no significant changes in blood pressure, electrolytes, or serum glucose occurred. Creatinine and estimated glomerular filtration rate (eGFR) showed a slight decline (88 ± 17 to 97 ± 23 μmol/L, p=0.036, and 72 ± 14 vs. 66 ± 16 ml/min/1.73m^2, p=0.020, respectively). At 6 months follow-up (n=8), median NT-proBNP decreased significantly from 736.6 [589.3–1193.3] to 531.6 [400.8–1018] ng/L (p=0.012). Creatinine and eGFR recovered to baseline levels. There were no significant changes in echocardiographic systolic sRV or left ventricular function. New York Heart Association class improved significantly in 4 out of 8 patients (p=0.046), who also showed an improvement in the 6-minute walk test or bicycle exercise test performance. One female patient developed an uncomplicated urinary tract infection. No patients discontinued treatment.

Conclusion

Dapagliflozin was well-tolerated in this small cohort of sRV failure patients. While the early results on the reduction of NT-proBNP and clinical outcome parameters are encouraging, large-scale prospective studies are warranted to thoroughly evaluate the effects of SGLT2i in the growing sRV failure population.

Introduction

With the improved survival of congenital heart disease patients, clinicians are frequently confronted with heart failure in this heterogeneous population. Complex congenital heart disease with a systemic right ventricle (sRV) forms a distinct entity where the morphological RV functions in the subaortic position and supports the systemic circulation. This occurs in the biventricular setting of transposition of the great arteries (TGA) after the atrial switch procedure according to Mustard or Senning, or in congenitally corrected TGA (ccTGA). Failure of the sRV is a frequent long-term complication in these patients; 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 heart failure.[1,2] Robust evidence for the use of heart failure medication in this group is lacking, and the mechanisms and treatment of sRV failure have been identified as major gaps of knowledge in the latest European and American adult congenital heart disease guidelines.[3,4]

Recently, sacubitril/valsartan (an angiotensin receptor-neprilysin inhibitor, ARNI) has been linked to reduction of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, sRV remodeling with improvement of systolic ventricular function, improvements in 6-minute walk test (6MWT) distance, New York Heart Association (NYHA) class, and quality of life in patients with sRV failure.[5,6] These results suggest that heart failure in sRV patients may indeed be amendable to timely pharmacological intervention.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a relatively novel class of drugs that have quickly become a pillar in the treatment of "conventional" left ventricular heart failure, demonstrating a reduced risk of worsening heart failure, hospitalization, and cardiovascular-related death.[7] Given the unmet need for evidence-based pharmacological strategies in sRV failure and the compelling evidence on the effectiveness of SGLT2i in the "conventional" heart failure population, SGLT2i have been prescribed to some patients with progressive sRV failure and insufficient response to classical pharmacological heart failure therapy, as demonstrated by *Egorova et al*. (2022).[8]

In this brief report, we describe the tolerability and short-term neurohumoral, echocardiographic, and clinical effects of dapagliflozin in the treatment of sRV patients with heart failure. Moreover, we discuss the rationale for and propose a future prospective evaluation of SGLT2i effects in this patient group.

Materials and methods

Participants

Adult patients with symptomatic sRV failure who were started on dapagliflozin 10 mg p.o. q.d. on top of current optimal medical therapy as part of compassionate care between April 2021 and January 2023 were reviewed for inclusion.

Inclusion criteria were: adults with an sRV in a biventricular circulation with underlying anatomy of TGA after the atrial switch procedure or ccTGA, progressive symptomatic heart failure with NYHA class ≥ II, and at least moderately reduced systolic sRV function as assessed by echocardiography. Progressive symptomatic heart failure was defined as progressive symptoms attributed to heart failure and/or a deterioration in exercise performance as assessed by bicycle exercise test, accompanied by an increase in NT-proBNP levels despite the pharmacological treatment.

Study design

All patients were followed up in the outpatient clinic according to the smart technology-supported care pathway at the Leiden University Medical Center, as previously described.[5] After baseline measurements, patients had an initial evaluation after 2 to 4 weeks and a structured outpatient clinic follow-up visit at 6 months.

Tolerability was evaluated by blood pressure and laboratory investigations (including creatinine, estimated glomerular filtration rate (eGFR), non-fasting plasma glucose, and electrolytes) after 2 to 4 weeks, discontinuation of treatment, and the occurrence of side effects or adverse events.

At the structured 6 months follow-up visit, the biomarker NT-proBNP was evaluated as a surrogate for neurohumoral activation status and heart failure-related prognosis. Furthermore, hemoglobin, hematocrit, electrolytes, creatinine, eGFR, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (GGT), HbA1c, non-fasting serum glucose, and uric acid changes were evaluated. Systolic sRV and left ventricular (LV) function were assessed by transthoracic echocardiography as previously described.[5,9] Changes in functional outcomes were assessed by NYHA functional class, 6MWT performance, and bicycle ergometry with VO_2 max.

Ethics approval statement

All tests and procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki declaration or comparable ethical standards. Appropriate local scientific

board approval was obtained and the need for written informed consent was waived by the institutional medical ethical board (protocol N22.120). All patients provided consent for registration of their data and publication.

Statistical analysis

All statistical analyses were performed in SPSS version 25 (IBM Corp, Armonk, NY). The figure was generated with Graphpad Prism version 9.3.1 (GraphPad Software, San Diego, California USA). Normally distributed continuous data were displayed as mean (± standard deviation) and non-normally distributed continuous data were displayed as median [interquartile range Q1–Q3]. Proportions were displayed as numbers (percentages). Normality was tested with the use of the Shapiro-Wilk test. For the comparison of continuous values between time points, paired samples t-tests or Wilcoxon signed-rank tests were used as appropriate. For the comparison of paired ordinal data, the Wilcoxon signed-rank test was used. A p-value < 0.05 was considered statistically significant.

Results

Ten consecutive patients were included in this retrospective cohort. Six (60%) had underlying anatomy of TGA late after the atrial switch, and 4 (40%) had ccTGA. Seven patients (70%) were female and the median age at treatment initiation was 50 years [46.5–52]. Baseline patient characteristics are shown in *Table 1*. All patients were on at least one heart failure drug, including beta-blocker, ARNI, mineralocorticoid receptor antagonists, or diuretics before starting dapagliflozin. Nine patients (90%) were on a maximum tolerated dose of an ARNI, and 70% were on diuretics before starting dapagliflozin.

At baseline, 4 patients had severely reduced and 6 had moderately reduced systolic sRV function. Three patients had a mechanical tricuspid valve and the other 7 patients had grade II tricuspid regurgitation. The systolic subpulmonary LV function was good in 8 and mildly reduced in 2 patients.

Tolerability

After 2–4 weeks of treatment with dapagliflozin, no statistically significant changes in systolic blood pressure (107 ± 17 to 103 ± 16 mmHg, p=0.509), diastolic blood pressure (67 ± 9 to 63 ± 10 mmHg, p=0.406), non-fasting plasma glucose levels (4.9 [4.4–6.4] to 5.0 [4.3–7.1] mmol/L, p=0.889), or electrolytes were observed. Creatinine increased (88 ± 17 to 97 ± 23 μmol/L, p=0.036) and eGFR decreased (72 ± 14 vs. 66 ± 16 ml/min/1.73m2, p=0.020) significantly. A 60-year-old female patient developed a urinary tract infection which was treated with oral antibiotics. No other side effects or adverse events were observed and none of the patients discontinued the treatment.

Table 1. Baseline patient characteristics

Baseline (n=10)	
Age, years [IQR1–IQR3]	50 [46.5–52]
Female (%)	7 (70)
Weight, kg (± SD)	73.9 ± 17.5
Body Mass Index, kg/m² (± SD)	24.2 ± 4.0
Anatomy (%)	
TGA atrial switch	6 (60)
ccTGA	4 (40)
Concomitant defects (%)	
ccTGA + VSD	1 (10)
ccTGA + VSD + monoatrium	1 (10)
TGA + VSD + PS	1 (10)
ccTGA + VSD + Ebstein-like TV	1 (10)
TGA + VSD + ASD + PS + PAPVD + persistent SVC	1 (10)
None	5 (50)
Number of cardiac surgeries [IQR1–IQR3]	1.5 [1–2]
Atrial switch procedure (%)	
Mustard	4 (40)
Senning	2 (20)
History of TV surgery (%)	
Mechanical TV	3 (30)
TV annuloplasty	2 (20)
History of atrial arrhythmia (%)	9 (90)
History of atrial ablation procedure (%)	6 (60)
Type II diabetes mellitus (on oral treatment) (%)	1 (10)
NYHA functional class (%)	
Class II	4 (40)
Class III	4 (40)
Class IV	2 (20)
Oxygen saturation at ambient air, % [IQR1–IQR3]	99 [98–99]
Systolic blood pressure, mmHg (± SD)	107 ± 17
Diastolic blood pressure, mmHg (± SD)	67 ± 9

Table 1. *Continued*

Baseline (n=10)	
eGFR, mL/min/1.73m^2 (± SD)	72 ± 14
Patients with a heart failure-related hospitalization in past year (%)	1 (10)
Pharmacological therapy (%)	
Beta blocker	5 (50)
ACE-i / ARB / ARNI	0 / 0 / 9 (90)
MRA	6 (60)
Diuretics (loop and/or thiazide)	7 (70)
Antiarrhythmic drugs	3 (30)
Cardiac Implantable Electronic Devices (%)	
AAIR-pacemaker	1 (10)
DDD-pacemaker	1 (10)
DDD-ICD	4 (40)
CRT-D	2 (20)
Baseline exercise performance	
6MWT distance, m [IQR1–IQR3]	604 [501–645]
VO_2 max, mL/kg/min (± SD)	15.2 ± 4.0
%-pred. VO_2 max (± SD)	54 ± 14
Baseline echocardiography	
sRV function (%)	
Moderately reduced	6 (60)
Severely reduced	4 (40)
sRV GLS, % (± SD)	-10.5 ± 3.3
sRV FAC, % (± SD)	19.1 ± 6.0
TAPSE, mm (± SD)	12 ± 2
Tricuspid regurgitation, grade (%)	
Grade I or less	3 (30)[$]
Grade II	7 (70)
Subpulmonary LV function (%)	
Good	8 (80)
Mildly reduced	2 (20)

Table 1. *Continued*

Baseline (n=10)

Proportions are presented as n (%). Values are presented as mean (± standard deviation) or median [IQR1–IQR3] as appropriate. *6MWT, 6-minute walk test; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASD, atrial septal defect; ccTGA, congenitally corrected transposition of the great arteries; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; FAC, fractional area change; GLS, global longitudinal strain; ICD, implantable cardioverter defibrillator; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAPVD, partial anomalous pulmonary venous drainage; PS, pulmonary stenosis; sRV, systemic right ventricle; SVC, superior vena cava; TAPSE, tricuspid annular plane systolic excursion; TGA, transposition of the great arteries; TV, tricuspid valve; VSD, ventricular septal defect.*
[$]The three patients with grade I or less tricuspid regurgitation at baseline all had a mechanical TV.

One heart failure-related hospitalization occurred during follow-up; patient 1 had a short admission (<24 h) after 4 months with mild congestion which resolved after a single intravenous administration of loop diuretics. Additionally, this patient required escalation in the dose of spironolactone and bumetanide despite treatment with dapagliflozin and was listed for heart transplantation. In the 6 months preceding SGLT2i therapy, this patient experienced 4 heart failure-related admissions. The dose of furosemide was reduced in patient 2 and triamterene could be stopped in patient 3. No concurrent changes in medical therapy occurred in the other 7 patients during follow-up.

Short-term effects of SGLT2i

Eight patients (80%) had a 6 months follow-up visit. From baseline to 6 months, median NT-proBNP decreased significantly from 736.6 [589.3–1,193.3] to 531.6 [400.8–1,018] ng/L (p=0.012) (*Figure 1*). Creatinine (85 [74–100] to 77 [67–108] μmol/L, p=0.575) and eGFR (71 ± 14 to 71 ± 19 ml/min/1.73m2, p=0.539) recovered after the initial deterioration in renal function, with no significant change from baseline to 6 months (*Table 2*). There were no significant changes in body weight (73.9 ± 17.5 to 71.0 ± 16.9 kg, p=0.957) or body mass index (mean 24.2 ± 4.0 to 24.1 ± 4.3 kg/m2, p=0.908). There were no statistically significant changes in systolic sRV or LV function and dimensions as assessed with transthoracic echocardiography from baseline to 6 months follow-up (*Table 3*). Changes in functional outcome parameters from baseline to 6 months are shown in *Table 4*. A significant improvement in NYHA class was observed in 4 out of 8 patients (p=0.046), and no patients experienced a clinical deterioration. These 4 patients also showed an improvement in either 6MWT distance or exercise test performance, although these changes were not statistically significant.

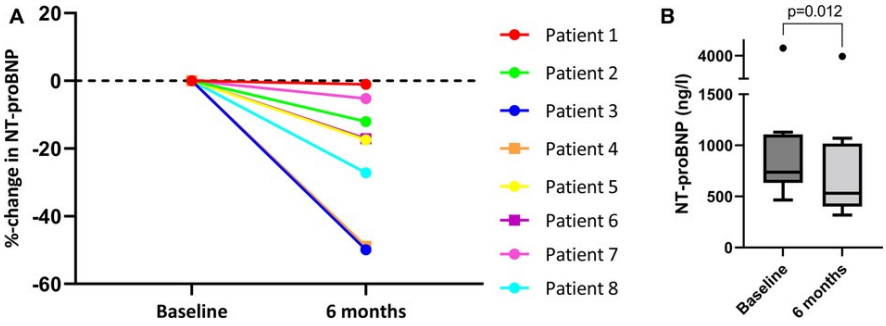

Figure 1. Changes in NT-proBNP from baseline to 6 months for patients 1–8
(**A**) Percentage change in NT-proBNP from baseline to 6 months follow-up for individual patients 1 to 8. (**B**) Box-and-whiskers plot presenting the absolute NT-proBNP (ng/L) levels at baseline and 6 months follow-up for patients 1 to 8. The p-value refers to the comparison of the median values between baseline and 6 months follow-up (Wilcoxon signed-rank test). *NT-proBNP, N-terminal pro-B-type natriuretic peptide*.

Table 2. Changes in laboratory parameters from baseline to 6 months for patients 1–8

	Baseline	6 months	p-value
NT-proBNP, ng/L [IQR1–IQR3]	736.6 [589.3–1193.3]	531.6 [400.8–1018]	0.012
Hemoglobin, mmol/L (± SD)	8.5 ± 1.4	8.3 ± 0.8	0.635
Hematocrit, L/L (± SD)	0.416 ± 0.063	0.408 ± 0.032	0.634
Sodium, mmol/L (± SD)	140 ± 3	139 ± 2	0.044
Potassium, mmol/L (± SD)	4.2 ± 0.3	4.3 ± 0.7	0.441
Creatinine, µmol/L [IQR1–IQR3]	85 [74–100]	77 [67–108]	0.575
eGFR, mL/min/1.73m^2 (± SD)	71 ± 14	71 ± 19	0.539
AST, U/L [IQR1–IQR3]	29 [23–38]	30 [22–38]	0.799
ALT, U/L [IQR1–IQR3]	30 [22–66]	30 [22–37]	0.401
GGT, U/L [IQR1–IQR3]	50 [28–173]	53 [31–93]	0.138
HbA1c, mmol/mol [IQR1–IQR3]	41.9 [38.3–44.0]	42.3 [37.9–42.9]	0.128
Serum glucose (non-fasted), mmol/L [IQR1–IQR3]	4.9 [4.4–6.4]	5.1 [4.6–6.2]	0.833
Uric acid, mmol/L (± SD)	0.45 ± 0.18	0.32 ± 0.14	0.088

Changes in laboratory parameters from baseline to 6 months follow-up. Values are presented as mean (± standard deviation) or median [IQR1-IQR3]. Paired t-test or Wilcoxon signed-rank tests are performed as appropriate. A*ST, aspartate transaminase; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; NT-proBNP, N-terminal pro-B-type natriuretic peptide.*

Table 3. Echocardiographic changes from baseline to 6 months for patients 1–8

	Baseline	6 months	p-value
sRV GLS, % [IQR1–IQR3]	-11.2 [-12.8– -8.2]	-11.4 [-12.5– -10.2]	0.889
sRV FAC, % (± SD)	19.1 ± 6.0	19.0 ± 7.1	0.707
sRV s' [IQR1–IQR3]	4.9 [4.4–6.0]	5.5 [4.0–6.5]	0.665
TAPSE, mm (± SD)	12.0 ± 1.9	12.6 ± 1.3	0.325
sRV EDD, mm (± SD)	55.0 ± 5.7	55.8 ± 6.3	0.897
Tricuspid regurgitation, grade [IQR1–IQR3]	2 [1–2]	2 [1–2]	1.000
LV GLS, % (± SD)	-22.4 ± 7.0	-20.9 ± 3.8	0.482
MAPSE, mm [IQR1–IQR3]	18 [17–22.5]	19.7 [16.5–22.8]	0.611
Mitral regurgitation, grade [IQR1–IQR3]	1 [1–2]	1 [1–2]	1.000

Changes in echocardiographic parameters from baseline to 6 months follow-up. Values are presented as mean (± standard deviation) or median [IQR1-IQR3]. Overall changes are not statistically significant, as assessed with paired t-test or Wilcoxon-signed-rank test as appropriate. *FAC, fractional area change; GLS, global longitudinal strain; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; sRV, systemic right ventricle; EDD, end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion*.

Table 4. Changes in NYHA class and exercise capacity from baseline to 6 months for patients 1–8

Patient	NYHA class at baseline	NYHA class at 6 months	Δ 6MWT (m)	Δ VO_2 max (mL/kg/min)	Δ %-pred. VO_2 max	Δ exercise capacity (W)	Δ %-pred. exercise capacity
		(p=0.046)	(p=0.345)	(p=0.499)	(p=0.386)	(p=0.793)	(p=0.723)
1	IV	III	NA	+6.1	+23	+43	+28
2	III	II	+34	-0.9	-1	+0	+0
3	III	II	+75	+2.1	+10	+20	+16
4	IV	III	-82	+1.2	+4	+1	+3
5	III	III	-65	-3.0	-13	-20	-19
6	III	III	NA	-0.3	+3	+1	+2
7	II	II	-129	0	+3	-28	-16
8	II	II	-7	+0.4	-2	0	+2

Absolute change from baseline to 6 months follow-up (Δ). Changes are not statistically significant, as is indicated by the p-values and assessed with paired t-test or Wilcoxon-signed-rank test as appropriate. *NYHA, New York Heart Association; 6MWT, 6-minute walking test*.

Discussion

Dapagliflozin was well-tolerated in this cohort of 10 patients with symptomatic sRV failure: (1) blood pressure, plasma glucose, and electrolytes remained stable while renal function recovered to baseline levels after an initial dip, (2) no patients discontinued treatment, (3) no relevant side effects were observed, and (4) no unexpected deterioration of heart failure was observed.

In the 8 patients with a structured 6 months follow-up visit, we observed a significant median NT-proBNP reduction of 17.3% [−43.5– -6.9]. To compare, a 45% reduction in NT-proBNP levels was documented at 6 months in sRV failure patients treated with sacubitril/valsartan.[5] While the reduction in NT-proBNP was greater in this larger cohort of sRV failure patients on sacubitril/valsartan, 9 out of 10 patients in the current study had progressive heart failure despite treatment with sacubitril/valsartan in maximally tolerated dose, suggesting that SGLT2i might be of additional value "on top of" sacubitril/valsartan. The one patient who was not on sacubitril/valsartan at baseline did not tolerate it previously. Sacubitril/valsartan was not recently stopped (<6 months) and also not started during the follow-up of the current study period.

A comparable magnitude of NT-proBNP reduction was documented in the large randomized controlled trials investigating SGLT2i in conventional left ventricular heart failure with reduced ejection fraction. In the DAPA-HF and EMPEROR-reduced trials, median NT-proBNP reductions of 13.7% and 12.9%, respectively were reported.[10,11] Whether this similar reduction in NT-proBNP levels will also be associated with a comparable improvement in clinical outcomes and mortality remains to be investigated.

NT-proBNP is released by both the ventricular and atrial myocytes as a response to elevated cardiac wall stress, and has prognostic value in sRV failure patients specifically; a decrease in NT-proBNP has been correlated with improved clinical status, reduced risk of hospitalization, and lower mortality in sRV failure patients.[12] Elevated NT-proBNP levels may thus indicate the presence of pressure and/or volume overload associated with heart failure in sRV patients.[13] The actual mechanisms of SGLT2i contributing to the beneficial effects observed in the general heart failure population are not yet fully understood. Potential mechanisms that could target the elevated wall stress and thus contribute to the decrease in NT-proBNP levels we observed are; (1) blood pressure lowering and stimulation of natriuresis and diuresis, thereby lowering cardiac afterload, (2) inhibition of sympathetic nervous system activation, and (3) improvement of vascular smooth muscle and endothelial function, decreasing vascular resistance and inducing direct vasorelaxation.[14]

Regarding the short-term outcomes, a significant improvement in NYHA class was observed. Nevertheless, there were no significant changes in any of the exercise parameters nor in the echocardiographic parameters assessing systolic ventricular function. This might be attributed to the limited cohort, small effect size, or the variability in the echocardiographic assessment of sRV function.

Another potential advantage of SGLT2i is the practical ease of implementation and adherence when compared to other heart failure drugs, as the target dose and starting dose are identical and can be implemented over a wide range of renal functions. When comparing SGLT2i to other drugs with more profound anti-hypertensive effects like ARNIs or beta blockers, SGLT2i might prove to be especially beneficial in relatively young adult congenital heart disease patients, in whom hypotension rather than hypertension usually is a limiting factor.

The initial results seem encouraging and demonstrate that SGLT2i treatment is feasible and safe, even in advanced sRV failure patients. Although no firm conclusions can be drawn regarding the clinical effects, the current data is promising and worthy of further validation in a larger prospective setting, particularly when considering the growing unmet need for adequate heart failure treatment in the adult congenital heart disease population. Therefore, we call for international collaboration and the initiation of a prospective trial to study the effects of SGLT2i as a promising treatment option for sRV failure.

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4

Effect of Sodium-Glucose Cotransporter 2 Inhibitors on Ventricular Function in Systemic Right Ventricular Failure

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Abstract

Background

Systemic right ventricle (sRV) patients are at an increased risk of developing heart failure. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) could be a valuable treatment option. This study investigated the changes in ventricular function in sRV failure patients in the first year after starting SGLT2i.

Methods

Adult sRV patients from the international, real-world ACHIEVE-SGLT2i registry were included if they had a clinical diagnosis of sRV failure, a transthoracic echocardiogram before starting SGLT2i, and at least one in the first year after starting available for analysis. The primary outcomes were changes in sRV global longitudinal strain (GLS) and fractional area change (FAC). Longitudinal changes were evaluated using linear mixed models.

Results

Thirty-nine sRV failure patients (46 ± 9.3 years old, 41% female) were included. Twenty-five (64%) had transposition of the great arteries after an atrial switch procedure and 14 (36%) had congenitally corrected transposition. sRV GLS improved significantly in the first 50 days (−1.4%-point per month, $p<0.001$) and stabilised afterwards (<0.1%-point per month, $p=0.520$). Though age had a significant overall negative effect on sRV GLS (0.1%-point per year of age, $p=0.049$), it did not influence the longitudinal changes after starting SGLT2i. sRV FAC also improved in the first 50 days (3.2%-point per month, $p=0.002$), after which sRV FAC deteriorated in patients with subpulmonary left ventricular pacing (−0.9%-point per month, $p=0.012$) while it stabilised in patients without pacing (0.1%-point per month, $p=0.573$). In the first 50 days, tricuspid annular plane systolic excursion also improved significantly in all patients (1.2 mm per month, $p=0.006$), and stabilised afterwards ($p=0.721$).

Conclusion

SGLT2i therapy is associated with improvements in systolic ventricular function in sRV failure patients. Despite early improvement in sRV FAC, there was a negative longer term correlation with subpulmonary left ventricular pacing, potentially reflecting adverse effects of subpulmonary ventricular pacing on sRV function.

Introduction

Heart failure (HF) is the leading cause of morbidity and mortality in the adult congenital heart disease (ACHD) population, and there is a lack of robust evidence for pharmacological treatment options.[1-3] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a novel group of drugs that substantially improve outcomes in conventional left ventricular HF across all ranges of ejection fraction, although the effects of SGLT2i on cardiac remodelling and ventricular function remain a topic of debate.[4]

Based on promising observational data, SGLT2i are increasingly considered a viable treatment option for patients with ACHD-related HF.[5] SGLT2i are safe and well-tolerated in ACHD patients, with early data suggesting that SGLT2i use is associated with reduced HF hospitalisation rates.[6] Systemic right ventricle (sRV) patients, including those with transposition of the great arteries (TGA) after an atrial switch procedure (Mustard or Senning) and congenitally corrected TGA (ccTGA), have a morphological right ventricle (RV) in the subaortic position, exposed to systemic pressures. Due to lifelong pressure overload, sRV patients are at a particularly high risk of developing HF.[7,8] Evidence suggests that the RV shows a stronger fibrotic response than the left ventricle (LV) to volume overload, and a recent meta-analysis demonstrated that SGLT2i therapy reduces pulmonary artery pressure and improves RV performance in conventional HF patients with RV dysfunction.[9,10] The proposed antifibrotic effects of SGLT2i might be one of the mechanisms by which the pathologic remodelling seen in the sRV could be ameliorated.[11]

Literature on the efficacy of SGLT2i in the sRV failure population is scarce, and the magnitude of benefit may vary depending on the unique morphological characteristics of sRV patients.[12-14] This study investigates the longitudinal changes in biventricular function as assessed with transthoracic echocardiography (TTE) in sRV patients in the first year after initiation of SGLT2i.

Methods

Study design and population

A retrospective cohort study was conducted in a subgroup of patients included in the international, real-world ACHIEVE-SGLT2i (Adult Congenital Heart disease International EValuation of the Effectiveness of SGLT2i) registry (NCT06932081). Adult sRV failure patients (≥18 years of age) with a biventricular circulation started on an SGLT2i were eligible for inclusion if they had a baseline TTE performed within 6 months before starting SGLT2i and at least one follow-up TTE between 6 weeks and 12 months after starting SGLT2i. Patients from the Center for Congenital Heart Disease Amsterdam-Leiden, location Leiden

University Medical Center (LUMC, Leiden, the Netherlands) and the Scottish Adult Congenital Cardiac Service at the Golden Jubilee University National Hospital (GJNH, Glasgow, United Kingdom) were included, driven by the availability of raw TTE scans for reanalysis.

sRV failure was adjudicated based on the universal definition of HF, entailing a clinical syndrome with symptoms and/or signs of HF, combined with elevated baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and/or objective evidence of pulmonic or systemic congestion.[15] The study was conducted in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[16]

Data collection and follow-up

All clinical data were retrieved retrospectively from the electronic patient files. TTEs obtained in an outpatient clinic setting as part of routine care, performed at varying intervals at physician's discretion, were included. TTEs obtained during hospitalisations or unplanned HF visits were excluded from analysis, as these were expected to reflect a state of (temporary) congestion, potentially introducing bias. All data were collected from the baseline visit and at each outpatient visit and/or hospitalisation until either: (1) 12-month follow-up, (2) the last date of data inclusion at the participating centre (if less than 12-month follow-up), (3) discontinuation of SGLT2i therapy, (4) any catheter or surgical intervention influencing the haemodynamic status, (5) loss to follow-up, or (6) death.

TTE analysis

All TTE exams were performed with commercially available ultrasound systems, and all images were retrieved for offline analysis with EchoPAC software (GE Healthcare, Chicago, Illinois, USA). RMLN performed the offline analyses, blinded to the patients' clinical status and supervised by two experienced European Association of Cardiovascular Imaging-certified ACHD imaging cardiologists (MVR and GRV). A dedicated comprehensive TTE analysis workflow was constructed as previously described, based on the consensus recommendations of the International Society of Adult Congenital Heart Disease.[17-19] The following parameters were evaluated: sRV global longitudinal strain (GLS, %), subpulmonary left ventricle (spLV) free wall strain (FWS, %), sRV and spLV fractional area change (FAC, %), tricuspid annular plane systolic excursion (TAPSE, mm), S' (cm/s), e' (cm/s), systemic atrioventricular valve (sAVV) inflow E and A velocity (cm/s), E/A ratio, E/e' ratio, and regurgitation grades. sRV GLS was measured with EchoPAC software, after manual delineation of the myocardium in the apical four-chamber view, including the interventricular septum. S' represented the peak systolic velocity, and e' the peak early diastolic velocity, both measured at the lateral

tricuspid annulus of the sRV. Global systolic sRV and spLV function were classified into four categories based on GLS, FAC and qualitative visual function assessment.

Primary outcome measures

The primary outcome measures were the longitudinal changes in sRV GLS and FAC. The influence of the following covariates on the longitudinal changes in sRV GLS and FAC was investigated: age at start SGLT2i, sex (male or female), sRV anatomy, inclusion centre, presence of sinus rhythm, single-site spLV pacing, sAVV regurgitation grade (≤grade 2 vs ≥grade 3), systolic blood pressure, and escalation in HF pharmacotherapy. Escalation in HF pharmacotherapy was defined as the addition of one of the four pharmacological pillars or a switch from an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker to an angiotensin receptor-neprilysin inhibitor.

Secondary outcome measures

Longitudinal changes in TAPSE, S', spLV FWS, spLV FAC, E/e' ratio, and E/A ratio were assessed as secondary outcome measures. The influence of the prespecified covariates on these parameters was also evaluated.

Statistical analysis

All statistical analyses were performed with SPSS V.25 (IBM Corp, Armonk, New York, USA) and R Statistical Software (V.4.3.1; R Core Team 2023). Linear mixed models were constructed with the 'nlme' package (V.3.1.165; R Core Team 2024). For the descriptive analysis, normally distributed continuous data were displayed as mean (± SD), non-normally distributed continuous data were presented as median (Q1 to Q3), and categorical data were presented as numbers (%). Groups were compared with unpaired t-tests, Mann-Whitney U-tests, or Fisher's exact tests as appropriate.

Linear mixed models were used to evaluate the relation between the TTE parameters and time since start SGLT2i, as previously described.[20] Both linear and non-linear temporal relations were explored with random intercepts, random slopes, and piecewise linear splines to model non-linear changes. Different correlation and variance structures were tested. The best fitting models were selected based on the Akaike information criterion (AIC)/Bayesian information criterion (BIC) or the likelihood ratio test if appropriate. Preference was given to the BIC because model parsimony was prioritised over the ability to predict future observations. Categorical covariates were included if there were at least 10 observations per category, to avoid model overfitting on sparse data. Both interaction and fixed effects of the covariates were tested. Residual analyses were performed to evaluate model fit. The

predicted fixed effects for the models were visualised with the corresponding 95% CIs for the fixed-effect variance, and coefficients were presented as change per month for ease of interpretation. A two-sided p value ≤0.05 was considered statistically significant.

Results

Of 58 sRV patients included in the ACHIEVE-SGLT2i registry by the LUMC and GJNH, 39 sRV failure patients initiated on an SGLT2i between April 2021 and May 2024 met the inclusion criteria and were included. The mean age was 46±9.3 years, 16 (41%) were female, dapagliflozin was prescribed in 34 (87.2%) and empagliflozin in 5 (12.8%). Fourteen patients (35.9%) had ccTGA, and 25 (64.1%) had TGA after an atrial switch procedure (80% Mustard and 20% Senning). Eleven patients (28.2%) had single-site spLV pacing, and atrial fibrillation/flutter was more commonly present in ccTGA patients than in TGA atrial switch patients at baseline (35.7% vs 4%, p=0.016) (*Table 1*).

Table 1. Baseline characteristics

	All (n=39)	**ccTGA (n=14)**	**TGA atrial switch (n=25)**	**P value**
Age, years	46.0 ± 9.3	46.9 ± 12.5	45.6 ± 7.2	0.726
Sex, female	16 (41.0)	5 (35.7)	11 (44)	0.740
Inclusion centre, GJNH	22 (56.3)	7 (50)	15 (60)	0.738
sAVV replacement	7 (17.9)	5 (35.7)	2 (8)	0.075
Subpulmonary outflow tract obstruction	2 (5.1)	1 (7.1)	1 (4)	1.000
HF diagnosis				
Systolic sRV failure	35 (89.7)	13 (92.9)	22 (88)	1.000
Biventricular systolic failure	3 (7.7)	1 (7.1)	2 (8)	1.000
Preserved systolic function	1 (2.6)	0	1 (4)	1.000
HF hospitalisation in the year preceding SGLT2i	5 (12.8)	3 (21.4)	2 (8)	0.329
HF pharmacotherapy				
ACEi/ARNI/ARB	37 (94.9)	12 (85.7)	25 (100)	0.123
ARNI	30 (76.9)	12 (85.7)	18 (72)	0.455
MRA	23 (59.0)	10 (71.4)	13 (52)	0.317
Beta-blocker	22 (56.4)	6 (42.9)	16 (64)	0.314
Diuretics	20 (51.3)	6 (42.9)	14 (56)	0.514

Table 1. *Continued*

	All (n=39)	ccTGA (n=14)	TGA atrial switch (n=25)	P value
Clinical parameters				
Body mass index, kg/m^2	25.4 ± 4.4	24.2 ± 3.8	26.1 ± 4.7	0.327
Heart rate, bpm	65(60–75)	70(64–76)	65(60–72)	0.102
Heart rhythm				
Sinus rhythm	21 (53.8)	7 (50)	14 (56)	0.750
Atrial rhythm	1 (2.6)	0	1 (4)	1.000
Atrial fibrillation/flutter	6 (15.4)	5 (35.7)	1 (4)	0.016
Atrial pacing	11 (28.2)	2 (14.3)	9 (36)	0.266
Ventricular pacing	13 (33.3)	6 (42.9)	7 (28)	0.482
Biventricular pacing	2 (5.1)	1 (7.1)	1 (4)	1.000
Systolic blood pressure, mmHg	114 ± 14	117 ± 13	112 ± 15	0.362
Diastolic blood pressure, mm Hg	71 ± 12	71 ± 14	70 ± 11	0.789
NT-proBNP, ng/L	726.6 [328.8–1139.5]	819.6 [295.2–1691.8]	714.2 [329.5–1129.0]	0.790

Values are n (%), mean±SD, or median (Q1–Q3). Groups were compared with unpaired t-tests, Mann-Whitney U-tests, or the Fisher's exact tests as appropriate. A*CEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; ccTGA, congenitally corrected transposition of the great arteries; GJNH, Golden Jubilee University National Hospital; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; sAVV, systemic atrioventricular valve; sRV, systemic right ventricle; TGA, transposition of the great arteries*.

In total, 97 TTEs were available for analysis. Patients had a median of 1 (1 to 2) follow-up TTEs over a median echocardiographic follow-up duration of 5.8 (3.2 to 11.0) months. There was no significant difference in follow-up duration between ccTGA and TGA atrial switch patients (5.7 (2.8 to 11.3) vs 5.9 (3.4 to 10.8) months, p=0.966). Patients with ccTGA had a significantly higher S' (8 (6.3 to 9) vs 5.5 (5 to 6.5) cm/s, p=0.025) and a better spLV FWS (−24.9 ± 5.6% vs −17.3 ± 6.7%, p=0.001) at baseline than TGA atrial switch patients (*Table 2*).

Table 2. TTE parameters at baseline

	All (n=39)	**ccTGA (n=14)**	**TGA atrial switch (n=25)**	**P value**
sRV function				0.895
Good	1 (2.6)	0	1 (4)	
Mildly reduced	3 (7.7)	1 (7.1)	2 (8)	
Moderately reduced	13 (33.3)	5 (35.7)	8 (32)	
Severely reduced	22 (56.4)	8 (57.1)	14 (56)	
spLV function				0.370
Good	22 (56.4)	9 (64.3)	13 (52)	
Mildly reduced	15 (38.5)	4 (28.6)	11 (44)	
Moderately reduced	1 (2.6)	1 (7.1)	0	
Severely reduced	1 (2.6)	0	1 (4)	
sAVV regurgitation grade				0.084
Grade 1 or less	15 (38.5)	7 (50)	8 (32)	
Grade 2	8 (20.5)	0	8 (32)	
Grade 3	7 (17.9)	4 (28.6)	3 (12)	
Grade 4	9 (23.1)	3 (21.4)	6 (24)	
spAVV regurgitation grade				0.244
Grade 1 or less	31 (81.6)	9 (64.3)	22 (91.7)	
Grade 2	3 (7.9)	2 (14.3)	1 (4.2)	
Grade 3	3 (7.9)	2 (14.3)	1 (4.2)	
Grade 4	1 (2.6)	1 (7.1)	0	
sRV function				
sRV GLS (%)	−10.4 ± 3.8	−10.3 ± 5.1	−10.4 ± 2.9	0.932
sRV FAC (%)	20.6 ± 7.5	21.1 ± 8.7	20.3 ± 7.0	0.741
TAPSE (mm)	10.2 ± 3.2	10.9 ± 3.8	9.7 ± 2.9	0.246
S' (cm/s)	6 (5–8)	8 (6.3–9)	5.5 (5–6.5)	0.025
Diastolic function				
E/A ratio	1.8 ± 0.7	1.7 ± 0.2	1.9 ± 0.9	0.714
E/e' ratio	9.3 ± 3.8	6.9 ± 1.7	11.0 ± 4.0	0.038

Table 2. *Continued*

	All (n=39)	ccTGA (n=14)	TGA atrial switch (n=25)	P value
spLV function				
spLV FWS (%)	−20.1 ± 7.3	−24.9 ± 5.6	−17.3 ± 6.7	0.001
spLV FAC (%)	46.1 ± 11.8	47 ± 9.9	45.6 ± 12.9	0.750

Values are n (%), mean ± SD, or median (Q1–Q3). Groups were compared with unpaired t-tests, Mann-Whitney U tests or the Fisher's exact tests as appropriate. *ccTGA, congenitally corrected transposition of the great arteries; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; sAVV, systemic atrioventricular valve; spAVV, subpulmonary atrioventricular valve; spLV, subpulmonary left ventricle; sRV, systemic right ventricle; TAPSE, tricuspid annular plane systolic excursion; TGA, transposition of the great arteries.*

Primary outcome measures

A non-linear relation between sRV GLS and time was observed. sRV GLS showed a significant improvement in the first 50 days after SGLT2i initiation (−1.4%-point per month, p<0.001) and stabilised afterward (p=0.520). Although older patients had a worse sRV GLS (intercept 0.1%-point per year of age, p=0.049), age at SGLT2i commencement did not influence the temporal changes (*Figure 1A*).

A similar temporal effect was observed for sRV FAC, significantly improving in the first 50 days (3.2%-point per month, p=0.002). After this improvement, patients with single-site spLV pacing had a significant deterioration in sRV FAC (−0.9%-point per month, p=0.012). In contrast, patients without spLV pacing remained stable (p=0.573) (*Figure 1B*). The other covariates did not significantly influence the sRV GLS and FAC changes after starting SGLT2i. Outputs and characteristics of all models are presented in Online Supplemental *Tables 1* and *2*.

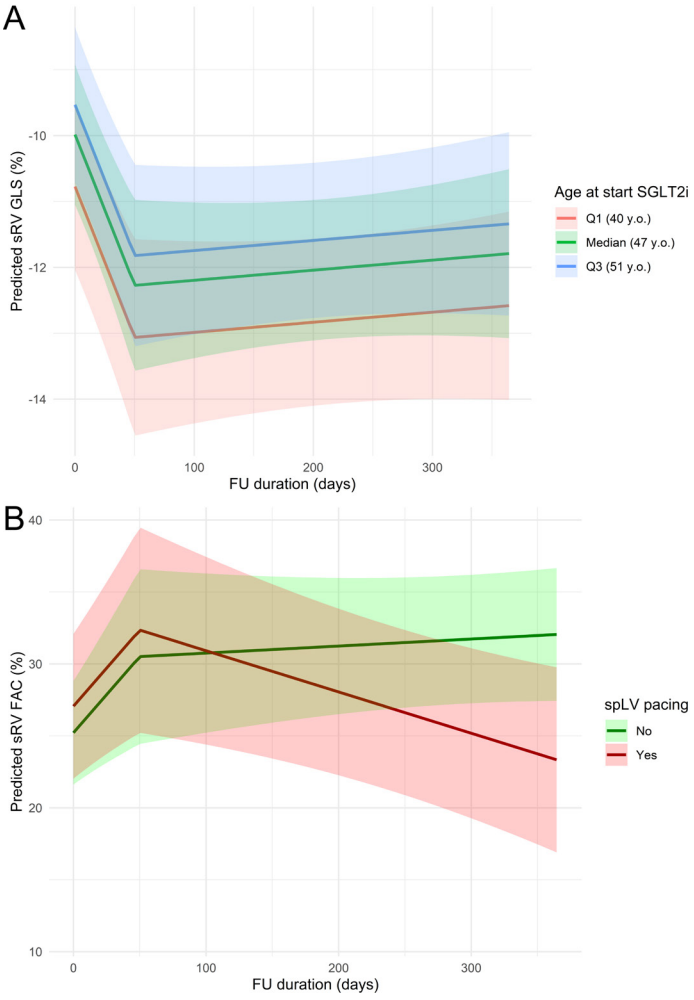

Figure 1. Changes in sRV GLS and FAC after starting SGLT2i

(**A**) Predicted longitudinal change in sRV GLS with 95% CIs. There is a significant improvement in the first 50 days after starting SGLT2i (−1.4%-point per month, p<0.001) and subsequent stabilisation (p=0.520). There was a significant negative effect of age (−0.1%-point per year of age, p=0.049), but age did not influence the temporal changes after starting SGLT2i. (**B**) Predicted longitudinal change in sRV FAC. There is a similar initial improvement in the first 50 days (3.2%-point per month, p=0.002), followed by a significant deterioration in patients with single-site spLV pacing (−0.9%-point per month, p=0.012). In contrast, patients without spLV pacing remained stable (p=0.573). *FAC, fractional area change; FU, follow-up; GLS, global longitudinal strain; SGLT2i, sodium-glucose cotransporter 2 inhibitor; spLV, subpulmonary left ventricle; sRV, systemic right ventricle.*

Secondary outcome measures

In the first 50 days, there was a significant improvement in TAPSE (1.2 mm per month, p=0.006), after which TAPSE stabilised (p=0.721) (*Figure 2A*). There was a significant interaction between change in S' and sRV anatomical subgroups. S' decreased significantly in patients with ccTGA in the first 50 days (−1.4 cm/s per month, p=0.014), after which there was a significant improvement (0.5 cm/s per month, p<0.001). S' remained stable in TGA atrial switch patients (≤50 days; 0.5 cm/s per month, interaction p=0.005, >50 days; −0.1 cm/s, interaction p<0.001) (*Figure 2B*).

Although TGA atrial switch patients had a significantly higher E/e' ratio than ccTGA patients at baseline (6.9 ± 1.7 vs 11.0 ± 4.0, p=0.038), no significant temporal changes in diastolic function markers E/A or E/e' ratio were observed (*Online Supplemental Figures 1* and *2*).

Patients with ccTGA had a significantly better overall spLV FWS than TGA atrial switch patients (intercept 6.5%-point, p<0.001) (*Figure 3A*). spLV FWS improved significantly in the first 50 days in both groups. This improvement was more pronounced in patients with single-site spLV pacing (−3.9%-point per month, interaction p=0.046) than in patients without spLV pacing (−1.5%-point per month, p=0.048). After 50 days, the change in spLV FWS stabilised and a differential association with pacing status was no longer observed (p=0.368). Patients with an escalation in HF pharmacotherapy during follow-up had a significantly higher spLV FAC at baseline than patients who did not have an escalation in pharmacotherapy (intercept 12.0%, p=0.003) (*Figure 3B*). Moreover, lack of escalation in HF pharmacotherapy after starting SGLT2i was associated with a stable spLV FAC over time (p=0.237), while an escalation in HF pharmacotherapy was associated with a deterioration of spLV FAC (−2.3%-point per month, p<0.001). A graphical abstract of the study is presented in *Figure 4*.

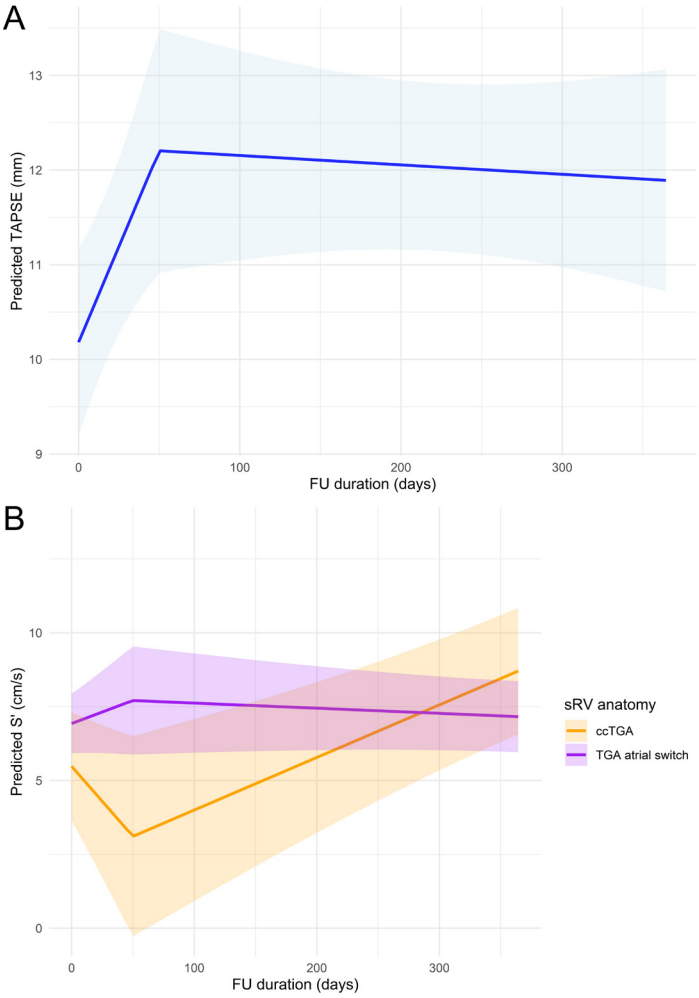

Figure 2. Changes in TAPSE and S' after starting SGLT2i

Changes in TAPSE and S' after starting SGLT2i. (**A**) Predicted longitudinal change in TAPSE with 95% CIs. A significant improvement can be appreciated in the first 50 days (1.2 mm per month, p=0.006). After 50 days, this was no longer significant (p=0.721). No covariates contributed significantly to the model. (**B**) Predicted change in S' over time. Patients with ccTGA had a significant decrease in S' in the first 50 days (−1.4 cm/s per month, p=0.014), followed by a significant improvement (0.5 cm/s per month, p<0.001). TGA atrial switch patients remained stable. *(cc)TGA, (congenitally corrected) transposition of the great arteries; FU, follow-up; SGLT2i, sodium-glucose cotransporter 2 inhibitor; sRV, systemic right ventricle; TAPSE, tricuspid annular plane systolic excursion*.

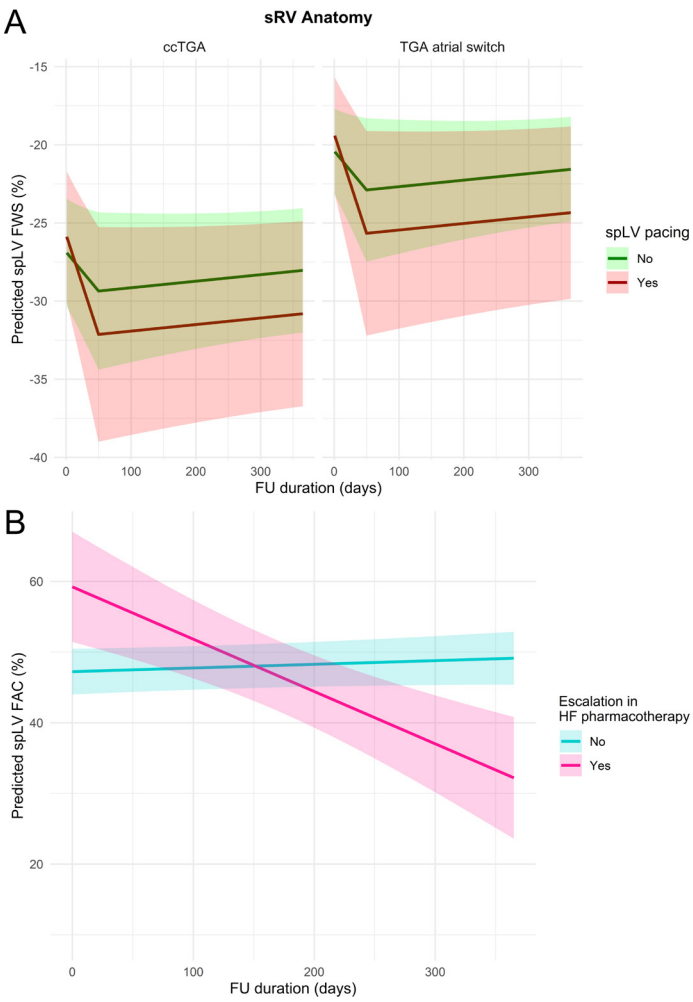

Figure 3. Changes in spLV FWS and FAC after starting SGLT2i

(**A**) Predicted longitudinal change in spLV FWS (%) with 95% CIs, faceted for sRV anatomical subgroups. There was a significant improvement in the first 50 days for patients without spLV pacing (−1.5%-point per month, p=0.048). This improvement was more pronounced in patients with spLV pacing (−3.9%-point per month, interaction p=0.046). After the first 50 days, there were no significant changes in both groups (p=0.368). Overall, ccTGA patients had a significantly better spLV FWS than TGA atrial switch patients (intercept 6.5%-point, p<0.001). (**B**) Predicted change in spLV FAC (%) over time. Patients with an escalation in HF pharmacotherapy during follow-up had a significantly higher spLV FAC at baseline (intercept 12.0%-point, p=0.003) and showed a significant deterioration (−2.3%-point per month, p<0.001) compared with patients without an escalation in pharmacotherapy (0.2%-point per month, p=0.237). *(cc)TGA, (congenitally corrected) transposition of the great arteries; FAC, fractional area change; FU, follow-up; FWS, free-wall strain; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; spLV, subpulmonary left ventricle; sRV, systemic right ventricle.*

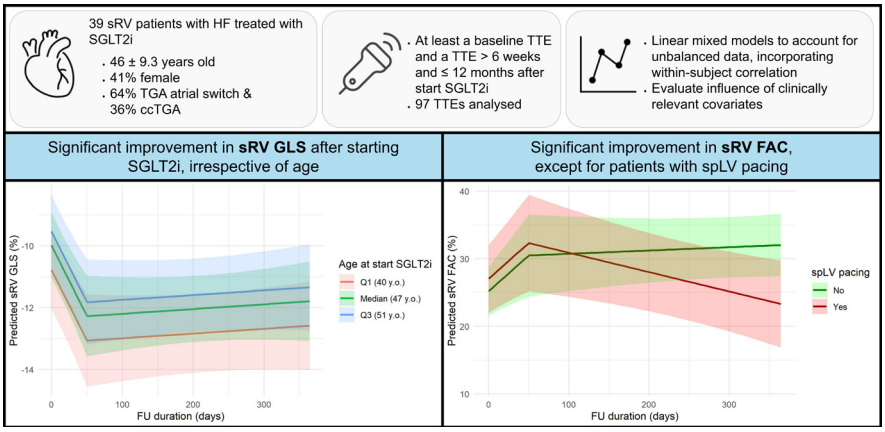

Figure 4. Effect of SGLT2i on ventricular function in sRV failure
This real-world evaluation of data from the ACHIEVE-SGLT2i registry demonstrated that SGLT2i are associated with improvements in systolic function in sRV failure patients. sRV GLS improved significantly in the first 50 days and stabilised afterwards. Age at start SGLT2i significantly influenced overall sRV GLS, as indicated by the separate lines for the first quartile (Q1), median and third quartile (Q3) of age. sRV FAC also improved significantly in the first 50 days. After 50 days, patients without spLV pacing remained stable, while patients with spLV pacing deteriorated. *(cc)TGA, (congenitally corrected) transposition of the great arteries; FAC, fractional area change; FU, follow-up; GLS, global longitudinal strain; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; spLV, subpulmonary left ventricle; sRV, systemic right ventricle; TTE, transthoracic echocardiography*.

Discussion

This study demonstrates that SGLT2i therapy is associated with an improvement in systolic sRV and spLV function parameters in sRV failure patients during the first year of treatment. sRV GLS improved significantly in the first 50 days after starting SGLT2i and remained stable afterwards. A relationship between age and sRV GLS has, to our knowledge, not been previously described, but lower LV GLS values have been reported with increasing age in the general population.[21] Our data indicate a similar relationship in the sRV cohort, with older patients having a worse overall sRV GLS, likely reflecting the cumulative detrimental effects of long-standing pressure overload on the morphological RV. This relationship might be more pronounced in sRV patients, who appear to suffer from premature multiorgan biological ageing processes compared with healthy peers.[22]

sRV FAC also improved significantly in the first 50 days, after which the change was modulated by the presence of single-site spLV pacing. Pacing-induced ventricular dysfunction is a well-documented phenomenon in sRV patients with chronic spLV pacing and has been associated with lower sRV FAC compared with non-paced controls.[23,24] The initial improvement in sRV FAC in both groups may be reflective of an early, beneficial

diuretic effect of SGLT2i, while the following gradual deterioration seen in the spLV pacing group suggests that these patients do not have a similar beneficial response to SGLT2i over the longer term. These findings are in line with reports of pacing-induced sRV dyssynchrony contributing to sRV dysfunction and limiting the effects of therapeutic interventions, and this study reinforces the notion that we should remain critical of spLV pacing in sRV patients.[25] Cardiac resynchronisation therapy and conduction system pacing are gaining recognition as strategies to counter some of these adverse effects, and while no patients received conduction system pacing, two patients received biventricular pacing in this study.[26]

Differences between ccTGA and TGA atrial switch patients

Baseline and temporal differences in S', E/e' ratio, and spLV FWS were found between ccTGA and TGA atrial switch patients, suggesting that atrial switch patients have worse systolic and diastolic function than ccTGA patients. The clinical implications of this remain uncertain.

Recent studies have revealed differences in the contraction patterns between ccTGA and TGA atrial switch patients.[27,28] While all contraction components contribute equally in ccTGA patients, atrial switch patients are most dependent on anteroposterior contraction, compensating for reduced longitudinal and radial contraction.[27,28] This might be due to embryological differences, and it is hypothesised that ccTGA patients are better equipped to handle the chronic sRV pressure overload as the RV functions in the systemic position immediately after birth, while atrial switch patients have to transition to an sRV circulation at a later stage with the atrial switch procedure creating rigid atrial baffles.[29] Surkova et al previously reported that the imbalance in contraction components in atrial switch patients might lead to an underestimation of sRV systolic function, as traditional TTE parameters focus on longitudinal contraction forces.[27] This could even be more pronounced in parameters assessed solely at the basal ventricular segment—such as S'—as relative basal hypokinesis has been described in TGA atrial switch compared with ccTGA patients.[28]

E/e' ratio, a marker of diastolic function, was significantly higher in atrial switch patients, suggesting worse diastolic function. While data on diastolic dysfunction in the sRV population are scarce and the value of 'E/e' is not well established in this population, these findings align with the hypothesis that the rigid atrial baffles in atrial switch patients contribute to reduced atrial function, exacerbating diastolic dysfunction.[30] Nonetheless, no temporal effect of SGLT2i on markers of diastolic function was observed. spLV FWS was improved in both groups but was consistently better in ccTGA patients, in line with previous work.[31]

These results should be interpreted cautiously as no significant differences between sRV anatomical subgroups were observed for our primary outcome measures. sRV GLS and FAC provide a more comprehensive evaluation of the myocardial contraction patterns. They have been extensively validated in the sRV population, correlate well with the gold standard cardiac magnetic resonance-derived sRV ejection fraction, and have a validated prognostic value.[19,32]

Concomitant HF medication changes

Patients who had an escalation in HF pharmacotherapy during follow-up showed a significant deterioration in spLV FAC over time compared with patients without intensification of their HF treatment, in whom the spLV FAC remained stable. Escalation in HF pharmacotherapy did not influence any of the other outcomes. The positive changes observed after starting SGLT2i are thus not likely to be attributable to the addition of other HF drugs during follow-up. The worsening in spLV FAC might be reflective of relative inertia of treatment initiation; therapeutic escalation was perhaps reactive instead of proactive in this patient cohort. This might at least in part be explained by the current ACHD guidelines, which do not provide specific recommendations for starting HF pharmacotherapy due to a lack of robust large-scale trials.[2,3] Importantly, a recent scientific statement from the American Heart Association does recommend careful consideration of initiating state-of-the-art medical therapy in children and adolescents with CHD from stage B HF onwards.[33] This is supported by a recent study demonstrating that ACHD patients on three or four HF drugs had better clinical outcomes and ventricular function than patients on just one or two, suggesting that a more proactive approach may be beneficial.[34]

SGLT2i for sRV failure in the current literature

Little is known about the effectiveness of SGLT2i for sRV failure. A recent study by Fusco et al is the only randomised study of SGLT2i in the sRV population to date.[12] Although not blinded nor placebo-controlled, 50 sRV patients were randomised to SGLT2i therapy or continuation of their present treatment. After 1 year, significant improvements in sRV FWS (+1.6%-point) and FAC (+3.5%-point) were reported in the SGLT2i group. Looking at population-level predictions of our sRV GLS model for a hypothetical 38-year-old patient (median age in Fusco et al), it predicts an improvement in sRV GLS of 1.8%-point from baseline to 1 year. In patients without spLV pacing, our sRV FAC model predicts an improvement of 6.8%-point from baseline to 1 year. This is more than the overall 3.5%-point improvement reported by Fusco et al but partially countered by the predicted 3.7%-point deterioration in patients with spLV pacing from baseline to 1 year in our study. It is important to acknowledge that in both studies, the vast majority were already receiving

sacubitril/valsartan (92% in Fusco et al, 77% in our cohort), which has also been associated with significant improvements in systolic sRV function.[18,35] The optimal sequencing of these HF therapies and potential synergistic effects remain to be established. While these comparisons should be approached with caution, the effect sizes predicted by our models in a real-world setting seem to align with the randomised study results.

Limitations

This study is limited by the retrospective design, small sample size, and lack of a randomised control group. The study aimed to provide a comprehensive evaluation of the longitudinal echocardiographic changes in biventricular function after starting SGLT2i. Although the findings are in line with and provide further mechanistic insight into the promising clinical findings reported for the sRV failure population, clinical outcomes and longitudinal biomarker surrogates such as natriuretic peptide levels were not included in this on-treatment analysis.[12,13,36] While escalation in HF pharmacotherapy was evaluated, detailed data on dose adjustments were unavailable. The influence of differences in HF pharmacotherapy at baseline on the changes after starting SGLT2i was also not evaluated. Intraobserver or interobserver variability was not evaluated given the previously published reproducibility of sRV strain, FAC, TAPSE and S' measurements in the sRV population by our study group and others.[12,19,37] ACHD research is often plagued by missing data, considerable individual-level variability, and a lack of well-structured prospective clinical trials. As such, follow-up intervals varied as they were scheduled at the discretion of the treating cardiologists. This study utilised mixed models to handle the unbalanced data effectively, and it provides a framework for real-world repeated measurements analysis in ACHD in the largest cohort of sRV patients on SGLT2i to date.

Conclusions

This real-world evaluation of data from the ACHIEVE-SGLT2i registry highlights the potential of SGLT2i therapy to improve systolic ventricular function in sRV failure patients in the first year of treatment. Significant improvement in sRV GLS was observed. Older patients exhibited worse overall sRV GLS but benefitted equally from treatment. A similar improvement was observed in sRV FAC, after which a differential effect based on chronic single-site spLV pacing was present, which might be reflective of the detrimental effects of spLV pacing on sRV function. These findings support the growing evidence for the use of SGLT2i in the sRV failure population, although the differences between patients emphasise the need for patient-tailored treatment strategies.

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5

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

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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.*

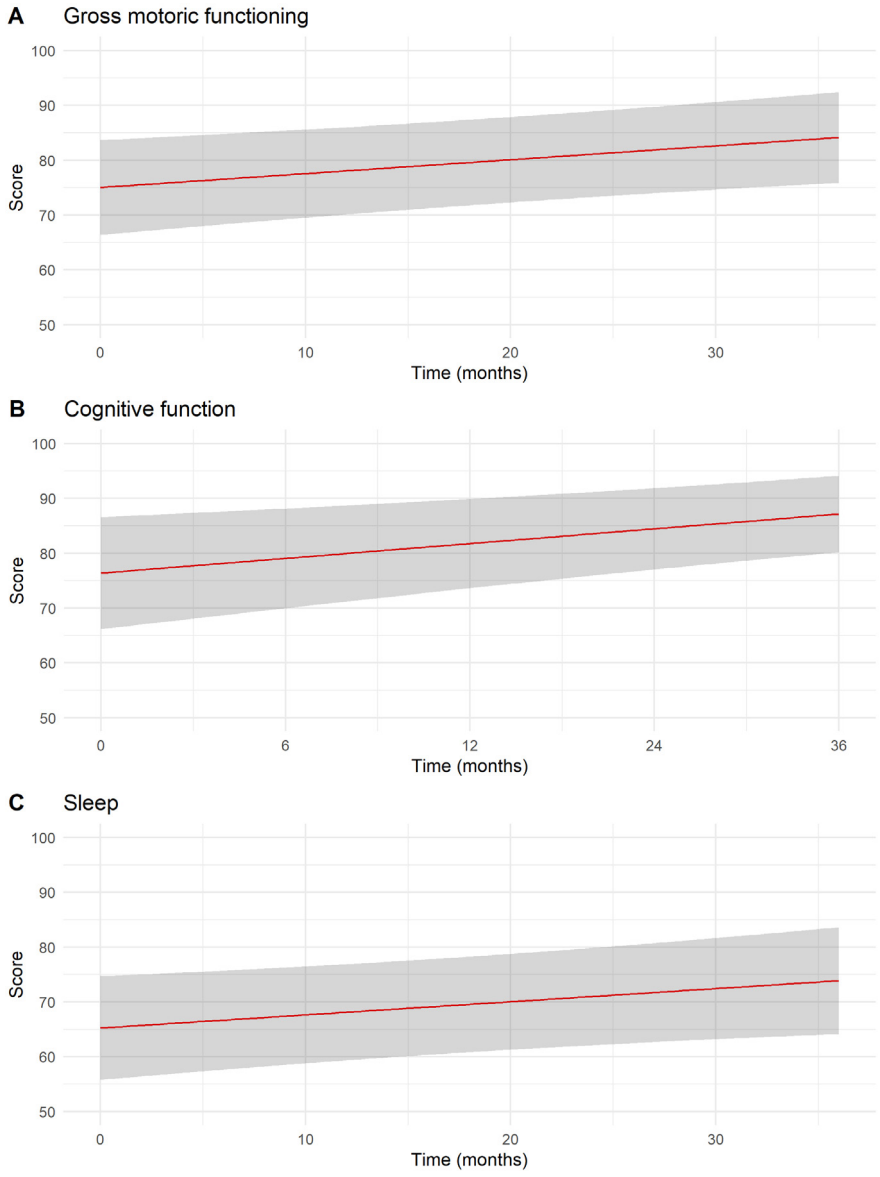

Figure 1. Predicted changes for the QOL domains with a significant change over time
The figure shows the predicted fixed effects of the linear mixed effects models (red line) with 95% CIs (grey band) for the five QOL domains that showed a significant improvement over time.

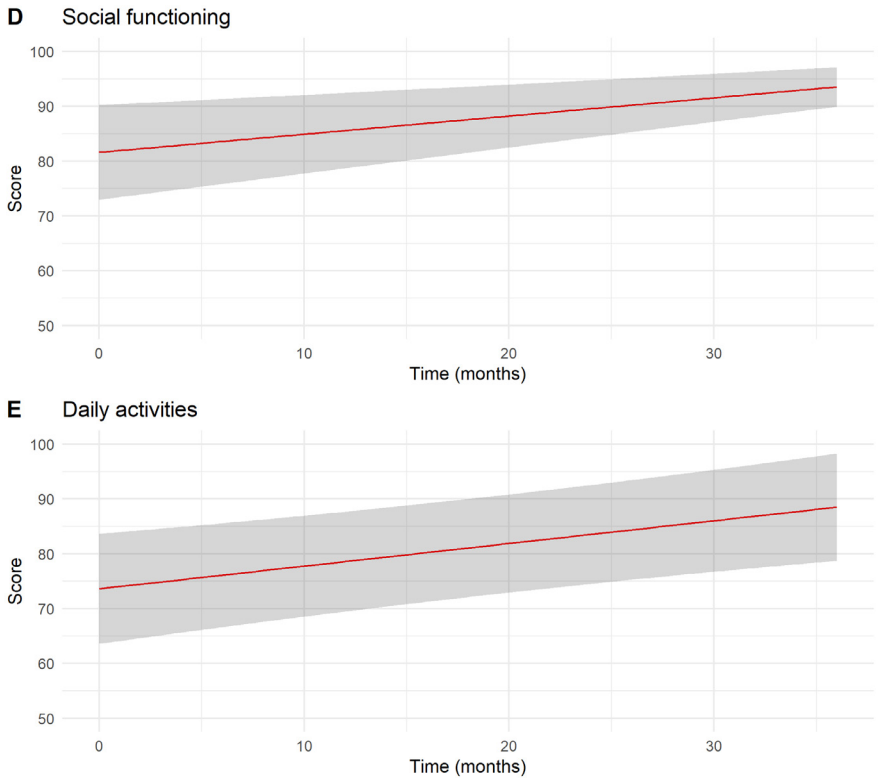

Figure 1. *Continued*

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.

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6

Real-World Experience with Sodium-Glucose Cotransporter 2 Inhibitors in Adults with Fontan Circulatory Failure

Neijenhuis RML, Cedars AM, Zaidi A, Torres-Viera G, Mazurek R, Walker NL, Zemrak F, MacDonald S, Hunter A, Kiès P, Bosch L, Swan L, Van Der Zwaan HB, Jukema JW, Jongbloed MRM, Veldtman GR, Egorova AD

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Abstract

Background

Patients with Fontan physiology frequently develop Fontan circulatory failure (FCF), but there are no evidence-based pharmacological treatment options.

Objectives

This study evaluated the safety and efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in FCF.

Methods

A real-world, multicenter study of all adult FCF patients included in the international ACHIEVE-SGLT2i registry (NCT06932081) was conducted. Data on side effects, treatment discontinuation, and clinical outcomes were collected. Longitudinal changes in serum biomarkers and clinical parameters from one year before to one year after SGLT2i initiation were evaluated using linear mixed models. Responses between patients with reduced (FCFrEF) versus preserved ventricular function (FCFpEF) were compared.

Results

Thirty-three FCF patients were started on SGLT2i between January 2017 and October 2024. The median age was 32 [20.5–42] years, 17 (51.5%) were female, 11 (33.3%) had FCFrEF, and 22 (66.7%) FCFpEF. Over a median follow-up of 8.0 [3.2–12.2] months, 5 (15.2%) patients reported side effects, of whom 3 (9.1%) permanently discontinued SGLT2i. There were 11 FCF-related hospitalizations in the year before SGLT2i and 7 during follow-up in 9 patients. Blood pressure and renal function remained stable. NT-proBNP increased from 186.3 [116.8–297.1] to 272.6 [180.7–411.3] ng/L in the year before treatment (+46.4%, p=0.022). In the year after starting SGLT2i, NT-proBNP levels decreased significantly to 200.4 [126.5–317.4] ng/L (-26.5%, p=0.010), in both FCFrEF and FCFpEF patients.

Conclusions

SGLT2i were safe and well-tolerated in adult patients with FCF. SGLT2i treatment was associated with a reduction in NT-proBNP, regardless of FCF phenotype.

Introduction

The Fontan operation, first performed in 1968 for patients with tricuspid atresia, has given patients with a single functional ventricle a viable chance at long-term survival without early transplant.[1] This monumental achievement in the management of patients with severe congenital heart disease has resulted in a rapidly expanding group of patients living with a Fontan circulation. In 2020, the estimated prevalence was 66 per million, with the majority (55%) being adults.[2] This growing group of adult Fontan patients suffers the sequelae of a circulation predicated on chronically elevated systemic venous pressure and reduced cardiac output. Long-term exposure to these physiologic stressors results in the majority of Fontan patients experiencing difficulties in carrying out their daily life activities. Fontan circulatory failure (FCF) is the umbrella term used to describe this state, characterized by a heterogeneous underlying etiology that frequently includes systolic and diastolic ventricular dysfunction, atrioventricular valve failure, and increased pulmonary vascular resistance.[3] The estimated overall prevalence of FCF is 30%, and approaches 100% in patients over 50 years of age.[4]

Due to the heterogeneous pathophysiological mechanisms underlying FCF, extrapolation of the guidelines for the management of conventional acquired heart failure is inappropriate.[5] Consequently, the identification of medical therapies that could benefit FCF patients has been identified as one of the key high-impact research questions in both the American and European adult congenital heart disease (ACHD) guidelines.[5, 6] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have become one of the four established "pillars" in the treatment of conventional heart failure, and the pleiotropic mechanisms by which SGLT2i are hypothesized to exert their beneficial effects makes them an interesting pharmacological treatment option for FCF.[7] In addition to their direct glucosuric and natriuretic properties, a range of off-target effects have been proposed, including improvements in cardiac mitochondrial function, reductions in cardiac fibrosis and oxidative stress, and enhancement of endothelial function.[7-9] The latter is of particular interest, given the central role of endothelial dysfunction in FCF.[10]

A few small studies have evaluated the use of SGLT2i in the Fontan population and reported promising results.[11-16] These studies may, however, be subject to publication bias, leaving the need for real-world experience and larger sample sizes to assess the clinical efficacy. In addition, the limited data available has shown that SGLT2i therapy may improve systolic ventricular function in single ventricle patients, and there may be a difference between patients with reduced and preserved ventricular function.[15] In view of these data, the present study aims to evaluate the safety and efficacy of SGLT2i in adults with FCF included in the international, real-world ACHIEVE-SGLT2i registry, and investigates differential responses

between FCF patients with a reduced ejection fraction (FCFrEF) and preserved ejection fraction (FCFpEF).

Materials and Methods

Study design

In this retrospective cohort study, all adults (≥ 18 years old) with FCF started on an SGLT2i and included in the international, real-world Adult Congenital Heart disease International EValuation of the Effectiveness of SGLT2i (ACHIEVE-SGLT2i) registry (NCT06932081), were eligible for inclusion.

The diagnosis of FCF was made by the treating cardiologist, based on a previously established extrapolation of the universal definition of heart failure to the Fontan circulation.[3, 17] Patients were classified as either FCFrEF (≥ moderately reduced systolic ventricular function) or FCFpEF (≤ mildly reduced systolic ventricular function) at SGLT2i initiation. This dichotomization was based on qualitative assessment of ventricular function at baseline transthoracic echocardiography, consisting of a combination of strain measurement, fractional area change, ejection fraction, and visual assessment. Data were collected retrospectively from the electronic health records at the participating centers, from 1 year before initiation of SGLT2i therapy onwards, and at each subsequent visit and/or hospitalization, as previously specified.[18]

Appropriate medical ethical board approval was obtained at all participating centers (coordinating center: Leiden University Medical Center Medical Research Involving Human Subjects Act [WMO] committee division 1 protocol reference 2022-068). The study was conducted in accordance with the principles of the 2013 Declaration of Helsinki, and complied with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement.[19]

Outcomes

Safety and tolerability of SGLT2i therapy were evaluated by assessing side effects, (reason for) treatment discontinuation, changes in systolic and diastolic blood pressure (mmHg) and changes in renal function measured with serum creatinine (μmol/L).

The primary efficacy outcome metric was change in the heart failure surrogate biomarker N-terminal pro–B-type natriuretic peptide (NT-proBNP, ng/L). Secondary efficacy outcomes were changes in: hemoglobin (mmol/L), hematocrit (L/L), albumin (g/L), aspartate transaminase (AST, U/L), alanine transaminase (ALT, U/L), alkaline phosphatase (ALP, U/L), gamma-glutamyltransferase (GGT, U/L), and body weight (kg). Differences in

these outcomes between FCFrEF and FCFpEF patients were assessed.

Data on FCF-related hospitalizations and mortality were also collected. An FCF-related hospitalization was defined as a hospital admission crossing a calendar day, with at least one of the following: 1) management of new or worsening heart failure symptoms with the initiation or increase of pharmacotherapy for FCF (as specified below), or intravenous inotropes, 2) management of ascites (including drainage), 3) management of lymphatic dysfunction.

Concomitant longitudinal changes in the following classes of pharmacotherapy for FCF were assessed, as potential confounders for evaluating the efficacy of SGLT2i therapy: 1) angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, or angiotensin receptor blockers, 2) mineralocorticoid receptor antagonists, 3) beta blockers, 4) diuretics, and 5) pulmonary vasodilators including phosphodiesterase type 5 inhibitors, prostacyclin analogs, and endothelin-1 receptor antagonists.

Statistical analysis

All statistical analyses were performed with SPSS v25 (IBM Corp, Armonk, NY, USA) and R Statistical Software (v4.4.2; R Core Team 2023). Normally distributed continuous variables were presented as mean ± standard deviation and compared with unpaired t-tests. Non-normally distributed continuous variables were presented as median [Q1 – Q3] and compared with Mann-Whitney U tests. Binary and categorical variables were presented as frequencies with percentages in parentheses, and compared with Chi-square, Fisher's exact tests, or McNemar's tests, as appropriate.

Linear mixed models were constructed using the "nlme" package (v3.1.167; R Core Team 2024) to account for unbalanced repeated measurements data, as both the number of observations per participant and the timing of follow-up assessments varied across individuals. To assess if the trajectory of an outcome variable changed after initiation of SGLT2i, time from day -365 to day +365 was included as a linear continuous variable, and an interaction term with a binary variable for treatment (on SGLT2i yes or no) was included as a fixed effect. To assess the potential difference in response to SGLT2i between FCFrEF and FCFpEF patients, the contribution of FCF phenotype as a significant binary covariate was tested. Due to the expected confounding effect of protein-losing enteropathy (PLE) on serum albumin, PLE status was included as a binary covariate in the model evaluating albumin changes. Random intercept models, random intercepts and slopes models, and different variance and correlation structures were tested to select the best-fitting model. Model selection was based primarily on the Bayesian information criterion (BIC), with

secondary consideration of the Akaike information criterion (AIC) or likelihood ratio tests when appropriate. Model parsimony was prioritized over predictive capacity and fit was verified through residual analysis. If the normalized residuals of the model showed significant deviation from normality, a Log_{10} transformation of the outcome variable was performed and normality was re-assessed. The fixed effects were visualized with corresponding 95% confidence intervals (CIs) for fixed-effect variance. To enhance clinical interpretability, the results were expressed as estimated values at day -365, day 0, and day 365, with 95% CIs. The percentages change in the year before and after starting SGLT2i were calculated. A two-sided p-value ≤0.05 was considered statistically significant.

Results

In total, 33 FCF patients who started an SGLT2i between January 2017 and October 2024 were identified at 7 tertiary ACHD centers in the Netherlands, United Kingdom, and United States, and included in the study (*Supplemental Figure 1*). The median age was 32 [20.5 – 42] years, 17 (51.5%) were female, and 1 (3%) had type 2 diabetes mellitus. Eleven patients (33.3%) were categorized as FCFrEF, and 22 (66.7%) as FCFpEF. There were no significant differences in the baseline characteristics between FCF phenotypes (*Table 1*).

Safety and tolerability

The majority were started on dapagliflozin (n=18, 54.5%). The recommended dose of 10 mg once daily was prescribed in most patients (n=31, 93.9%). SGLT2i was initiated during an FCF-related hospitalization in 4 (12.1%) patients. Over a median follow-up duration of 8.0 [3.2 – 12.2] months, 5 patients (15.2%) experienced side effects, of whom 3 (9.1%) permanently discontinued SGLT2i therapy (*Figure 1*). The reported side effects are presented in Supplemental Table 1. One patient switched from dapagliflozin to empagliflozin due to abdominal discomfort, after which the complaints resolved. A patient with type 2 diabetes mellitus switched from dapagliflozin 10mg once daily to empagliflozin 25 mg once daily after 1 year due to persistently elevated HbA1c values. No other SGLT2i therapy changes occurred.

At baseline, the mean systolic blood pressure was 111 ± 12 mmHg and the median diastolic blood pressure was 66 [61 – 74] mmHg. No significant changes after starting SGLT2i were observed (p=0.443 and p=0.680 respectively), nor were there differences between FCFrEF and FCFpEF. All patients had a creatinine-based estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73m^2 at baseline. Serum creatinine did not change significantly after starting SGLT2i (p=0.648) and there were no differences between FCF phenotypes. The estimates for all mixed models are presented in *Table 2*. The mixed model outputs are presented in *Supplemental Table 2* and the characteristics in *Supplemental Table 3*.

Table 1. Baseline characteristics

	All (n=33)	FCFrEF (n=11)	FCFpEF (n=22)	P-value
Age, y	32 [20.5 – 42]	21 [20 – 41]	34 [22.5 – 43.5]	0.329
Sex, female	17 (51.5)	5 (45.5)	12 (54.5)	0.721
Type and dose of SGLT2i				0.712
Dapagliflozin	18 (54.5)	7 (63.6)	11 (50)	
10 mg OD	16 (48.5)	7 (63.6)	9 (40.9)	
5 mg OD	2 (6.1)	0	2 (9.1)	
Empagliflozin 10 mg OD	15 (45.5)	4 (36.4)	11 (50)	
Anatomy				0.245
RV dominant (hypoplastic left heart syndrome)	10 (30.3)	5 (45.5)	5 (22.7)	
RV dominant (other)	5 (15.2)	2 (18.2)	3 (13.6)	
LV dominant	15 (45.5)	3 (27.3)	12 (54.5)	
Biventricular	2 (6.1)	0	2 (9.1)	
Mixed/indeterminate ventricle	1 (3)	1 (9.1)	0	
Fontan type				0.225
Extracardiac Fontan	16 (48.5)	7 (63.6)	9 (40.9)	
Lateral tunnel	10 (30.3)	4 (36.4)	6 (27.3)	
Atriopulmonary Fontan	6 (18.2)	0	6 (27.3)	
Other (bidirectional cavopulmonary connection + interrupted left-sided IVC + hepatic veins connected directly to PA)	1 (3)	0	1 (4.5)	
FCF-related hospitalization in the year preceding SGLT2i	8 (24.2)	2 (18.2)	6 (27.3)	0.687
SGLT2i started during FCF-related hospitalization	4 (12.1)	1 (9.1)	4 (18.2)	0.643
Protein-losing enteropathy	2 (6.1)	0	2 (9.1)	0.542
Type 2 diabetes mellitus (on oral therapy)	1 (3)	0	1 (4.5)	1.000

Table 1. *Continued*

	All (n=33)	FCFrEF (n=11)	FCFpEF (n=22)	P-value
CIED	9 (27.3)	2 (18.2)	7 (31.8)	0.681
CIED type				1.000
DDD pacemaker	5 (15.2)	1 (9.1)	4 (18.2)	
AAI pacemaker	3 (9.1)	1 (9.1)	2 (9.1)	
S-ICD	1 (3)	0	1 (4.5)	
Physical examination findings				
Weight, kg (n=31)	72.4 ± 12.5	72 ± 12.2	74 ± 12.4	0.674
BMI, kg/m^2 (n=31)	26.5 ± 4.6	25.3 ± 4.4	27.6 ± 4.7	0.220
Heart rate, bpm (n=31)	73 ± 11	76.6 ± 11.4	71.1 ± 10.8	0.188
Oxygen saturation, % (n=30)	94 [91.8 – 96]	94.5 [92 – 96.3]	94 [91.3 – 95.8]	0.491
Systolic blood pressure, mmHg (n=31)	111 ± 12	113 ± 10	110 ± 12	0.519
Diastolic blood pressure, mmHg (n=31)	66 [61 – 74]	69 [66 – 76]	64 [60 – 73]	0.280
Laboratory parameters				
Hemoglobin (mmol/L)	9.7 [8.7 – 10.2]	10 [9.4 – 10.9]	9.6 [8.1 – 10]	0.058
Hematocrit (L/L)	0.452 ± 0.045	0.475 ± 0.038	0.440 ± 0.045	0.078
Mean Corpuscular Volume (fL)	88.7 [87.2 – 92.6]	88.6 [87.7 – 91.8]	89.7 [83.3 – 92.8]	0.927
Creatinine (μmol/L) (n=29)	72 ± 12	75 ± 14	71 ± 11	0.389
eGFR, mL/min/1.73m^2 (n=27)	73 [60 – 98]	60 [60 – 90]	84[60 – 105]	0.147
eGFR ≥60 mL/min/1.73m^2 (n=27)	27 (100)	9 (100)	18 (100)	-
NTproBNP (ng/L) (n=17)	240.2 [160.6 – 482.6]	255.3 [164.2 – 487.4]	220.8 [111.5 – 534.5]	0.773

Values are n (%), mean ± standard deviation, or median [Q1-Q3]. Independent non-parametric data were compared with the Mann-Whitney U test and parametric data with the unpaired t-test. Independent categorical data were compared with the Chi-square or Fisher's exact test, as appropriate. Data were available for all patients unless specified otherwise. *BMI, body mass index; CIED, cardiac implantable electronic device; eGFR, estimated glomerular filtration rate; FCF, Fontan circulatory failure; FCFpEF, Fontan circulatory failure with preserved ejection fraction; FCFrEF, Fontan circulatory failure with reduced ejection fraction; HF, heart failure; IVC, inferior vena cava; LV, left ventricle; OD, once daily; PA, pulmonary artery; RV, right ventricle; S-ICD, subcutaneous implantable cardioverter defibrillator; SGLT2i, sodium-glucose cotransporter 2 inhibitor*.

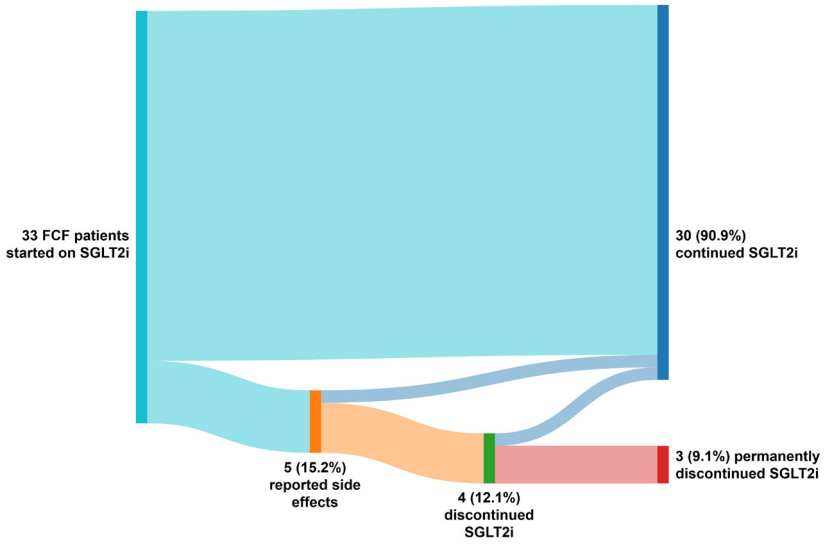


Figure 1. Safety and tolerability of SGLT2i
Side effects and discontinuation of SGLT2i therapy in 33 FCF patients over a median follow-up of 8.0 [3.2 – 12.2] months. *FCF, Fontan circulatory failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor.*

Efficacy

In the year before starting SGLT2i, NT-proBNP increased by 46.4%, from 186.3 [116.8 – 297.1] to 272.6 [180.7 – 411.3] ng/L (p=0.022). In the year after starting SGLT2i, this trend reversed, and a significant 26.5% decrease in NT-proBNP to 200.4 [126.5 – 317.4] ng/L (p=0.010) was observed (*Figure 2*). There were no significant differences in this response between FCFrEF and FCFpEF patients.

There were no significant changes in the year before or after starting SGLT2i therapy in hemoglobin, hematocrit, albumin, AST, ALT, ALP, GGT, or body weight. Patients with FCFpEF had significantly lower overall hemoglobin (-1.0 mmol/L, p=0.025), hematocrit (-0.04 L/L, p=0.025), and ALT (-7.4 U/L, p=0.022) compared to FCFrEF patients. The two patients with PLE had a significantly lower overall serum albumin than patients without PLE (-9.6 g/L, p=0.009). FCF phenotype did not significantly influence the other variables.

Table 2. Mixed models yearly estimates and changes

	Estimate	95% CI	% change[a]	P-value
Safety				
Creatinine (µmol/L)				
Day -365	68.340	62.127 – 74.552	+7.2	0.082
Day 0	73.272	68.262 – 78.282		
Day 365	80.715	72.264 – 89.166	+10.1	0.648
Systolic blood pressure (mmHg)				
Day -365	117.904	109.693 – 126.110	-6.6	0.101
Day 0	110.136	106.001 – 114.271		
Day 365	107.744	100.666 – 114.821	-2.2	0.443
Diastolic blood pressure (mmHg)				
Day -365	67.242	61.184 – 73.301	-0.7	0.894
Day 0	66.783	63.699 – 69.867		
Day 365	64.199	58.966 – 69.433	-3.9	0.680
Efficacy				
NT-proBNP (ng/L)[b]				
Day -365	186.255	116.779 – 297.064	46.4	0.022
Day 0	272.648	180.718 – 411.342		
Day 365	200.391	126.524 – 317.381	-26.5	0.010
Hemoglobin (mmol/L)				
FCFrEF				
Day -365	9.814	9.061 – 10.566	+3.1	0.224
Day 0	10.115	9.413 – 10.818		
Day 365	10.526	9.763 – 11.288	+4.1	0.793
FCFpEF				
Day -365	8.792	8.173 – 9.411	+3.4	0.224
Day 0	9.093	8.565 – 9.622		0.025
Day 365	9.504	8.873 – 10.134	+4.5	0.793
Hematocrit (L/L)				
FCFrEF				
Day -365	0.466	0.435 – 0.496	+3.7	0.106

Table 2. *Continued*

	Estimate	95% CI	% change[a]	P-value
Day 0	0.483	0.455 – 0.511		
Day 365	0.508	0.477 – 0.539	+5.2	0.656
FCFpEF				
Day -365	0.425	0.400 – 0.451	+4.1	0.106
Day 0	0.442	0.421 – 0.464		0.025
Day 365	0.468	0.442 – 0.493	+5.7	0.656
Albumin (g/L)				
No PLE				
Day -365	44.082	41.400 – 46.765	+5.4	0.097
Day 0	46.447	44.389 – 48.506		
Day 365	46.436	43.659 – 49.213	<-0.1	0.318
PLE				
Day -365	34.444	27.653 – 41.235	+6.9	0.097
Day 0	36.809	30.252 – 43.366		0.009
Day 365	36.798	30.157 – 43.439	<-0.1	0.318
AST (U/L)				
Day -365	24.204	20.006 – 28.402	+8.2	0.322
Day 0	26.191	22.971 – 29.411		
Day 365	26.080	21.883 – 30.277	-0.4	0.523
ALT (U/L)				
FCFrEF				
Day -365	28.821	23.178 – 34.465	-2.6	0.710
Day 0	28.083	22.975 – 33.190		
Day 365	31.718	25.916 – 37.520	+12.9	0.184
FCFpEF				
Day -365	21.401	16.877 – 25.925	-3.4	0.710
Day 0	20.663	17.075 – 24.251		0.022
Day 365	24.298	19.707 – 28.888	+17.6	0.184
ALP (U/L)[b]				
Day -365	90.713	77.683 – 105.930	-0.6	0.921

Table 2. *Continued*

	Estimate	95% CI	% change[a]	P-value
Day 0	90.152	78.888 – 103.024		
Day 365	100.916	86.270 – 118.048	+11.9	0.255
GGT (U/L)[b]				
Day -365	56.753	41.740 – 77.164	+15.3	0.277
Day 0	65.427	52.067 – 82.215		
Day 365	87.848	67.627 – 114.117	+34.3	0.426
Weight (kg)				
Day -365	71.714	66.854 – 76.574	+2.4	0.379
Day 0	73.426	69.443 – 77.409		
Day 365	75.142	70.735 – 79.549	+2.3	0.999

[a]The percentage change after the 'Day -365' estimate is calculated as the percentage change from the day 0 estimate to the day -365 estimate: ('day 0' – 'day -365')/'day -365' * 100). The change after the 'Day 365 estimate is calculated in a similar fashion. [b]These models were fitted on a log10 transformed variable due to significant departure from normality of the normalized residuals for the normal scale variable. In this table, the estimates have been back-transformed to the original scale for interpretation. *ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; FCF, Fontan circulatory failure; FCFpEF, Fontan circulatory failure with preserved ejection fraction; FCFrEF, Fontan circulatory failure with reduced ejection fraction; GGT, gamma-glutamyltransferase; NT-proBNP, N-terminal pro–B-type natriuretic peptide*.

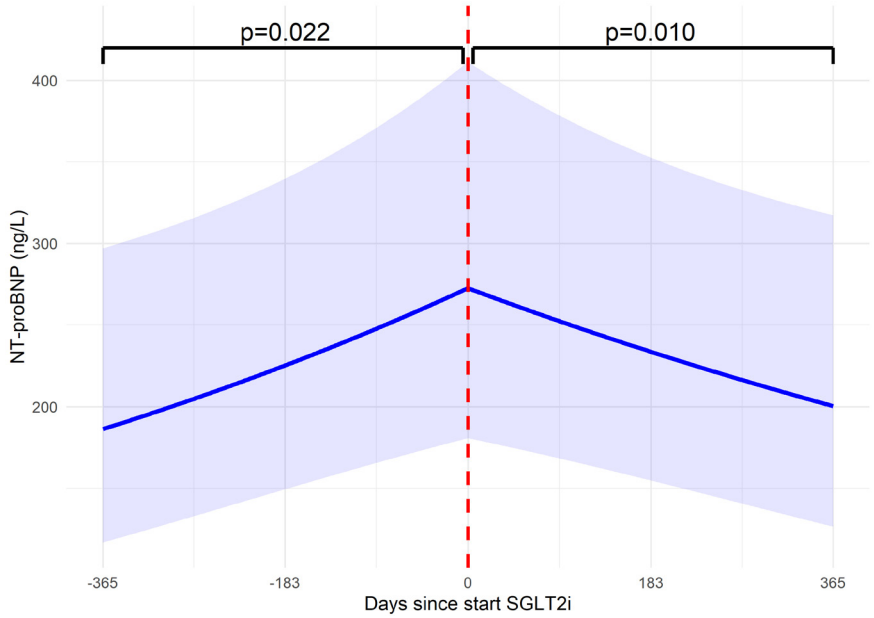


Figure 2. NT-proBNP changes in the year before and after starting SGLT2i

Changes in NT-proBNP (ng/L) in the year before and after starting SGLT2i. In the year before starting SGLT2i, there was an estimated 46.4% increase in NT-proBNP (p=0.022). In the year after starting, there was a significant reversal of the trajectory, with an estimated decrease of 26.5% (p=0.010). This indicates that starting SGLT2i significantly impacted and reversed NT-proBNP. The dashed red line indicates when SGLT2i therapy was started. *NT-proBNP, N-terminal pro–B-type natriuretic peptide; SGLT2i, sodium-glucose cotransporter 2 inhibitor*.

Clinical outcomes

A total of 18 FCF-related hospitalizations, with a median length of stay of 5.5 [2.5 – 12.3] days, were documented in 9 patients; 11 in the year before starting SGLT2i, and 7 during follow-up. The timeline for the FCF-related hospitalizations is presented in *Figure 3*. Additionally, 2 patients underwent atrial ablation procedures for arrhythmias during follow-up, and 1 underwent lymphatic embolization. One patient with Loeys-Dietz syndrome died after emergency thoracic endovascular aneurysm repair for a type B aortic dissection. No other patients died during follow-up and none were lost to follow-up.

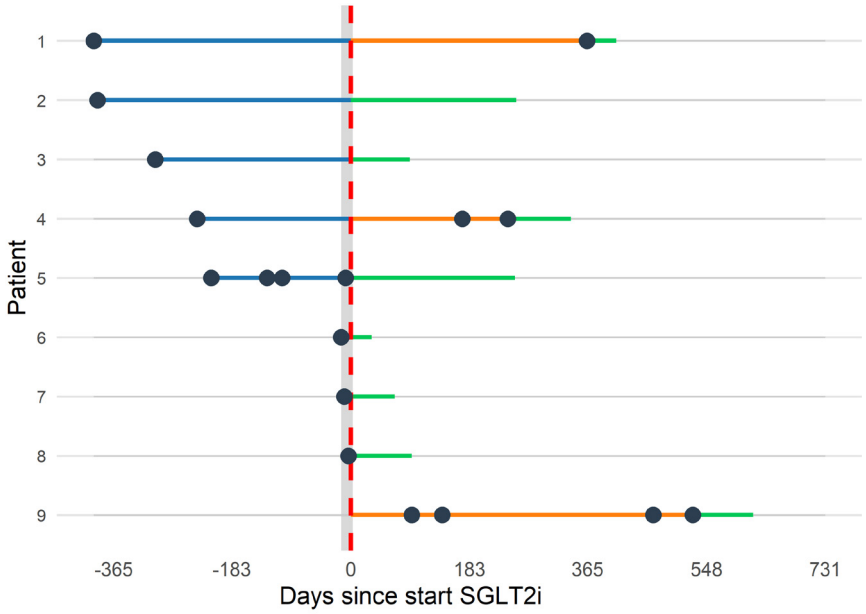


Figure 3. Timeline of FCF-related hospitalizations

Timeline of the occurrence of FCF-related hospitalizations in the year before starting SGLT2i (blue, n=11) and during follow-up (orange, n=7). The green lines indicate the time until the most recent follow-up without hospitalization. The dashed red line indicates when SGLT2i was started. Dots that fall within the light gray band indicate FCF-related hospitalizations during which SGLT2i was started (which was the case in patients 5, 6, 7, and 8). *FCF, Fontan circulatory failure; SGLT2i, sodium-glucose cotransporter 2 inhibitors.*

Concomitant FCF pharmacotherapy changes

All but one patient (97%) used at least one of the "conventional" guideline-directed medical heart failure therapy classes at baseline, 17 patients (51.5%) used two, and 11 patients (33.3%) three medication classes when SGLT2i was started. The proportion of patients using each medication class at baseline, stratified for FCF phenotype, is presented in *Figure 4*. FCFpEF patients more frequently used diuretics than FCFrEF patients at baseline (81.8% vs

45.5%, p=0.049), while other medication classes did not differ significantly. From baseline to most recent follow-up, there were no significant changes in the use of any of the FCF pharmacotherapy classes (*Supplemental Table 4*).

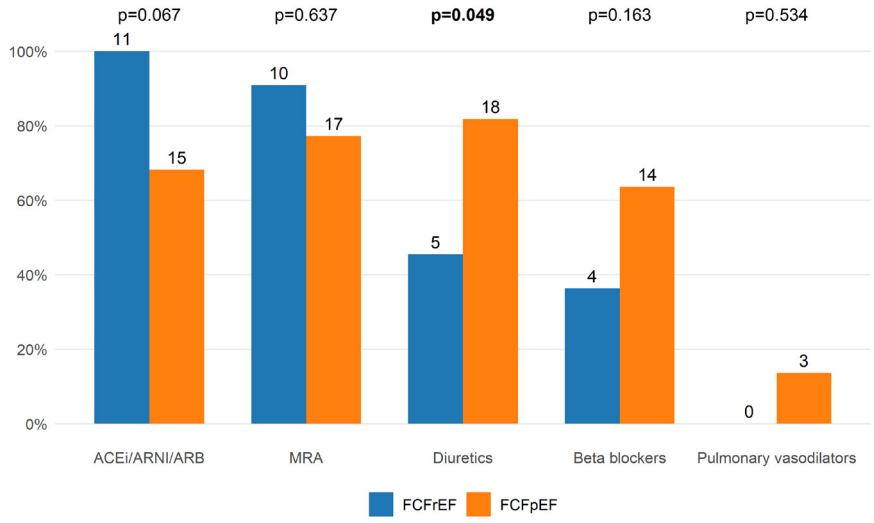


Figure 4. FCF pharmacotherapy at baseline
Proportion of patients using different FCF pharmacotherapy classes at baseline, separated for FCF type (FCFrEF n=11, FCFpEF n=22). The total number of patients using each pharmacotherapy class is shown at the top of each bar. FCFpEF patients more frequently used diuretics at baseline than FCFrEF patients (81.8% vs 45.5%, p=0.049). *ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; FCF, Fontan circulatory failure; FCFpEF, Fontan circulatory failure with preserved ejection fraction; FCFrEF, Fontan circulatory failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist*.

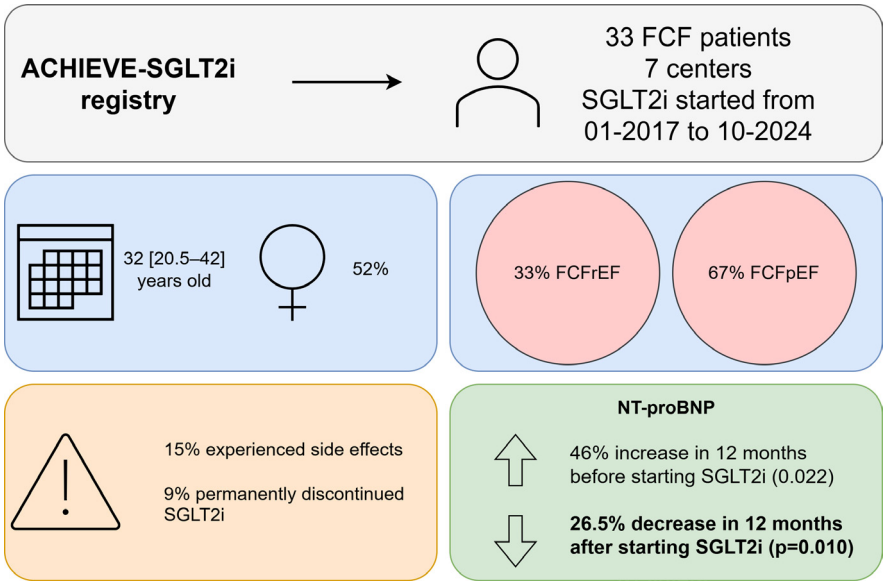
Discussion

This real-world multicenter study evaluated SGLT2i in the adult Fontan population. The most important findings are that SGLT2i were safe and well-tolerated in patients with FCF, and SGLT2i treatment was associated with a significant decrease in NT-proBNP, in both FCFrEF and FCFpEF patients (*Central Illustration*).

Safety and tolerability of SGLT2i in Fontan patients

In the current study, 5 patients (15.2%) experienced side effects, of whom 3 (9.1%) permanently discontinued SGLT2i therapy. These findings are in line with the previous report of 174 ACHD patients using SGLT2i.[18] However, when directly comparing the results, we should acknowledge the influence of the small sample size on the reported

percentages. Importantly, there were no new or serious side effects, and it is reassuring that no significant deterioration of blood pressure or renal function was observed. Therefore, these findings suggest that SGLT2i have a comparable safety profile and are tolerated well in the FCF population.



Central Illustration. SGLT2i in Adults with Fontan Circulatory Failure
In this real-world multicenter evaluation of the use of SGLT2i in 33 adult FCF patients included in the ACHIEVE-SGLT2i registry, SGLT2i were safe and well-tolerated. SGLT2i treatment was associated with NT-proBNP reduction, regardless of FCF phenotype. *FCF, Fontan circulatory failure; FCFpEF, Fontan circulatory failure with preserved ejection fraction; FCFrEF, Fontan circulatory failure with reduced ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SGLT2i, sodium-glucose cotransporter 2 inhibitors*.

NT-proBNP in the Fontan population

Several studies have reported a significant reduction in NT-proBNP after starting SGLT2i in ACHD patients with a biventricular circulation.[20-23] To our knowledge, this is the first study to report a significant reduction in NT-proBNP among FCF patients after SGLT2i initiation. Although natriuretic peptides have established prognostic value in ACHD, their role in the Fontan population is less well-established.[5, 24] There is some evidence that NT-proBNP levels vary between the Fontan circulation types, with atriopulmonary and atrioventricular connection Fontans exhibiting higher NT-proBNP levels than patients with a total cavopulmonary correction, likely caused by the chronic exposure of atrial tissue to supranormal pressures.[25] Despite the inclusion of all Fontan subtypes in our study, an overall reduction in NT-proBNP was observed. Elevated NT-proBNP levels have been associated

with significant ventricular dilatation, reduced ejection fraction, and long-term clinical events in Fontan patients regardless of the type of Fontan repair.[26, 27] Supporting this, the recently published Fontan Adult Brompton (FAB) clinical score study demonstrated significantly higher NT-proBNP levels among patients who died or underwent transplantation compared with survivors, reinforcing its potential as a surrogate marker of long-term prognosis.[28]

Differential response to SGLT2i between FCF phenotypes

Distinctly different underlying pathophysiological mechanisms of FCF have been identified, and significant systolic ventricular dysfunction appears to be the most prevalent underlying cause of FCF.[29] We hypothesized that the response to SGLT2i might be different between FCFrEF and FCFpEF patients, in part based on a recent study evaluating the echocardiographic effects of SGLT2i in patients with single ventricle circulatory failure. In that study, fractional area change only improved significantly in patients with at least moderately reduced ventricular function at baseline, although improvements in free wall strain and isovolumic acceleration were seen across all ranges of systolic ventricular function.[15] *Konduri et al*. also distinguished between FCFrEF and FCFpEF patients and reported sequential natriuretic peptides only for five FCFrEF patients after starting SGLT2i. They concluded that SGLT2i could be particularly effective in FCFrEF patients with elevated natriuretic peptides.[13] The current study differs from these findings and demonstrates a significant reduction in NT-proBNP in both FCFrEF and FCFpEF patients. Although based on a limited sample size, the association with a reduction in NT-proBNP across FCF phenotypes is promising. Nonetheless, treatment response may be heterogeneous, reflecting different pathophysiological mechanisms of FCF. As the ACHIEVE-SGLT2i registry data did not allow for detailed hemodynamic phenotyping, future research should focus on elucidating the effects of SGLT2i in the different pathophysiological phenotypes of FCF, including patients with significant atrioventricular valve regurgitation, elevated pulmonary vascular resistance/pressures, and/or restrictive physiology.[29]

FCF is a complex cardiovascular syndrome, characterized by disruption in the delicate balance between ventricular preload and systemic afterload.[5] Due to this balance, the systemic effects of SGLT2i could potentially be detrimental in some FCF patients. Despite this, the off-target effects may explain both improvements in systolic ventricular function and the improvements in NT-proBNP reported here.[15] The contributions of the pleiotropic mechanisms of action of SGLT2i in FCF remain unknown, and future studies should explore how these various mechanisms of action contribute to benefits in distinct FCF phenotypes.

Overall differences between FCF phenotypes

While no significant differences in the response to SGLT2i were observed between FCFrEF and FCFpEF patients in this study, FCFpEF patients had lower overall serum hemoglobin and hematocrit. Although these values remained within the normal reference ranges, it is important to note that reference values are lacking for Fontan patients. In particular, hemoglobin values for (mildly) cyanotic patients are significantly higher than for non-cyanotic patients, and normal or slightly decreased hemoglobin values may be inadequate for Fontan patients.[30, 31] In conventional heart failure, patients with preserved ejection fraction often have a lower hemoglobin and higher prevalence of anemia compared to patients with reduced ejection fraction, and anemia is an independent risk factor for mortality in heart failure patients.[32, 33] The estimated hemoglobin of 9.1 mmol/L in FCFpEF compared to 10.1 mmol/L in FCFrEF patients at SGLT2i initiation may represent a similar, underrecognized difference, and systematic screening for anemia (and underlying iron deficiency) should be included as part of routine clinical care.

The prognostic significance of ALT in heart failure is less clear.[34, 35] While there is no literature on the differences in hepatic serum biomarkers between FCFrEF and FCFpEF patients, over 80% of Fontan patients exhibit abnormal hepatic serum biomarkers over time, and patients frequently develop Fontan-associated liver disease (FALD).[36] Although ALT values stayed within the normal range (10–45 U/L) in this study, and more detailed hepatic function information was not available, the overall higher ALT observed in FCFrEF patients could be reflective of more pronounced hepatic congestion and hepatic hypoxemic injury due to significant ventricular dysfunction.[37]

Clinical outcomes

After starting SGLT2i, 7 FCF-related hospitalizations occurred in just 3 patients, 2 of whom also had an FCF-related hospitalization in the 12 months before initiating SGLT2i. 'Frequent admitters' are a well-described phenomenon in conventional heart failure, with repeated hospitalizations being a marker of advanced disease and worse outcomes. This pattern appears to be present in the FCF cohort described here.[38] We have to emphasize that the reduction in FCF-related hospitalizations observed from the year before to after starting SGLT2i was influenced by the limited follow-up duration and limited sample size, precluding further analysis. Hence, these data should only be regarded as hypothesis-generating.

Limitations

This study has several limitations. First, this study is limited by the single-arm, retrospective, real-world setup, and the anatomical and surgical heterogeneity inherent to the Fontan population. Linear mixed models were used to account for within-patient correlations and

unbalanced data, with data from the year before starting SGLT2i serving as the patients' control data. While randomized controlled trials remain the gold standard, real-world registries provide essential evidence that advances clinical care in the Fontan population. Second, the lack of (exercise) catheterization data in the registry prevented detailed stratification of the underlying hemodynamic mechanisms of FCF. The dichotomization of patients into FCFrEF and FCFpEF oversimplifies the complex phenotypes of FCF, and future studies should aim to evaluate the benefits of SGLT2i for different underlying causes. Third, although all patients had preserved renal function at baseline and there was no deterioration after SGLT2i, creatinine-based eGFR estimation is influenced by skeletal muscle and may overestimate actual renal function in the Fontan population, which is known to be subject to sarcopenia. Twenty-four-hour urine creatinine clearance would have provided a more accurate estimate of renal function. Cystatin C-based eGFR estimation also appears more accurate in Fontan patients and may be more sensitive in detecting renal dysfunction and SGLT2i-related changes.[39] Unfortunately, neither were performed routinely. Fourth, functional performance was not evaluated in this study due to the limited availability of exercise testing data in the registry, while it is very relevant for a comprehensive evaluation of the potential efficacy of SGLT2i in the Fontan population. Conventional maximal exercise parameters, such as VO_2 max, may not fully capture "Fontan performance", and therefore, submaximal exercise parameters may be of additional value in capturing clinically meaningful changes.

Conclusion

This real-world, multicenter study is the largest experience to date evaluating SGLT2i in adults with FCF. In this cohort of 33 patients, SGLT2i treatment was safe and well-tolerated, and associated with a significant reduction in NT-proBNP in both FCFrEF and FCFpEF phenotypes. Future research should confirm these observations in larger cohorts with longer follow-up, and focus on identifying patients who are most likely to benefit from SGLT2i treatment. Preferably, this should be done through prospective studies incorporating detailed hemodynamic phenotyping, to evaluate treatment response between the different underlying causes of FCF.

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7

Echocardiographic Effects of Sodium-Glucose Cotransporter 2 Inhibitors in Single Ventricle Circulatory Failure

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Abstract

Background

Single ventricle patients are at high risk of developing circulatory failure. There is limited evidence for pharmacological treatment. This study assessed the echocardiographic changes in ventricular function during sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy in patients with single ventricle failure (SVF).

Methods

SVF patients with a baseline transthoracic echocardiogram within six months before starting SGLT2i and at least one echocardiographic examination within twelve months follow-up were included from a real-world international registry of adult congenital heart disease patients on SGLT2i. Mixed models were used to evaluate longitudinal changes in ventricular function and differences between patients with SVF with ≥ moderately reduced systolic function (SVFrEF) and with ≤ mildly reduced function (SVFpEF).

Results

Thirteen patients were included. The median age was 21 (2–42) years, 8 (61.5 %) were female, 10 (76.9%) had a Fontan circulation, 8 (61.5%) had SVFrEF, and 5 (38.5%) SVFpEF at the start of SGLT2i. The mean follow-up was 7.6 ± 3.3 months. End-systolic area decreased significantly in all patients (-1.6 cm^2 per month, p=0.007) in the first 100 days. Fractional area change improved in the first 100 days in SVFrEF patients (3.5%-point per month, p<0.001), while SVFpEF patients remained stable. There was a significant improvement in the free wall strain in all patients (-0.3%-point per month, p=0.036) but not in global longitudinal strain (p=0.087). Isovolumic acceleration also improved in the first 100 days (0.5 m/s^2 per month, p=0.010).

Conclusions

Echocardiographic signals of improved ventricular function were observed in the first year of SGLT2i therapy in patients with SVF.

Introduction

Patients with single ventricle physiology represent one of the most complicated hemodynamic subtypes within adult congenital heart disease (ACHD). In this heterogeneous population, most patients 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'. Single ventricle patients who do not undergo Fontan palliation 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.[1] Ultimately, single ventricle physiology patients are prone to develop heart failure at a significantly higher rate than other congenital heart disease groups. Fontan failure occurs in over 30 % of patients across all ages, and prevalence increases to nearly 100 % in patients over 50 years old.[2] Heart failure 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 age 50.[3]

Despite this high morbidity and mortality burden, the current ACHD guidelines provide few recommendations for the management of single ventricle circulatory failure and substantiate this key knowledge gap as being due to a poor understanding of the underlying failure mechanisms and the absence of evidence-based treatment options.[1,4] The guidelines do emphasize that pharmacotherapy should be initiated cautiously given the delicate balance between ventricular preload and systemic afterload.

In recent years, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a cornerstone in managing conventional heart failure.[5,6] Although SGLT2i appear safe and well-tolerated in the ACHD population, there have been few small studies that specifically evaluated SGLT2i in the single ventricle population or included single ventricle patients, and potential beneficial effects remain to be elucidated.[7-14] Systolic and diastolic ventricular dysfunction are the most prevalent causes of single ventricle circulatory failure.[15] Due to the proposed pleiotropic mechanisms of action, SGLT2i are a promising treatment option for single ventricle circulatory failure, and their effect on ventricular function deserves further evaluation.[16] This study aimed to delineate comprehensively the longitudinal echocardiographic changes in ventricular function observed during the first year of SGLT2i therapy in patients with single ventricle circulatory failure.

Methods

Study design

Patients with a physiological single ventricle circulation included in the international, real-world ACHIEVE-SGLT2i (Adult Congenital Heart disease International EValuation of the Effectiveness of SGLT2i) registry (National Clinical Trial number: NCT06932081) were assessed for eligibility for this retrospective on-treatment study. Patients with single ventricle physiology (≥18 years of age) had to be initiated on an SGLT2i for symptomatic circulatory failure and had to have a baseline transthoracic echocardiogram (TTE) within six months before starting SGLT2i and at least one TTE in the outpatient setting between six weeks and twelve months follow-up available for offline analysis.

Single ventricle circulatory failure was adjudicated by the treating cardiologists who initiated SGLT2i, based on an extrapolation of the universal definition of heart failure to the complex single ventricle hemodynamics.[17] Patients with heart failure symptoms and ≥ moderately reduced systolic systemic ventricular function were classified as having single ventricle failure with a reduced ejection fraction (SVFrEF), and patients with ≤ mildly reduced systolic ventricular function as single ventricle failure with a preserved ejection fraction (SVFpEF), in line with previous literature.[8]

Ethics

Appropriate medical ethical board approval was obtained at the participating centers (Leiden University Medical Center Medical Research Involving Human Subjects Act (WMO) committee division 1 protocol reference 2022-068, Southwest – Central Bristol Research Ethics Committee reference 24/SW/0036). The study was conducted in accordance with the ethical standards of the institutional and/or national research committees, 2013 Declaration of Helsinki, and in line with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[18]

Data collection and TTE assessment

All clinical data were retrieved from the electronic health records. All TTEs obtained in an outpatient clinic setting as part of routine care, performed at variable time points, were included. Data was collected until: 1) 12 months follow-up, 2) the last date of data inclusion (if occurring at less than 12 months follow-up), 3) permanent discontinuation of SGLT2i therapy, 4) any catheter or surgical intervention influencing the patient's hemodynamic status, 5) loss to follow-up, or 6) death. R.M.L.N. was blinded to the patient's clinical status when performing the offline analyses, and supervised by two experienced European Association of Cardiovascular Imaging (EACVI) certified ACHD imaging cardiologists (M.V.R., G.R.V.). Each case was reviewed jointly by R.M.L.N., M.V.R., and G.R.V.

before analysis to reach a consensus on the relevant anatomical landmarks and image interpretation, enhancing internal consistency. A dedicated TTE evaluation workflow was adapted to the single ventricle population.[19] The following parameters were assessed: systemic ventricle end-diastolic diameter (mm), apex-base length (mm), mid diameter (mm), free wall thickness (mm), end-diastolic area (cm^2), end-systolic area (cm^2), fractional area change (FAC, %), tricuspid/mitral annular plane systolic excursion (TAPSE/MAPSE, mm), systemic ventricle global longitudinal strain (GLS, %), free wall strain (FWS, %), separate segmental strain (%), and atrioventricular valve (AVV) regurgitation grades. Additionally, the tissue Doppler imaging parameters isovolumic acceleration (IVA, m/s^2), S' (m/s), and e' (m/s) were measured at the lateral wall adjacent to the dominant AVV. E and A velocities (m/s) were measured over the dominant AVV. Strain measurements were performed using Q-analysis in EchoPAC™ (GE Healthcare, Chicago, IL, USA). The endocardial border was traced manually in the apical four-chamber view, including the interventricular septum if present and when contributing to the systolic function. Systolic systemic ventricle function was additionally classified into four qualitative categories based on a combination of GLS, FAC, and visual assessment. A detailed depiction of the ventricular function assessment is presented in *Figure 1*.

Statistical analysis

The statistical analyses were performed with SPSS v25 (IBM Corp, Armonk, NY, USA) and R Statistical Software (v4.4.2; R Core Team 2023). Normally distributed continuous variables were presented as mean ± standard deviation, non-normally distributed continuous variables as median (interquartile range), and categorical variables as frequencies with percentages in parentheses. The "nlme" package (v3.1.167; R Core Team 2024) was used to construct linear mixed models with various specifications to assess the longitudinal relationship between TTE parameters and time, modeled as a continuous variable in days, as previously published.[20] To enhance clinical interpretability, time-dependent coefficients were expressed as changes per month. Differential responses during follow-up between SVFrEF and SVFpEF patients were investigated by including the failure phenotype as a binary covariate. Random intercepts and the addition of random slopes were explored. To model potential non-linear changes, piecewise linear splines models were tested. Various correlation and variance structures were also assessed. Model selection was based primarily on the Bayesian information criterion (BIC), with secondary consideration of the Akaike information criterion (AIC) or likelihood ratio tests when appropriate. Model parsimony was prioritized over predictive capacity in the model selection process, and fit was verified through residual analysis. The predicted fixed effects were visualized with corresponding 95 % confidence intervals for fixed-effect variance. Statistical significance was defined as a two-sided p-value ≤ 0.05.

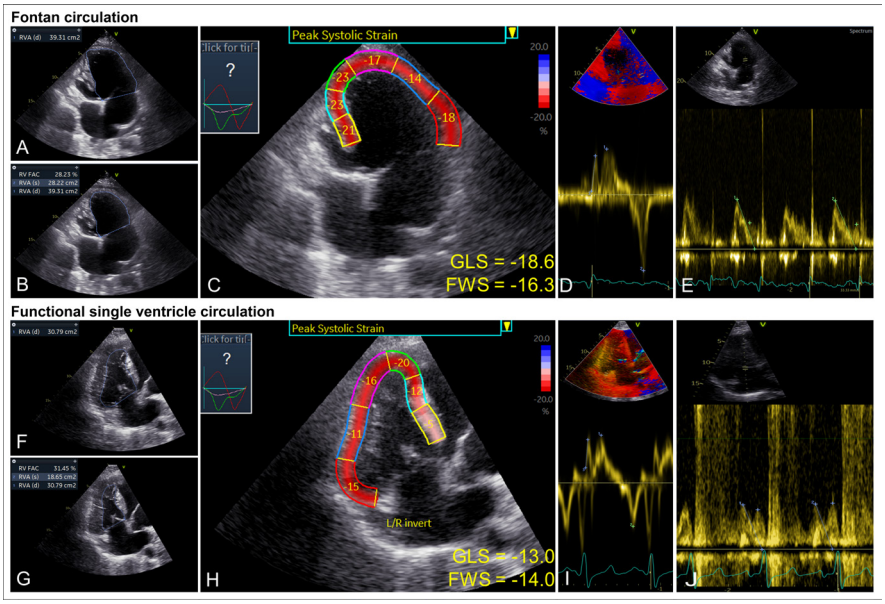


Figure 1. TTE assessment methodology

The top part of figure (A–E) shows the ventricular function assessment in a patient with tricuspid atresia and a left ventricle dominant Fontan circulation, the bottom part (F–J) in a patient with congenitally corrected transposition of the great arteries, double-outlet right ventricle, subaortic ventricular septal defect, and pulmonary atresia, palliated with a Glenn shunt and Blalock-Thomas-Taussig shunts. A&F) end-diastolic area (cm^2), B&G) end-systolic area (cm^2) and FAC calculation, C&H) strain analysis including GLS, segmental strain values, and calculation of the FWS by averaging the 3 lateral strain segments, D&I) tissue Doppler imaging measurements S' (measurement 1, m/s), e' (measurement 2, m/s), and IVA (slope measurement 3, m/s2), E&J) E and A velocities (m/s) measured on (at least) two complexes on pulsed-wave Doppler. *FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; IVA, isovolumic acceleration; RV, right ventricle; RVA, right ventricle area; TTE, transthoracic echocardiography.*

Results

Baseline characteristics

Thirteen patients with single ventricle circulatory failure initiated on SGLT2i therapy between December 2021 and October 2023 were included. The median age was 21 (20–42) years old, 8 (61.5%) were female, 10 (76.9%) had a Fontan circulation, 8 (61.5 %) had SVFrEF, and 5 (38.5%) SVFpEF. Dapagliflozin 10 mg once daily was started in 9 (69.2 %) patients, and empagliflozin 10 mg once daily in 4 (30.8%). The mean echocardiographic follow-up duration was 7.6 ± 3.3 months and 35 TTEs were included for analysis. All patients had a baseline TTE assessment, 6 patients had 1 follow-up TTE, 5 patients had 2, and 2 patients had 3. Detailed baseline characteristics and TTE parameters are presented in *Table 1*, *Table 2*, and individual anatomical and echocardiographic characteristics in *Supplementary Table 1*.

Table 1. Baseline characteristics

	n=13
Age, y	21 (20–42)
Sex, female	8 (61.5)
Single ventricle anatomy	
Fontan	
RV dominant (hypoplastic left heart syndrome)	5 (38.5)
LV dominant	4 (30.8)
Mixed/indeterminate ventricle	1 (7.7)
Other (double-outlet right ventricle + ventricular septal defect ± other lesions)	3 (23.1)
Fontan type	
Extracardiac Fontan	8 (61.5)
Lateral tunnel Fontan	2 (15.4)
Single ventricle failure phenotype	
SVFrEF	8 (61.5)
SVFpEF	5 (38.5)
Protein-losing enteropathy	1 (7.7)
Plastic bronchitis	0
Type 2 diabetes mellitus	0
Number of cardiac surgeries	3 (3–4)
Pacemaker	4 (30.8)
Pharmacotherapy	
MRA	11 (84.6)
ACEi/ARB/ARNI	9 (69.2)
Beta-blocker	8 (61.5)
Diuretic	8 (61.5)
PDE5 inhibitor	0
Clinical parameters	
Body surface area, m^2	1.75 (1.46–1.79)
Heart rate, bpm	73 ± 8
Heart rhythm	
Sinus rhythm	10 (76.9)
Atrial rhythm	1 (7.7)

Table 1. *Continued*

	n=13
Atrial pacing	1 (7.7)
Ventricular pacing	1 (7.7)
Systolic blood pressure, mmHg	111 ± 14
Diastolic blood pressure, mmHg	67 ± 7

Values are n (%), mean ± standard deviation, or median (Q1–Q3). *ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; PDE5, phosphodiesterase type 5; RV, right ventricle; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SVFrEF/SVFpEF, single ventricle failure with reduced/preserved ejection fraction*.

Table 2. TTE parameters at baseline

	n=13
Systemic ventricle dimensions	
End-diastolic diameter, mm	61 ± 17
Apex base length, mm	75 ± 8
Mid diameter, mm	54 ± 9
Free wall thickness, mm	9 ± 2
End-diastolic area, cm^2	38.1 ± 6.6
End-systolic area, cm^2	28.8 ± 6.9
Global systolic ventricular function	
Good	3 (23.1)
Mildly reduced	2 (15.4)
Moderately reduced	5 (38.5)
Severely reduced	3 (23.1)
Dominant AVV regurgitation	
Grade 1 or less	2 (15.4)
Grade 2	2 (15.4)
Grade 3	9 (69.2)
Grade 4	0
Systolic function parameters	
GLS, % (n=12)	−13.9 ± 3.3

Table 2. TTE parameters at baseline

	n=13
FWS, % (n=12)	−13.3 ± 4.2
FAC, %	24.8 ± 9.1
TAPSE/MAPSE, mm (n=12)	11.1 ± 1.8
S', cm/s (n=8)	6.0 ± 0.8
IVA, m/s^2 (n=8)	1.9 ± 0.9
Diastolic function parameters	
E/A ratio (n=9)	1.7 ± 0.6
E/e' ratio (n=7)	6.3 (5.5–11.7)

Values are n (%), mean ± standard deviation, or median (Q1–Q3). Data is available for all patients unless specified otherwise. *AVV, atrioventricular valve; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; IVA, isovolumic acceleration; TAPSE/MAPSE, tricuspid/mitral annular plane systolic excursion; TTE, transthoracic echocardiography.*

Ventricular remodeling

No temporal changes were observed in end-diastolic diameter (p=0.682), apex-base length (≤100 days; p=0.062, >100 days; p=0.067), mid diameter (p=0.846), free wall thickness (p=0.087), or end-diastolic area (≤100 days; p=0.323, >100 days; p=0.071) after initiation of SGLT2i therapy. End-systolic area decreased significantly in the first 100 days of treatment (−1.6 cm^2 per month, p=0.007), after which there was a non-significant increasing trend (0.6 cm^2 per month, p=0.051) (*Figure 2A*).

Systolic ventricular function

SVFrEF patients had a significant improvement in FAC in the first 100 days (3.5%-point per month, p<0.001), after which FAC remained stable (p=0.141). SVFpEF patients remained stable in the first 100 days, which differed significantly from the improvement observed in the SVFrEF patients (−0.1%-point per month, interaction p=0.007). After 100 days, there were no significant changes between SVFrEF and SVFpEF patients (p=0.081). The predicted changes in FAC are presented in *Figure 2B*. No temporal changes in TAPSE/MAPSE were observed. SVFpEF patients did have significantly higher overall TAPSE/MAPSE values than SVFrEF patients (2.7 mm, p=0.010) (*Supplementary Figure 1*).

Although there was no significant overall improvement in GLS after starting SGLT2i (−0.1%-point per month, p=0.087), there was a significant improvement in FWS (−0.3%-point per month, p=0.036) and basal lateral segmental strain over time (−0.3%-point

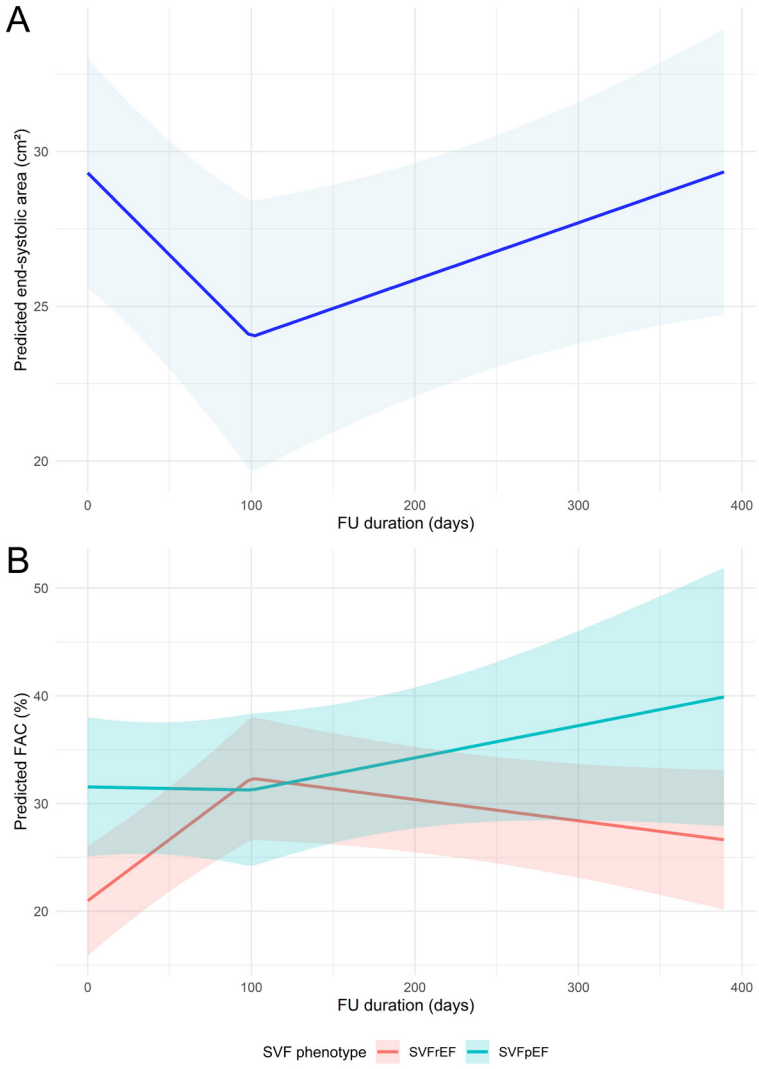


Figure 2. Changes in end-systolic area and FAC after starting SGLT2i

A) End-systolic area decreased significantly in the first 100 days after starting SGLT2i (−1.6 cm2 per month, p=0.007), after which there was an increasing trend (0.6 cm2 per month, p=0.051). **B**) Patients with SVFrEF had a significant improvement in FAC in the first 100 days (3.5%-point per month, p<0.001), after which the change was not significant (p=0.141). SVFpEF patients had a significantly different trajectory from the SVFrEF patients and remained stable in the first 100 days (−0.1%-point per month, interaction p=0.007), after which the change was no longer significantly different between groups (interaction p=0.081). *FAC, fractional area change; FU, follow-up, SGLT2i, sodium-glucose cotransporter 2 inhibitor; SVF, single ventricle failure, SVFrEF/SVFpEF, single ventricle failure with reduced/preserved ejection fraction.*

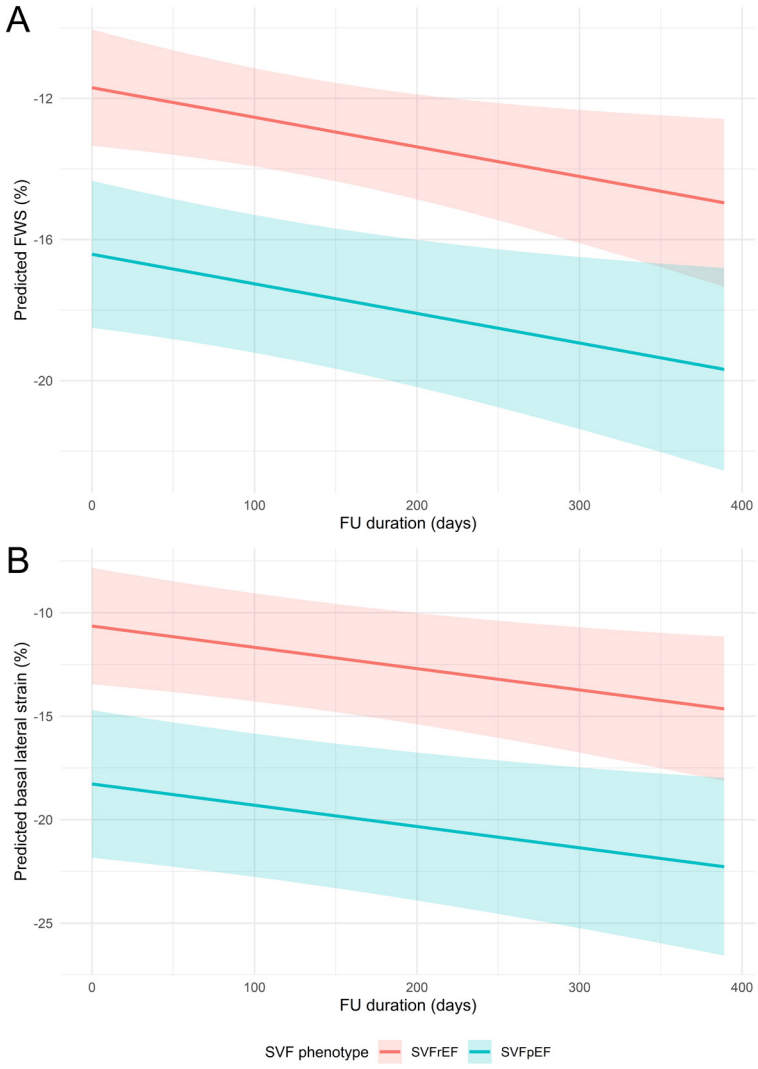


Figure 3. Changes in FWS and basal lateral strain after starting SGLT2i

A) Predicted longitudinal changes in FWS (%) after starting SGLT2i. There was a significant improvement in FWS over time (−0.3%-point per month, p=0.036). SVFpEF patients had significantly better strain values (4.7%-point lower than SVFrEF patients, p=0.003). **B**) Predicted longitudinal changes in basal lateral segmental strain (%). There was a significant improvement over time (−0.3%-point per month, p=0.032), and SVFpEF patients also had significantly better basal lateral segmental strain (7.6%-point lower than SVFrEF patients, p=0.006). *FU, follow-up; FWS, free wall strain; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SVF, single ventricle failure, SVFrEF/SVFpEF, single ventricle failure with reduced/preserved ejection fraction.*

per month, p=0.032) (*Figure 3*). All other strain segments demonstrated a trend towards improvement, but none were statistically significant. Compared to SVFrEF patients, SVFpEF patients had a significantly better overall GLS (−5.3%-point, p<0.001), FWS (−4.7%-point, p=0.003), mid septal segmental strain (−5.0%-point, p=0.018), mid lateral segmental strain (−4.9%-point, p=0.026), and basal lateral segmental strain (−7.6%-point, p=0.006) (*Supplementary Figures 2–4*). The temporal response in strain measurements to SGLT2i showed no significant differences for the single ventricle failure phenotypes.

IVA improved significantly in the first 100 days after starting SGLT2i (0.5 m/s^2 per month, p=0.010), and remained stable afterwards (p=0.075). SVFrEF patients had a significantly lower overall IVA than SVFpEF patients (1.3 m/s^2, p=0.027) (*Figure 4*). There were no temporal changes in S', E/A ratio or E/e' ratio after starting SGLT2i (p=0.889, p=0.626, and p=0.289 respectively). The individual changes of all parameters with significant temporal changes after starting SGLT2i are included in *Supplementary Figure 5*. All mixed model outputs and characteristics are presented in *Supplementary Tables 2* and *3*.

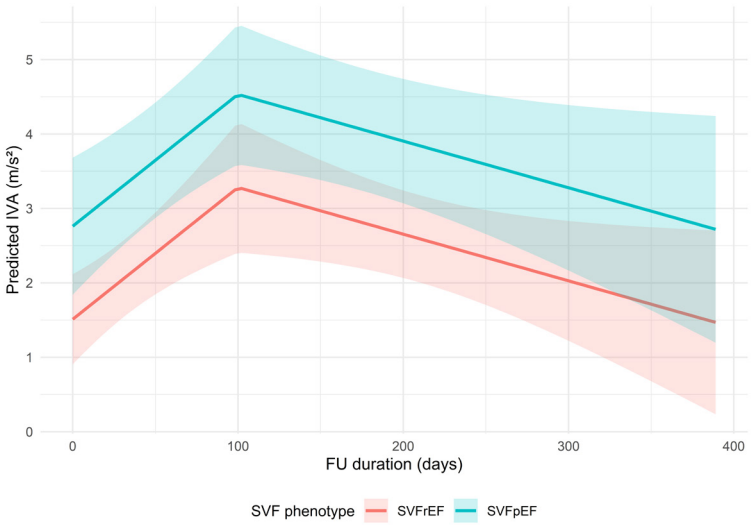


Figure 4. Changes in IVA after starting SGLT2i
There was a significant improvement in IVA in the first 100 days after starting SGLT2i (0.5 m/s^2 per month, p=0.010), after which there was a decreasing trend (−0.2 m/s^2 per month, p=0.075). SVFrEF patients had a significantly lower overall IVA than SVFpEF patients (1.3 cm^2, p=0.027). *FU, follow-up; IVA, isovolumic acceleration; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SVF, single ventricle failure, SVFrEF/SVFpEF, single ventricle failure with reduced/preserved ejection fraction.*

Discussion

The main findings of this study are that in the first year of SGLT2i therapy for single ventricle circulatory failure, 1) there was a significant decrease in the end-systolic area of the systemic ventricle in all patients and a significant improvement in FAC in SVFrEF patients in the first 100 days, 2) there was a significant improvement in FWS and basal lateral segmental strain in all patients over time, although the GLS did not improve, and 3) there was a significant improvement in IVA in all patients in the first 100 days after SGLT2i initiation.

Phenotyping single ventricle circulatory failure

Single ventricle circulatory failure was categorized as either SVFrEF or SVFpEF. This dichotomization has been utilized previously, including in another recent study evaluating the use of SGLT2i in 14 Fontan patients.[8,21] *Konduri et al.* observed a reduction in NT-proBNP in 5 patients with at least moderately reduced ventricular function and concluded that SGLT2i might benefit Fontan patients with reduced ventricular function.[8] The current study focused on echocardiographic analyses, and clinical stratification of patients as SVFrEF or SVFpEF correlated with significant differences in multiple systolic function parameters. Moreover, an early improvement in FAC was only observed in SVFrEF patients, supporting the notion that SGLT2i may be of particular benefit in patients with reduced systolic ventricular function in the context of single ventricle circulatory failure.

Although systolic dysfunction is the most prevalent cause of single ventricle circulatory failure, the chronic state of hemodynamic stress in the single ventricle population does not always lead to contractile dysfunction, and it is imperative to recognize that a dichotomous categorization of single ventricle circulatory failure is an oversimplification.[22-24] Moreover, the observed discordance between GLS, FAC, and visual function assessment in some patients highlights the complexity of categorizing ventricular dysfunction. *Van Puyvelde et al*. identified five distinct and often co-existing mechanisms of Fontan failure: systolic ventricular dysfunction, AVV regurgitation, high pulmonary vascular resistance, restrictive physiology, and pathway obstruction.[23] Due to the lack of availability of invasive hemodynamic data and limited sample size, it was not possible to evaluate the changes after starting SGLT2i for each of these etiologies in the current cohort. Future research should aim to assess the treatment response in these different phenotypes, as SGLT2i might have deleterious effects on cardiac output in single ventricle circulation patients who are particularly preload-dependent, such as those with obstruction or high pulmonary vascular resistance physiologies.[10]

TTE in single ventricle patients

Imaging of single ventricle patients is challenging. Due to the heterogeneity in ventricular

geometry and individual anatomy, the imaging protocol for Fontan patients proposed by the International Society of Adult Congenital Heart Disease (ISACHD) used as reference for this study regards FAC as the most reliable marker of systolic function, as it makes no assumptions about ventricular geometry.[19] Additionally, FAC has been shown to correlate well with invasive pressure-volume loop indices of systolic function.[25] While the ISACHD protocol does not discuss the value of strain analysis, IVA is mentioned as a potentially interesting parameter that does not rely on ventricular geometry. However, no robust correlation between IVA and invasive pressure-volume loops could be established.[19,25] Moreover, there appear to be only two other studies that evaluated IVA in the single ventricle population.[26,27] So, while an overall improvement in IVA was observed after starting SGLT2i, and it appears to be an appealing geometry- and load-independent surrogate of myocardial contraction, better validation of IVA is required in the single ventricle population. The value of more conventional echocardiographic systolic function parameters (including strain) as independent predictors of adverse clinical outcomes has been demonstrated, and TTE remains a valuable tool for monitoring longitudinal changes in ventricular function in this cohort.[21,28]

SGLT2i in the single ventricle population

To our knowledge, there have been four studies specifically focusing on the use of SGLT2i in single ventricle/Fontan circulation patients. The first case series published in 2022 by *Muneuchi et al*. included 5 adult Fontan patients who all experienced increased urinary output and reduced edema and/or pleural effusion. No echocardiographic data was evaluated.[7] This was followed by the work of *Konduri et al.*, predominantly including pediatric Fontan patients. No formal analysis of the echocardiographic changes was performed, but improvements in global echocardiographic ventricular systolic function were observed in 3 out of 9 patients with sequential measurements available, suggesting that reverse remodeling may be possible.[8] *Skorek et al*. included 17 adult Fontan patients and found a significant improvement in VO_2 max after starting SGLT2i. They did not observe improvements in S', TAPSE/MAPSE, E/A ratio, E/e' ratio, or NT-proBNP. Finally, *Gaydos et al*. recently published a cohort of 25 Fontan patients on SGLT2i, and again found no significant changes in ventricular function.[10] The last two studies both had a mean follow-up of around 11 months and comparisons were only made from baseline to the last follow-up. Our study included a more comprehensive systolic function assessment with repeated assessments per patient and observed significant improvements already in the first 100 days. This could indicate that any beneficial effects of SGLT2i on systolic ventricular function occur early after treatment initiation, which could not be captured by the previous studies.
All four studies concluded that SGLT2i therapy was well-tolerated in the single ventricle population, with cautious signs of beneficial effects.[7–10] These findings are congruent with

the first results from the ACHIEVE-SGLT2i registry published in 2024, demonstrating that SGLT2i were safe and well-tolerated in 174 adults with congenital heart disease, of which 12 with single ventricle physiology.[11] Apart from survival analysis showing no differences in the freedom from heart failure hospitalization between systemic ventricular morphology subgroups, no echocardiographic data on the single ventricle cohort was reported in that study.[11]

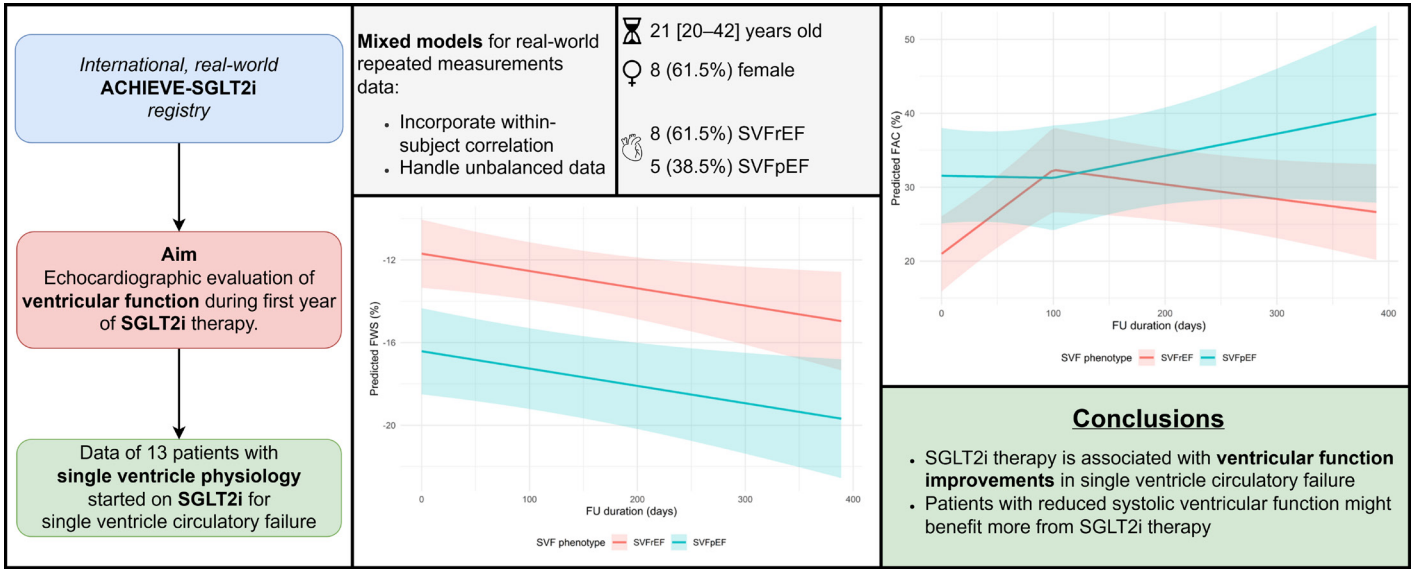
Limitations

This real-world multicenter study is inherently limited by the retrospective design, lack of a control group, and small population size, which reflects the rarity of this type of circulatory failure. The aim was to provide a comprehensive evaluation of longitudinal echocardiographic changes in ventricular function after initiating SGLT2i therapy. Additional statistical analysis of clinical outcome and biomarker data (including natriuretic peptides) was precluded by a paucity of available data. Future research should prioritize correlating biomarkers and imaging data with clinical events to elucidate the potential benefits and mechanisms of action of SGLT2i in single ventricle circulatory failure. Echocardiographic imaging remains challenging in this heterogeneous population. Although high reproducibility of echocardiographic strain and volume measurements has previously been reported in the single ventricle population, intra- or inter-observer variability assessment was not performed in this study.[28,29] Nonetheless, the current study contributes valuable insights to the existing literature by incorporating detailed echocardiographic analysis of sequential TTEs. Mixed models were utilized to correct for individual-level variability, allow the inclusion of unbalanced data with variable follow-up intervals, and provide much-needed evidence for the growing population of single ventricle physiology patients suffering from heart failure.

Conclusions

This study reassuringly demonstrates that SGLT2i therapy is associated with echocardiographic improvements in patients with single ventricle circulatory failure. This includes significant improvements in FWS and basal lateral segmental strain in the first year of treatment, a significant decrease in end-systolic area, and a significant improvement in IVA in both SVFrEF and SVFpEF patients. The observed improvement in FAC specifically in SVFrEF patients suggests that there may be differential responses to SGLT2i therapy between different single ventricle circulatory failure phenotypes. These findings add to the growing evidence for using SGLT2i in single ventricle circulatory failure. Nonetheless, larger comparative studies are imperative to evaluate the response to SGLT2i between different single ventricle circulatory failure phenotypes, study the long-term clinical outcomes, and elucidate the prognostic role of SGLT2i in this complex patient population.

Graphical abstract



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DEVICE INTERVENTIONS FOR ACHD-RELATED HF

PART 2

8

Contemporary Management Strategies of Baffle Leaks in Adults with a Failing Systemic Right Ventricle Late after Atrial Switch: A Case Series and Literature Overview

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Abstract

Baffle leaks are a frequently encountered and often overlooked complication after the atrial switch procedure for transposition of the great arteries. Baffle leaks are present in up to 50% of non-selected patients, and while they initially may not cause clear symptoms, they can complicate the hemodynamic course and influence the prognosis in this complex patient group. A shunt from the pulmonary venous atrium (PVA) to the systemic venous atrium (SVA) can lead to pulmonary overflow and subpulmonary left ventricular (LV) volume overload, while a shunt from the SVA to the PVA can result in (exercise-associated) cyanosis and paradoxical embolism. We report three cases of baffle leaks in patients with systemic right ventricular (sRV) failure late after the atrial switch procedure. Two symptomatic patients who presented with exercise-associated cyanosis due to SVA to PVA shunting over the baffle leak underwent successful percutaneous baffle leak closure with a septal occluder device. One patient with overt sRV failure and signs of subpulmonary LV volume overload due to PVA to SVA shunting was managed conservatively, as baffle leak closure was expected to lead to an increase in sRV end-diastolic pressure and aggravation of sRV dysfunction. These three cases illustrate the considerations made, challenges faced, and necessity of a patient-tailored approach when addressing baffle leaks.

Introduction

Transposition of the great arteries (TGA) is the second most common cyanotic congenital heart defect after Tetralogy of Fallot and affects 2 to 3 out of every 10,000 live births.[1] TGA is characterized by atrioventricular concordance and ventriculo-arterial discordance; the aorta is positioned above the right ventricle (RV) and the pulmonary artery above the left ventricle (LV). In the modern era, TGA is typically managed with the arterial switch procedure to correct the ventriculo-arterial discordance. However, until around the 1980s, patients with TGA underwent the atrial switch procedure according to Mustard or Senning.[2,3] This procedure involves rerouting the systemic and pulmonary venous returns via intra-atrial baffles, resulting in a systemic right ventricle (sRV) that supplies the systemic circulation and a subpulmonary LV that supplies the pulmonary circulation.

The morphological and functional characteristics of the sRV, which are not equipped to chronically sustain the pressure of the systemic circulation, lead to a range of long-term complications. Over 50% of patients with TGA who underwent the atrial switch procedure develop symptomatic heart failure by the age of 45 years, and their 40-year survival rate varies from 82 to 90%.[4,5] While heart failure and arrhythmias are well-known late sequelae after the atrial switch operation, baffle-associated complications, such as baffle leaks and stenosis, are frequently overlooked. Baffle leaks are reported in up to 50% of non-selected and asymptomatic patients late after the atrial switch procedure.[6] Although these leaks may not directly cause symptoms, they can complicate the hemodynamic course of this complex patient group. 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 subpulmonary (left) ventricular volume overload and pulmonary overflow, while a right-to-left shunt (from the SVA to the PVA) can result in cyanosis and paradoxical embolism.

The diagnosis of baffle leaks can be challenging due to the low sensitivity of transthoracic echocardiography, and might necessitate contrast echocardiography, cardiac magnetic resonance imaging (MRI), computed tomography (CT), and/or exercise testing.[7,8] The 2020 adult congenital heart disease (ACHD) guidelines of the European Society of Cardiology (ESC) recommend the closure of baffle leaks in symptomatic patients and in patients with a suspicion of paradoxical emboli (class I recommendation). Closure should be considered in asymptomatic patients with substantial ventricular volume overload (class IIa recommendation).[7] Nonetheless, the benefits of intervention remain unclear as there is a discrepancy between a high prevalence of baffle leaks and a low prevalence of associated symptoms and related clinical deterioration.[9]

This case series presents three cases of adult TGA patients with reduced systolic sRV function and baffle leaks late after the atrial switch procedure, illustrating the patient-tailored approach to the management of baffle leaks in the modern era.

Case descriptions

Patient A

A 53-year-old woman born with TGA who underwent atrial correction according to Mustard at the age of 3 years was reviewed in the outpatient clinic due to sRV failure. She had a rate adaptive atrial (AAI-R) pacemaker implanted at the age of 29 due to sick sinus syndrome, which was upgraded to a primary prevention dual chamber implantable cardioverter-defibrillator (DDD-ICD) at the age of 45. She had a history of an ambulant, uncomplicated COVID-19 infection two years ago and has since been checking her peripheral oxygen saturations (SpO_2) at home. The patient now reports that SpO_2 drops to 87% at ambient air during daily activities.

She was in New York Heart Association (NYHA) functional class III despite pharmacological treatment with a beta-blocker, an angiotensin receptor-neprilysin inhibitor (ARNI), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i). Bicycle exercise ergometry revealed an exercise capacity of 100 watts (95% of what was predicted) with a VO_2 max of 19.5 mL/min/kg (66% of what was predicted) with progressive decline in SpO_2 to 77% at maximal effort. Her SpO_2 in ambient air was 97% at rest, and she was euvolemic. Transthoracic echocardiography (TTE) showed a poor systolic function of the dilated sRV and trivial tricuspid regurgitation. The function of the subpulmonary LV was normal (*Figure 1A,B*). Subsequent agitated saline contrast echocardiography showed a significant interatrial shunt from the SVA to the PVA (right-to-left) during Valsalva, and additional color Doppler examination confirmed the presence of a leak in the interatrial baffle (*Figure 1C*). Invasive hemodynamic evaluation showed mildly elevated pulmonary artery pressures (PAP) (26/18 mmHg, mean PAP 21 mmHg) and elevated sRV end-diastolic pressures (114/8-19 mmHg). The subpulmonary LV pressures were 40/1-9 mmHg, and no significant LV outflow tract gradient or baffle obstruction was present. A PVA to SVA shunt was present at rest (Qp:Qs 1:2.3), and an SVA to PVA shunt physiology with significant desaturation occurred during exercise as mimicked by the Valsalva maneuver in the catheterization laboratory. The patient was discussed with the heart team. Given the severity of symptomatic exercise-induced hypoxemia and the lack of PVA to SVA shunting during exercise—preventing dynamic 'pressure relief' for the sRV despite elevated sRV end-diastolic pressures at rest—it was decided to close the baffle leak percutaneously.

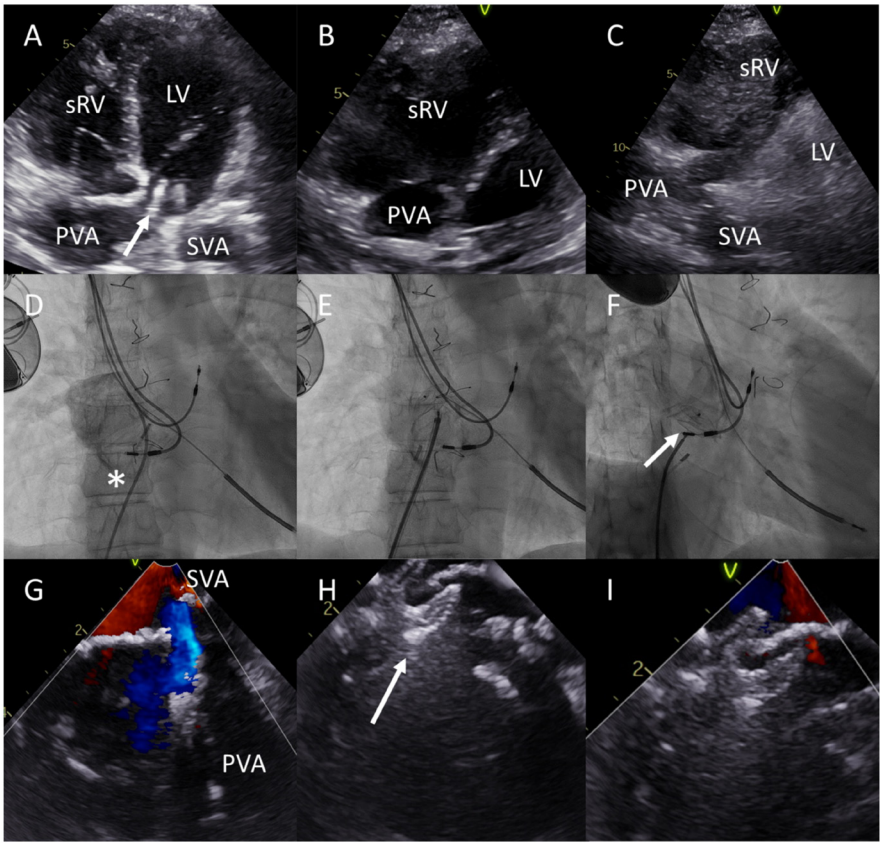

Figure 1. Baffle leak visualisation and closure in patient A

(**A**,**B**) Apical four chamber and subcostal views, respectively show the atrial baffle (arrow) that directs blood from the systemic venous atrium (SVA) to the subpulmonary left ventricle (LV) and from the pulmonary venous atrium (PVA) to the dilated systemic right ventricle (sRV). (**C**) Agitated saline contrast echocardiography confirms significant interatrial shunting from the SVA to the PVA during Valsalva, with bubbles filling the sRV cavity within 3 heart beats. (**D**–**F**) Anterior-posterior (**D**,**E**) and right inferior oblique (**F**) fluoroscopy projections during intracardiac echocardiography (ICE, probe indicated with an asterisk (*) in (**D**)) guided closure of the baffle leak with a 10 mm Amplatzer Septal Occluder (arrow in **F**). Note the two atrial pacing wires and an implantable cardioverter-defibrillator (ICD) lead in the LV. (**G**–**I**) ICE imaging during closure of the baffle leak. Note the shunting from the SVA to the PVA during Valsalva through the baffle defect (**G**), the discs of the Amplatzer Septal Occluder in situ (**H**, arrow) and the alleviation of the interatrial shunt (**I**).

The patient underwent a successful baffle leak closure with a 10 mm Amplatzer Septal Occluder (Abbott, Chicago, IL, USA). The procedure was performed using left femoral access under local anesthesia with fluoroscopic and intracardiac echocardiography (ICE) guidance (*Figure 1D–I*). No residual shunt could be detected using ICE at the end of the procedure. At 3 months follow-up, no residual shunt could be visualized on TTE, and the patient showed no desaturations below 95% at ambient air during bicycle exercise ergometry with a stable exercise capacity.

Patient B

A 47-year-old woman with TGA late after the atrial switch procedure according to Senning, was analyzed in the outpatient clinic due to progressive dyspnea and decreased exercise tolerance over the past year. She had a history of concomitant pulmonary valve commissurotomy, resection of an infundibular pulmonary stenosis, and ventricular septal defect (VSD) closure at the age of two years. She had two uncomplicated pregnancies at the ages of 23 and 24, respectively. A third pregnancy at the age of 26 years was terminated during the first semester due to a decline in clinical condition and persistent hypertension. In the following decades, as the sRV progressively deteriorated to a moderately reduced systolic function, she underwent a total of five atrial tachycardia ablation procedures, and a dual chamber (DDD) pacemaker was implanted due to sick sinus syndrome (with two atrial leads to enable atrial antitachycardia pacing).

Upon presentation, she was in NYHA functional class III. Pharmacological treatment included a beta-blocker, an ARNI, a mineralocorticoid receptor antagonist, a loop diuretic, amiodarone, and a vitamin K antagonist. Bicycle exercise ergometry revealed a reduced exercise capacity of 80 watts (61% of what was predicted) and a VO_2 max of 12.5 mL/min/kg (48% of what was predicted). SpO_2 decreased from 93% at ambient air at rest to 84% at maximal effort. TTE showed a stable, moderately reduced function of the sRV, trivial tricuspid regurgitation, and preserved function of the subpulmonary LV. Suspicion of a baffle leak was raised by the apical four chamber view, which revealed systolic flow from the SVA to the PVA (right-to-left) at rest (*Figure 2A,B*). Significant interatrial shunting was further confirmed by agitated saline contrast echocardiography (*Figure 2C*). The contrast echocardiography was complicated by an air embolic transient ischemic attack, from which the patient, luckily, fully recovered. Computed tomography (CT) imaging confirmed the presence of a baffle leak of approximately 10–12 mm in diameter and showed no significant calcifications in proximity to the leak (*Figure 2D*). An invasive hemodynamic evaluation in euvolemia showed normal PAP (17/2 mmHg, mean PAP 7 mmHg), a wedge pressure of 4 mmHg, low sRV end-diastolic pressures (81/2–5 mmHg), and excluded any significant baffle

obstruction with low gradients in the venous returns. The subpulmonary LV pressures were 30/2–4 mmHg, and no significant LV outflow tract gradient was present. The patient was discussed with the heart team; percutaneous device closure was deemed technically feasible, and recommended given the symptomatic exercise-exacerbated hypoxemia due to SVA to PVA shunting through the baffle leak.

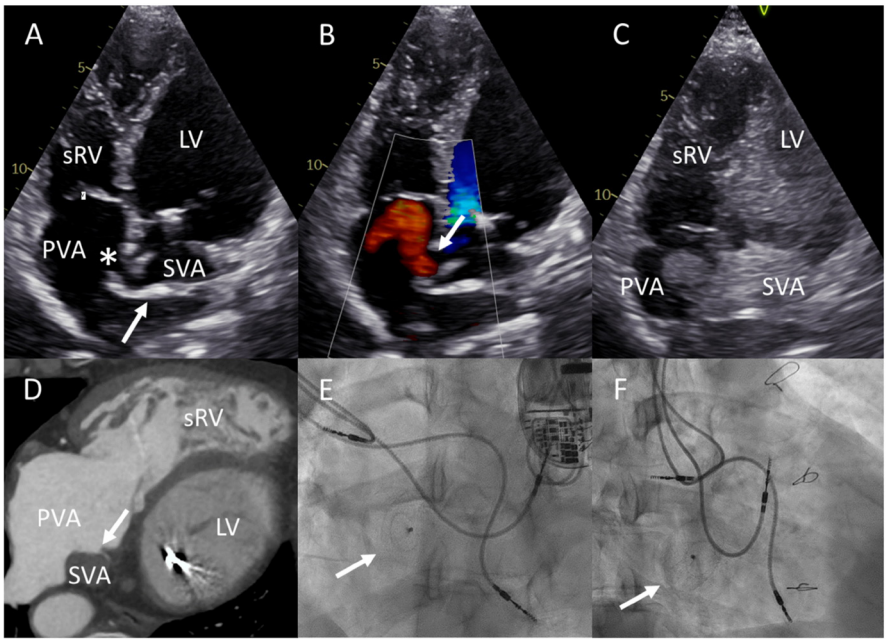

Figure 2. Baffle leak visualization and closure in patient B
(**A**) Apical four chamber view shows that the atrial baffle (arrow) directs systemic venous return atrium (SVA) to the subpulmonary left ventricle (LV) and the pulmonary venous return atrium (PVA) to the systemic right ventricle (sRV). The baffle leak is indicated by an asterisk (*). (**B**) Color Doppler apical four chamber view demonstrates SVA to PVA shunting through the baffle leak. (**C**) Significant interatrial shunting confirmed by agitated saline contrast echocardiography. Note the contrast opacification of the SVA and subpulmonary LV, and the jet crossing the baffle leak into the PVA. (**D**) Axial slice through a computed tomography scan at the level of the atria shows the baffle leak (arrow). (**E,F**) Left anterior oblique and right superior oblique fluoroscopy projections, respectively show the Occlutech Figulla Flex II Atrial Septal Defect (ASD) Occluder (arrow) projecting over the interatrial baffle. Note the presence of one ventricular (LV) and two atrial (SVA) pacemaker leads.

Patient C

A 60-year-old woman with TGA with VSD, secundum ASD, mild infundibular pulmonary stenosis, partial anomalous pulmonary venous drainage, and a persistent left superior vena cava was evaluated in the outpatient clinic due to progressive sRV failure. She underwent the

atrial switch procedure according to Mustard with VSD closure at 11 years of age, followed by surgical closure of a baffle leak at 30 years of age, and combined tricuspid valve restrictive annuloplasty with a second surgical baffle leak closure at 43 years of age. She had a history of paroxysmal supraventricular tachycardias, for which she had undergone two catheter ablation procedures. A DDD-pacemaker was implanted due to sick sinus syndrome. The system was later upgraded to a transvenous DDD-ICD due to symptomatic episodes of ventricular tachycardia, and she required chronic ventricular pacing due to symptomatic atrioventricular conduction block and bradycardia-induced (non-sustained) polymorphic ventricular tachycardia. At the age of 57 years (three years prior to the current evaluation), the patient was diagnosed with a cardiobacterium hominis endocarditis involving a small, hemodynamically not significant baffle leak and the pacemaker leads (*Figure 3A,B*). Her perioperative risk was deemed too high for surgical intervention, and given the good response to antibiotic therapy, she was initiated on long-term suppression therapy.

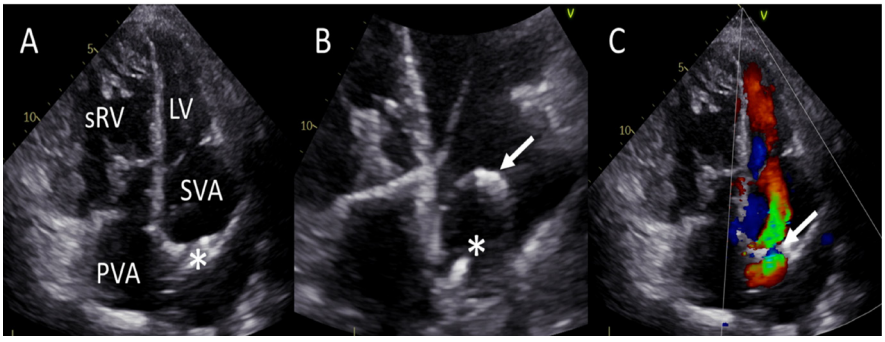

Figure 3. Baffle leak visualization in patient C
(**A**) Apical four chamber view shows the systemic venous return atrium (SVA), left ventricle (LV), the dilated and hypertrophied systemic right ventricle (sRV), and the pulmonary venous atrium (PVA). There is a suspicion of a baffle defect (asterisk (*) in (**A**)). (**B**) A small mobile structure suspicious of a vegetation (asterisk (*) in (**B**)) can be seen on the SVA side of the baffle defect. Note the atrial lead (arrow). (**C**) Color flow Doppler apical four chamber view demonstrates a PVA to SVA shunt over the baffle defect (arrow).

She was now in NYHA functional class II-III despite pharmacological treatment with a beta-blocker, an ARNI, a SGLT2i, a loop diuretic, and a vitamin K antagonist. Bicycle exercise ergometry revealed a reduced exercise capacity of 50 watts (51% of what was predicted) and a VO_2 max of 8.7 mL/min/kg (36% of what was predicted). SpO_2 remained above 95% during exercise. TTE showed a dilated sRV with moderately to severely reduced systolic function, signs of dyssynchrony, and mild tricuspid regurgitation. The subpulmonary LV had preserved systolic function but was dilated. During diastole, there was a septal shift towards the sRV, consistent with volume overload of the subpulmonary LV. TTE also

demonstrated the presence of a hemodynamically significant baffle leak with a PVA to SVA (left-to-right) shunt causing volume overload of the subpulmonary LV and contributing to the LV dilatation (*Figure 3C*).

The case was discussed in the heart team. The PVA to SVA flow over the baffle leak was deemed to have an unloading effect due to the elevated sRV end-diastolic pressure. A closure of the leak was therefore expected to increase the sRV pressures and potentially aggravate systolic sRV dysfunction. Combined with the lack of cyanosis, closure of the baffle leak at this point was therefore deferred, and it was decided to first attempt to optimize the systolic sRV function. Given the pacing-induced sRV dyssynchrony observed under chronic subpulmonary LV pacing, the patient was considered to be a good candidate for epicardial sRV lead placement and cardiac resynchronization therapy.

Discussion

In this case series, we describe the clinical considerations and contemporary management strategies for baffle leaks in adult patients with TGA late after the atrial switch procedure. The first two cases suffered from progressive sRV failure and exercise-associated cyanosis due to SVA to PVA shunting upon exertion. The baffle leaks were successfully closed through catheter intervention, eliminating the exercise-associated hypoxemia. The third patient had progressive sRV failure without significant cyanosis, yet with a PVA to SVA shunt that resulted in a volume overload of the subpulmonary LV, while "unloading" the failing sRV. The baffle leak closure was deferred, and the initial management strategy focused on optimizing the sRV function. These three cases illustrate the considerations made and challenges faced when choosing the optimal management strategy for an individual patient with a baffle leak.

Prevalence and diagnosis of baffle leaks

Baffle leaks are a common complication late after the atrial switch procedure, and they are present in up to 50% of non-selected and asymptomatic patients.[6] As a significant proportion of TGA patients suffer from heart failure late after the atrial switch procedure,[4] it can be difficult to suspect a baffle leak based on symptoms alone.

The ESC and American Heart Association (AHA) ACHD guidelines state that baffle leaks can be best diagnosed routinely with (contrast) echocardiography. Transesophageal echocardiography, cardiopulmonary exercise test, and/or cardiac MRI have an additive role in the diagnosis and evaluation of baffle leaks.[7,8] In a large study investigating the prevalence of baffle leaks, only 8 out of 65 patients had a clinical suspicion prior to diagnosis. Moreover,

color Doppler TTE could only accurately identify the baffle leak in 2 out of 65 patients,[6] illustrating the challenges of shunt identification on routine TTE.

In the first two cases, a clinical suspicion of a baffle leak was present prior to diagnosis. Self-registered desaturation, objectified using an in-hospital bicycle exercise ergometry (exercise-associated cyanosis), played an important role in identifying the hemodynamic consequences of a baffle defect in a group of patients with a high a priori risk. Agitated saline contrast echocardiography and/or CT were used to confirm the diagnosis in our patients. While generally considered a safe procedure, patient B suffered from a transient ischemic attack directly after contrast echocardiography due to cerebral embolization of air bubble contrast. Transient visual disturbances have previously been described after agitated saline contrast echocardiography for baffle leak diagnosis.[6]

Cardiac MRI can provide more reliable and robust quantification of the interatrial shunt magnitude than echocardiography, although small shunts can easily be missed.[7,9] Nevertheless, it is often not feasible in the atrial switch TGA population due to a high prevalence of non-compatible cardiac implantable electronic devices and epicardial and/or abandoned leads.[10] For these reasons, a cardiac MRI could not be performed in any of the three cases described.

Although, to the best of our knowledge, no data has been published on exercise catheterization of TGA patients with baffle defects, exercise hemodynamics have been described as being of incremental value in understanding functional limitations in patients with a Fontan circulation.[11] Right heart catheterization during exercise may therefore better reflect on the exercise-associated complaints of the TGA patients with a failing sRV and a baffle leak and provide insight into the dynamic pathophysiological changes that take place at exertion. Although at present not standard practice in the majority of centers, performing a right heart catheterization during exercise is likely to facilitate our understanding of shunting in the context of a baffle leak and heart failure, possibly unmasking a leak at an earlier stage and guiding patient-tailored treatment.

Patients A and C underwent the atrial switch procedure according to Mustard, and patient B according to Senning. A trend towards fewer baffle leaks after the Mustard compared with the Senning procedure has previously been described.[12] As baffle leaks generally occur along the extensive suture lines surrounding the atrial baffle, one can hypothesize that this difference might be attributed to less tension on the suture lines after the Mustard technique, as a larger amount of synthetic or pericardial material is used to create the baffle.

Management of baffle leaks

The current AHA ACHD guidelines are less explicit in giving direct recommendations for the management of baffle leaks than the ESC guidelines.[7,8] Judging the management of the three cases in light of the ESC guidelines, cases A and B were symptomatic patients with cyanosis during exercise and therefore had a class I indication for percutaneous baffle leak closure (level of evidence: C).[7] Case C presented a challenging dilemma of closure versus conservative management. This patient presented with progressive sRV dysfunction but without specific symptoms related to her long-existing baffle leak. Eventually, dilatation of the subpulmonary LV developed due to PVA to SVA shunting, and thus percutaneous closure should be considered if feasible according to the ESC guidelines (class IIa indication, level of evidence: C).[7]

The decision was made to manage the baffle leak conservatively in this patient, as we expected closure to lead to further elevation of sRV end-diastolic pressures and aggravation of sRV dysfunction. A potentially positive effect of a baffle leak with "ASD-like physiology" has been described in the literature. By placing a volume load on the subpulmonary LV through the PVA to SVA shunt, the interventricular septum is splinted and might support the sRV function in a manner similar to retraining the LV with a pulmonary artery band or in cases with left ventricular outflow tract obstruction/pulmonary stenosis.[13] Nevertheless, this does not seem to apply to our patient C, as there we observed a diastolic septum shift towards the sRV and a systolic shift towards the subpulmonary LV. This could actually negatively influence the sRV instead of supporting it and seems to be caused by volume-overload with a lack of pressure-overload in the subpulmonary LV.

The ESC guidelines also suggest covered stents as an option for percutaneous baffle leak closure.[7] The use of covered stents has predominantly been described for the treatment of concomitant baffle leaks and stenosis.[6,10,14] In a previous study, isolated baffle leaks were present in the minority of patients with baffle complications (17%), and a combination of occluders and/or covered stents was used to close the leaks without any major adverse events.[15] There are to date no publications comparing the two techniques, and a patient-specific, anatomy-tailored approach is essential. In our cases, no covered stents were used to avoid "jailing" of the pacing leads.

While historically baffle complications were managed surgically, perioperative mortality for surgical baffle revision after the atrial switch procedure has been reported in up to 36% of cases.[16] Percutaneous interventions are the preferred option in these adult patients, given the usually high perioperative risk due to previous thoracotomies, extensive adhesions, and concomitant heart failure.

Conclusions

Baffle leaks are present in up to 50% of non-selected patients late after the atrial switch procedure, and while they initially may not cause clear symptoms, their existence can complicate the hemodynamic course and influence the prognosis in this complex patient group. Inherent to the nature of this case series, no conclusions can be drawn to advise specific treatment strategies for patients with a baffle leak. Nonetheless, this case series demonstrates the clinical considerations in an individual, patient-tailored approach when assessing baffle leak hemodynamics in the context of sRV failure. It illustrates the feasibility of a catheter interventional management strategy using septal occluder devices for successfully alleviating exercise-associated cyanosis. Moreover, it highlights the complexity of choosing a treatment strategy in "relatively" asymptomatic patients with signs of ventricular volume overload due to PVA to SVA shunting. Although intervention should be considered in these patients, this may not always be the best option. A clear evidence-based approach is currently missing to make these challenging treatment decisions. Future research should focus on defining more robust criteria for baffle leak closure and the optimal timing window, especially for seemingly asymptomatic patients.

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9

Real-World Data on the Effects of Cardiac Resynchronization Therapy in Adults with Congenital Heart Disease

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Abstract

Background

Cardiac resynchronization therapy (CRT) is well-established in acquired heart failure, but evidence in adults with congenital heart disease (ACHD) remains limited. Current guidelines, extrapolated from non-congenital populations, may not fully address the anatomical and electrophysiological complexities in ACHD. This study aimed to evaluate the safety and efficacy of CRT in ACHD, focusing on changes in QRS duration, systemic ventricular function (SVF), and New York Heart Association (NYHA) class.

Methods

A retrospective multicenter cohort study was conducted across two tertiary ACHD centers. ACHD patients who underwent CRT implantation between 2014 and 2024 were included. Primary outcomes were QRS duration, SVF, and NYHA class at 3, 6, and 12 months post-implantation, and peri-procedural clinical and device-related outcomes were assessed. Mixed models were used to analyze longitudinal changes, adjusting for de novo vs. upgrade CRT implantation, left bundle branch block (LBBB) vs. non-LBBB QRS morphology, and systemic left vs. right ventricle (sRV) anatomy.

Results

101 patients were included. The mean age was 53±14 year, 41 (40.6%) were female and 48 (47.5%) underwent an upgrade procedure to CRT. Twenty-two patients (21.8%) had mild, 57 (56.4%) moderate, and 22 (21.8%) severe congenital heart disease, and 16 (15.8%) had a sRV. Six patients (5.9%) experienced a procedure-related complication requiring revision (6.6 per 100 patient-years follow-up), and one patient (1.0%) died from end-stage heart failure in the year after CRT implantation. CRT was associated with significant improvements in QRS duration, SVF, and NYHA class at 3, 6, and 12 months ($p<0.05$ for all). QRS reduction was more pronounced after upgrade procedures. Improvements in QRS, SVF, and NYHA class extended to patients with a sRV and with non-LBBB QRS morphology. At one year follow-up, 68 patients (72.3%) showed improvement of at least 1 class of NYHA and/or SVF.

Conclusion

This study supports CRT as a safe and effective therapy in ACHD patients, including those with sRV or non-LBBB QRS morphology, emphasizing the need for individualized decision-making beyond standard guidelines.

Introduction

Over the past decades, the clinical practice of congenital heart disease has shifted from childhood mortality towards chronic morbidity in adulthood. As a result, the adult congenital heart disease (ACHD) population is increasing, with more long-term complications, of which heart failure (HF) is now the leading cause of morbidity and mortality.[1] Despite this growing clinical burden, evidence for management strategies of ACHD-related HF is still limited. Therefore, current recommendations are largely extrapolated from studies in HF patients with acquired heart disease.[1]

Cardiac resynchronization therapy (CRT) has been demonstrated to be effective in the treatment of electromechanical dyssynchrony in symptomatic HF patients without congenital heart disease, leading to functional improvement and a reduction in HF-associated morbidity and mortality.[2-4] For patients with ACHD with a systemic left ventricle (sLV), current guidelines recommend applying conventional CRT indications.[1, 5, 6] However, these are based on studies in patients with anatomically normal hearts. In ACHD, complex anatomies, surgically induced scar tissue, and associated lesions may influence CRT response.[5] Ill-defined indication criteria and doubts about efficacy of CRT in ACHD may lead to underuse, potentially resulting in suboptimal care for patients.[7]

Smaller studies have shown promising results for CRT in ACHD patients, although those patients have often not met the classical guideline-based criteria for CRT.[8-11] Moreover, heterogeneity in patient selection and the lack of a uniform definition of response complicate the interpretation of efficacy and limit comparability between studies.[12] To expand upon previous findings and contribute to closing the existing evidence gap, this multicenter study evaluates real-world data from the largest available cohort of ACHD patients treated with CRT to date. Specifically, the objectives of the study are to assess: (1) the anatomical and clinical characteristics of ACHD patients undergoing CRT implantation, (2) the peri-procedural clinical and device-related outcomes, and (3) the longitudinal changes in QRS duration, systemic ventricular function (SVF), and New York Heart Association (NYHA) functional class in the year after CRT implantation.

Methods

Study design and population

This retrospective multicenter cohort study included all consecutive ACHD patients who underwent CRT implantation between January 2014 and December 2024 in two European tertiary ACHD centers (Leiden University Medical Center (LUMC), Leiden, the Netherlands, and Barts Heart Centre, St Bartholomew's Hospital, London, United

Kingdom). Both de novo implantations and upgrade procedures to CRT were included. Exclusion criteria were age <18 years at the time of CRT implantation and patient objection to the use of retrospective data. The study was approved by the ethics committee of the LUMC (Medical Research Involving Human Subjects Act [WMO] committee division 1, protocol reference 2023-035). At Barts Heart Centre, the study was approved in accordance with local institutional policy. All tests and procedures were performed as part of standard clinical care, and the need for written informed consent was waived. The study was conducted in accordance with the ethical standards of the relevant institutional and national research committees and complied with the Declaration of Helsinki.

Data collection and follow-up

All data were retrieved from the electronic health records at the participating centers. Baseline parameters included patient demographics, past medical history, medication use, clinical parameters at implantation, NYHA functional class, laboratory parameters, 12-lead electrocardiography (ECG), and transthoracic echocardiographic data, where available. Cardiac implantable electronic device (CIED) procedural information was collected, as well as the initial indication for CRT. Follow-up visits were scheduled according to the local post-implantation protocols. For analysis purposes, follow-up assessments were categorized into three predefined time points: 3 (± 1) months, 6 (± 2) months, and 12 (± 4) months post-procedure. Follow-up evaluations conducted within these intervals were categorized accordingly. Follow-up events outside these intervals were excluded. If multiple evaluations occurred within the same interval, the one closest to the target time point was retained. Follow-up data included clinical and ECG parameters, transthoracic echocardiography assessment, CIED/lead parameters, and CIED-related complications. SVF classes were categorized as good, mildly reduced, moderately reduced, or severely reduced, in accordance with the established guidelines.[13] Quantification methods included Simpson's biplane or three-dimensional ejection fraction, global longitudinal strain, fractional area change (FAC) for systemic right ventricles (sRV), and global visual assessment. Data on HF events (urgent HF visits and HF hospitalizations), referral for left ventricular assist device implantation and/or heart transplantation, and mortality were also collected.

Statistical analysis

All statistical analyses were performed in SPSS version 25 (IBM Corp, Armonk, NY) and R Statistical Software (v4.4.2; R Core Team 2023). For the descriptive analysis, normally distributed continuous data were presented as mean ± standard deviation, skewed data as median [interquartile range], and categorical data as counts (percentages). Paired Student's t-tests were used for within-group comparisons of normally distributed continuous variables.

To evaluate longitudinal changes in QRS duration, SVF, and NYHA class at 3, 6, and 12 months following CRT implantation, mixed models were used because they account for the within-patient correlation of repeated measurements and appropriately handle unbalanced data. Mixed models allowed us to include all available data points, providing robust estimates of temporal trends even when not all patients had complete assessments at every time point. The Linear and Nonlinear Mixed Effects Models (nlme) package (v3.1.167; R Core Team 2024) was used to construct linear mixed models for the longitudinal changes in the continuous parameter QRS duration. Cumulative link mixed models were constructed for the ordinal parameter SVF class with the "ordinal" package (v2023.12.4.1; R Core Team 2024). The "lme4" package (v1.1.36; R Core Team 2024) was used to construct generalized linear mixed models for the binary parameter NYHA functional class (NYHA class I or II versus NYHA class >II). Results of the cumulative link mixed models were presented as the cumulative odds ratios for each follow-up time point compared to baseline, with a cumulative odds ratio <1 indicating an overall improvement in SVF class and a cumulative odds ratio >1 indicating a worsening. Results of the generalized linear mixed models were presented as odds ratios, with an odds ratio <1 indicating a lower odds of having NYHA class >II compared to baseline, and an odds ratio >1 indicating a higher odds of having an NYHA class >II. All data were included in the mixed models, including patients in NYHA class I and those with preserved SVF at baseline, who, by definition, could not demonstrate an improvement by definition but were at risk of deterioration.

The effects of the following three binary covariates were evaluated in each model: 1) de novo versus upgrade CRT procedure, 2) left bundle branch (LBBB) pattern versus non-LBBB pattern on 12-lead ECG at baseline, and 3) sLV versus sRV anatomy. Each covariate was first included with a time interaction to test if the covariate had a significant effect on the outcome of interest after CRT implantation. If this was not significant, the fixed effect was tested without interaction. If this was also not significant, the covariate was not included in the final model. Different correlation and variance structures were tested. Because model parsimony was prioritized over predictive capacity, model selection was primarily based on the Bayesian information criterion (BIC), with secondary consideration of the Akaike information criterion (AIC) or likelihood ratio tests where appropriate. The model fit was evaluated through residual analysis. Fixed effects were visualized with corresponding 95% confidence intervals for fixed-effect variance. A two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Overall, 101 ACHD patients underwent CRT implantation between 2014 and 2024. The mean age at implantation was 53 ± 14 years, and 41 (40.6%) were female. All patients had a biventricular circulation, and according to the current European Society of Cardiology classification of congenital heart disease, 22 (21.8%) had mild, 57 (56.4%) moderate, and 22 (21.8%) severe congenital heart disease.[14] The baseline characteristics are summarized in *Table 1*.

Table 1. Patient characteristics at baseline

Baseline Characteristics	**n=101**
Age (y)	53.2 ± 13.6
Body Mass Index (kg/m^2) (n=73)	25.8 [21.9–28.5]
Sex (female)	41 (40.6%)
Cardiac history	
Mild congenital complexity	22 (21.8%)
Aortic valve disease or BAV	9 (8.9%)
Repaired ASD, Sinus venosus defect, VSD or PDA	13 (12.9%)
Moderate congenital complexity	57 (56.4%)
Repaired TOF	15 (14.9%)
Congenital aortic stenosis (SAS/SVAS)	12 (11.9%)
Aortic coarctation	9 (8.9%)
ACAOS	4 (4.0%)
VSD with associated abnormalities or shunt	4 (4.0%)
AVSD (including primum ASD)	3 (3.0%)
Marfan syndrome (and related HTAD), Turner Syndrome	2 (2.0%)
Pulmonary stenosis	2 (2.0%)
TGA after arterial switch	2 (2.0%)
PAPVR/TAPVR	1 (1.0%)
ASD secundum type unrepaired	1 (1.0%)
Sinus venosus defect unrepaired	1 (1.0%)
Ebstein anomaly	1 (1.0%)
Severe congenital complexity	22 (21.8%)

Table 1. *Continued*

Baseline Characteristics	**n=101**
ccTGA	14 (13.9%)
CHD related to pulmonary vascular disease (incl. Eisenmenger syndrome)	4 (4.0%)
TGA after Mustard atrial switch procedure	2 (2.0%)
Double outlet ventricle	2 (2.0%)
Number of prior cardiac surgeries	1 [1.0 – 2.5]
Systemic left ventricle	85 (84.2%)
Systemic right ventricle	16 (15.8%)
Comorbidities	
Valvular heart disease	33 (32.7%)
Hypertension	26 (25.7%)
Hyperlipidemia	16 (15.8%)
Renal dysfunction (eGFR 30 mL/min/1.73m2)	16 (15.8%)
Coronary Artery Disease	14 (13.9%)
Cerebrovascular disease	12 (11.9%)
COPD	6 (5.9%)
Peripheral Artery Disease	4 (4.0%)
Electrocardiographic data (n=98)	
QRS (ms)	179 ± 39
Narrow QRS (< 120 ms)	5 (5.1%)
Broad QRS (≥ 120 ms)	93 (94.9%)
LBBB pattern	33 (33.7%)
RBBB pattern	16 (16.3%)
Ventricular pacing	37 (37.8%)
Ventricular escape rhythm	7 (7.1%)
Types of rhythms	
Pre-CRT subpulmonary ventricular pacing	37 (37.8%)
Sinus rhythm	33 (33.7%)
Pre-CRT atrial pacing	22 (22.4%)
AT/AF or atrial flutter	25 (25.5%)
Ventricular escape rhythm	7 (7.1%)

Table 1. *Continued*

Baseline Characteristics	**n=101**
NYHA functional class (n=94)	
I – II	48 (51.1%)
> II	46 (48.9%)
Echocardiography	
Systemic ventricle ejection fraction biplane (%) (n=65)	31.4 ± 10.6
Systemic ventricle function class (%) (n=96)	
Good	4 (4.2%)
Mildly reduced	13 (13.5%)
Moderately reduced	44 (45.8%)
Severely reduced	35 (36.5%)
SAVV regurgitation class (%) (n=86)	
I	32 (37.2%)
II	32 (37.2%)
III	15 (17.4%)
VI	7 (8.1%)
Heart failure medication	
ACEi/ARNI/ARB	77 (76.2%)
Diuretics	56 (55.4%)
MRA	43 (42.6%)
Beta-blockers	76 (75.2%)
SGLT2i	10 (9.9%)

Proportions are presented as n (%). Values as mean ± standard deviation or median [interquartile range], as appropriate. Data were available for all 101 patients unless otherwise specified. AAOCA (Anomalous Aortic Origin of a Coronary Artery), *ACAOS (Anomalous Coronary Artery from the Opposite Sinus), ACEI (Angiotensin-Converting Enzyme Inhibitor), ARB (Angiotensin Receptor Blocker), ARNI (Angiotensin Receptor-Neprilysin Inhibitor), ASD (Atrial Septal Defect), ASD-I (Atrial Septal Defect Type I); ASD-II (Atrial Septal Defect Type II), AT/AF (atrial tachycardia/atrial fibrillation), AOS (Aortic Stenosis), AVSD (Atrioventricular Septal Defect), BAV (Bicuspid Aortic Valve), ccTGA (Congenitally Corrected Transposition of the Great Arteries), COPD (Chronic Obstructive Pulmonary Disease), CRT (Cardiac Resynchronization Therapy), TGA (Transposition of the Great Arteries), DORV (Double Outlet Right Ventricle), eGFR (Estimated Glomerular Filtration Rate), HTAD (Heritable Thoracic Aortic Disease), LBBB (Left Bundle Branch Block), MRA (Mineralocorticoid Receptor Antagonist), NYHA (New York Heart Association), PAPVR (Partial Anomalous Pulmonary Venous Return), PDA (Patent Ductus Arteriosus), PFO (Patent Foramen Ovale), RBBB (Right Bundle Branch Block), SAS (Subaortic Stenosis), SAVV (Systemic Atrioventricular Valve), SGLT2i (Sodium-Glucose Cotransporter 2 Inhibitor), SVAS (Supravalvular Aortic Stenosis), TAPVR (Total Anomalous Pulmonary Venous Return), TOF (Tetralogy of Fallot), VSD (Ventricular Septal Defect)*

The most common diagnoses were systemic right ventricle (sRV) in 16 patients (15.8%), including 14 with congenitally corrected transposition of the great arteries (ccTGA, 13.9%) and 2 with transposition of the great arteries (TGA) after a Mustard atrial switch procedure (2.0%), and tetralogy of Fallot (n=15, 14.9%).

At baseline, 33 patients (33.7%) were in sinus rhythm and 25 (25.5%) in atrial tachycardia/atrial fibrillation or flutter. The mean QRS duration on 12-lead surface ECG was 179 ± 39 ms; LBBB pattern was present in 33 patients (33.7%) while right bundle branch block (RBBB) pattern in 16 (16.3%). Thirty-seven patients (37.8%) had subpulmonary ventricular pacing and seven patients (7.1%) had underlying complete heart block with a broad ventricular escape rhythm. Five patients (5.1%) had a narrow QRS complex, which included 3 cases of post-operative complete heart block in whom a CRT was implanted directly in anticipation of a high percentage of ventricular pacing, and 2 cases with atrial fibrillation planned for a pace-and-ablate strategy. Among the 14 patients with ccTGA, 3 exhibited a LBBB pattern on 12-lead surface ECG, 1 had a RBBB pattern, 9 had subpulmonary ventricular pacing, and baseline ECG was unavailable for 1 patient. Of the 2 patients with TGA after atrial switch, one had subpulmonary ventricular pacing at baseline, while the other demonstrated an RBBB pattern on 12-lead surface ECG.

In the complete cohort, SVF was good in 4 (4.2%), mildly reduced in 13 (13.5%), moderately reduced in 44 (45.8%), and severely reduced in 35 patients (36.5%). Forty-six patients (48.9%) were in NYHA functional class > II at CRT implantation.

Indication for device implantation/upgrade

Device-related data are presented in *Table 2*. Nearly half of the patients (n=48, 47.5%) had a pre-existing pacing system and underwent an upgrade to CRT. Most patients (n=86, 85.1%) had a CRT indication according to the current guidelines.[15] Fifteen patients (14.9%) received CRT outside of conventional guideline indications. In 6 of them, a high ventricular pacing burden had already led to a decline in SVF to mildly reduced levels, prompting the expert team to proceed with CRT without awaiting further deterioration. In 8 patients, a high anticipated pacing need combined with mildly reduced SVF was considered sufficient rationale to implant CRT proactively; 3 of these 8 patients still had preserved SVF at the time of implantation. One additional patient underwent CRT-D implantation for secondary prevention of sudden cardiac death in the setting of RBBB and mildly reduced SVF. No patients received conduction system pacing (either His bundle pacing or left bundle branch area pacing).

Table 2. Patient characteristics at baseline

Technical CRT data	**n=101**
CRT-P	37 (36.6%)
CRT-D	64 (63.4%)
CIED pre-CRT	48 (47.5%)
Systemic ventricle lead location	
Posterolateral	38 (37.6%)
Lateral	31 (30.7%)
Anterolateral	17 (16.8%)
Epicardial	11 (10.9%)
Posterior	3 (3.0%)
Inferolateral	1 (1.0%)
Systemic ventricle lead polarity	
Quadripolar	64 (63.4%)
Bipolar	26 (25.7%)
Unipolar	11 (10.9%)
Total leads post-CRT	
Three leads	69 (68.3%)
Four leads	17 (16.8%)
Two leads	9 (8.9%)
Five leads	6 (5.9%)
Systemic ventricle lead impedance (Ω, n=85)	735 [592–1005]
Systemic ventricle lead capture threshold (J/s, n=91)	1.1 [0.8–1.6]
Systemic ventricle lead impulse width (ms, n=89)	0.4 [0.4–0.5]
Systemic ventricle lead sense (mV, n=43)	7.5 [1.9–17.4]
Reason for CRT implantation	
Conventional class I – IIb indication*	86 (85.1%)
Indication outside established guidelines*	15 (14.9%)

Proportions are presented as n (%). Values median [interquartile range]. Data were available for all 101 patients unless otherwise specified. * Guidelines refer to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *CIED: Cardiac Implantable Electronic Device, CRT: Cardiac Resynchronization Therapy, CRT-D: Cardiac Resynchronization Therapy with Defibrillator, CRT-P: Cardiac Resynchronization Therapy with Pacemaker, LBBB: Left Bundle Branch Block, LVEF: Left Ventricular Ejection Fraction*

Periprocedural course and device-related follow-up

Of 101 patients, 37 (36.6%) received a CRT-pacemaker and 64 patients (63.4%) a CRT-defibrillator. The implantation approach was transvenous in 90 (89.1%) of patients, while the remaining 11 patients underwent surgical epicardial lead placement. Lead positioning was guided by coronary venous anatomy, inter-lead spacing, lead stability, and electrical parameters. The transvenous systemic ventricular lead was implanted in the lateral (n=31, 34.4%) or posterolateral (n=38, 42.2%) region in the majority of cases.

At one year follow-up, 11 patients (10.9%) had 14 CRT-related early complications (15.3 per 100 patient-years follow-up), with 6 (5.9%) requiring pocket and/or lead revision (6.6 per 100 patient-years follow-up) (*Table 3*). Of these complications, lead displacement (n=5) and pocket hematoma (n=4) were the most prevalent. Only one patient had an infection, which was limited to the skin and subcutaneous tissue, without communication with the pocket and thus did not require lead or device extraction. The infection resolved with a course of antibiotics (flucloxacillin, in consultation with the microbiology department). In total, 3 ICD shocks were delivered, of which 2 were appropriate. However, it is important to note that these incidence rates reflect only early complications (i.e., within the first year after CRT).

For the whole cohort, electrical parameters of the systemic ventricular lead remained stable throughout follow-up. No significant differences were observed between baseline and 12-month follow-up in R-wave sensing (p=0.327), capture threshold (p=0.206), or lead impedance (p=0.224), indicating consistent lead performance.

Efficacy of CRT during 1-year follow-up

In total, 96 patients had at least one follow-up visit and 68 patients had a follow-up visit at 12 months (54 patients had a visit at 3 months, and 63 at 6 months). One patient died 13 months after the CRT implant due to end-stage HF, four patients were lost to follow-up, and four patients were withdrawn from follow-up. Of these, one patient was listed for heart transplantation, one underwent surgical aortic valve replacement for severe aortic stenosis, one received a percutaneous mechanical circulatory support device for acute hemodynamic support in the context of severe sepsis and septic shock, and in one patient CRT was discontinued due to coronary sinus lead dysfunction. As the indication for CRT was no longer present at that time, no new coronary sinus lead was implanted. In total, there were 10 HF events within the first year, involving 9 unique patients (8 urgent HF visits and 2 HF hospitalizations). At one year follow-up, 68 patients (72.3%) showed improvement of at least 1 class of NYHA and/or SVF.

Table 3. Follow-up data

Procedure-related complications	**n=14**
Major complications (required revision procedure)	6 (5.9%)
Lead displacement	5 (5.0%)
Reversed A and V leads in header	1 (1.0%)
Minor complications (managed with conservative treatment)	8 (7.9%)
Hematoma	4 (4.0%)
Superficial incisional infection	1 (1.0%)
Self-containing dissection of superior vena cava	1 (1.0%)
Bleeding	1 (1.0%)
Deep venous thrombosis	1 (1.0%)
Heart failure related events	n=10
Urgent heart failure visit	8 (80.0%)
Heart failure hospitalization	2 (20.0%)
ICD therapy	n=3
Appropriate ICD shocks given	2 (66.6%)
Inappropriate ICD shocks given	1 (33.3%)
Follow-up status	
Lost to follow-up	4 (4.0%)
Death	1 (1.0%)
Withdrawal from follow-up	4 (4.0%)
Listed for LVAD or heart transplantation	1 (1.0%)
CRT lead-capping or extraction	1 (1.0%)
Surgical aortic valve replacement for severe aortic stenosis	1 (1.0%)
Percutaneous mechanical circulatory support device	1 (1.0%)

Proportions are presented as n (%). Data were available for all 101 patients unless otherwise specified. *CRT: Cardiac Resynchronization Therapy, ICD: Implantable Cardioverter-Defibrillator, LVAD: Left Ventricular Assist Device*

QRS duration

QRS duration reduced at 3, 6, and 12 months after CRT implantation ($p<0.001$ for all time points) (*Figure 1A*). At baseline, patients who underwent an upgrade to CRT had a significantly broader QRS than patients who underwent de novo CRT implantation ($p<0.001$) (*Figure 1B*). There was also a significant difference during follow-up between patients who underwent an upgrade procedure and patients who underwent de novo CRT implantation. Patients who underwent an upgrade procedure showed a reduction in QRS duration at each time point ($p=0.002$ at 3, $p<0.001$ at 6, and $p<0.001$ at 12 months), while patients who underwent de novo CRT implantation had a less marked QRS narrowing and only demonstrated a significant QRS reduction at 6 months ($p=0.025$). All exact mixed model results are presented in *Table 4*. The model characteristics are presented in *Additional Table S1*. The individual QRS changes are presented in *Additional Figure S1*, and the residual analyses for the mixed models are in *Additional Figures S2 to S4*.

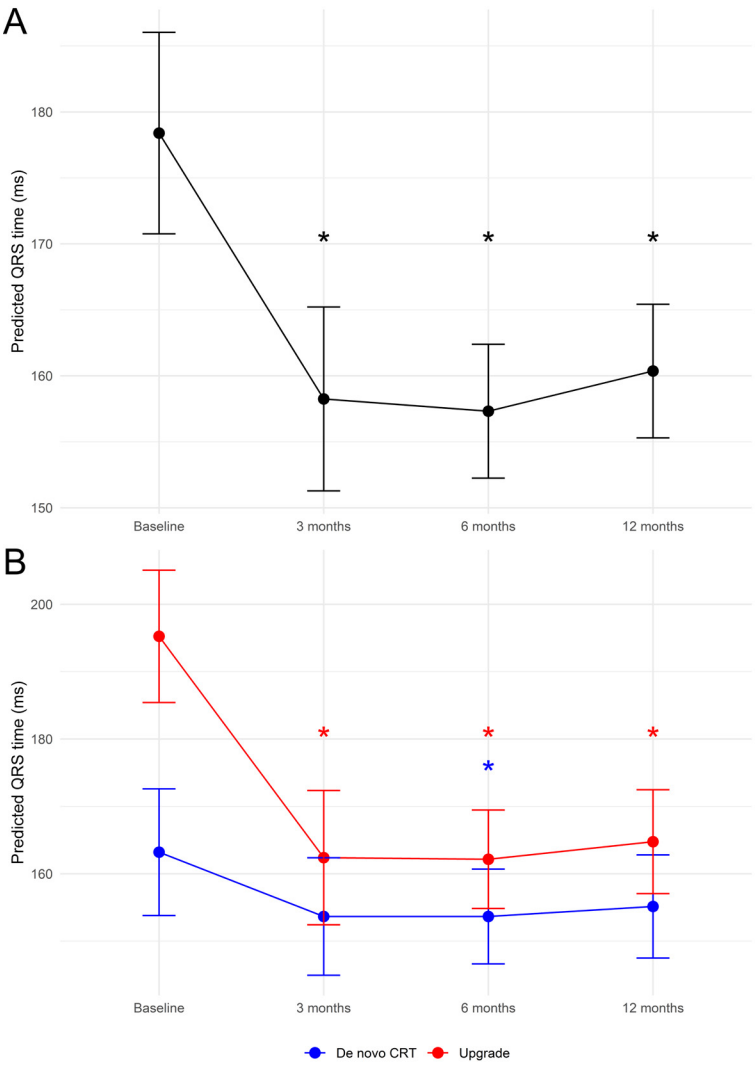


Figure 1. Change in QRS duration after CRT implantation
Panel A shows the longitudinal changes in the model-estimated (predicted) QRS duration (ms) after CRT implantation in the whole population, based on the fixed effects of the linear mixed model. After implantation, there is a significant reduction in QRS duration across all time points. Panel B shows that there is a differential effect between patients who received a de novo CRT implant and who underwent an upgrade procedure. At baseline, upgrade patients had a significantly longer QRS which reduced significantly at each time point. De novo CRT patients only had a significant QRS reduction at 6 months after implantation. The asterisks (*) indicate statistically significant changes.

Table 4. Mixed model outputs

	Estimate	95% CI	P-value
QRS model 1			
Baseline	178.40	170.76 – 186.03	<0.001
3 months vs baseline	-20.15	-27.18 – -13.11	<0.001
6 months vs baseline	-21.08	-27.49 – -14.67	<0.001
12 months vs baseline	-18.03	-24.68 – -11.39	<0.001
QRS model 2			
De novo CRT			
Baseline	163.21	153.81 – 172.62	0.000
3 months vs baseline	-9.55	-19.31 – 0.22	0.058
6 months vs baseline	-9.55	-17.82 – -1.28	0.025
12 months vs baseline	-8.06	-16.84 – 0.72	0.074
Upgrade CRT			
Baseline	195.24	181.65 – 208.84	0.000
3 months vs baseline	-32.84	-47.47 – -18.21	0.002
6 months vs baseline	-33.08	-44.96 – -21.20	<0.001
12 months vs baseline	-30.48	-42.99 – -17.96	<0.001
	OR	**95% CI**	**P-value**
SVF class model 1			
3 months vs baseline	0.21	0.05 – 0.90	0.035
6 months vs baseline	0.06	0.02 – 0.18	<0.001
12 months vs baseline	0.13	0.05 – 0.35	<0.001
SVF class model 2			
3 months vs baseline	0.21	0.05 – 0.88	0.032
6 months vs baseline	0.07	0.02 – 0.19	<0.001
12 months vs baseline	0.14	0.05 – 0.37	<0.001
LBBB at baseline	9.61	2.68 – 34.40	<0.001
sRV at baseline	12.00	2.13 – 67.60	0.005
NYHA class			
3 months vs baseline	0.11	0.03 – 0.40	<0.001
6 months vs baseline	0.04	0.01 – 0.17	<0.001
12 months vs baseline	0.06	0.02 – 0.21	<0.001

Table 4. *Continued*

Estimates for the linear mixed models for continuous variable QRS duration in milliseconds are displayed as absolute baseline values and the change compared to baseline for the 3, 6, and 12 months follow-up intervals. Estimates for cumulative link mixed models for ordinal variable SVF class are displayed as the cumulative ORs, with an OR <1 constituting a lower odds of occupying a worse SVF class (= improvement) compared to baseline, and an OR >1 constituting a higher odds of occupying a worse SVF class. Estimates for generalized linear mixed models for binary variable NYHA class are displayed as ORs, with an OR <1 indicating a lower odds of having NYHA class >II (= improvement), and an OR >1 indicating a higher odds of having an NYHA class >II. All ORs were adjusted for intra-patient clustering via random intercepts. *CI, confidence interval; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; NYHA, New York Heart Association; OR, odds ratio; sRV, systemic right ventricle; SVF, systemic ventricular function*.

SVF class

SVF class improved significantly at 3 (p=0.035), 6 (p<0.001), and 12 months (p<0.001) after CRT implantation, as can be appreciated from *Figure 2A*. This improvement remained significant across all time points, regardless of the presence of LBBB at baseline or systemic ventricle anatomy (*Figure 2B*). Nevertheless, patients with a LBBB at baseline had significantly higher cumulative odds for worse overall SVF than patients without LBBB (p<0.001). Similarly, sRV patients had significantly higher cumulative odds for worse overall SVF than sLV patients (p=0.005).

NYHA class

NYHA class improved significantly at 3, 6, and 12 months after CRT implantation (p<0.001 for all time points) (*Figure 3*). None of the covariates (de novo CRT versus upgrade, LBBB versus non-LBBB at baseline, or sLV versus sRV) significantly influenced the observed improvements in NYHA class after CRT. A summary of the main findings is presented in the *Graphical Abstract*.

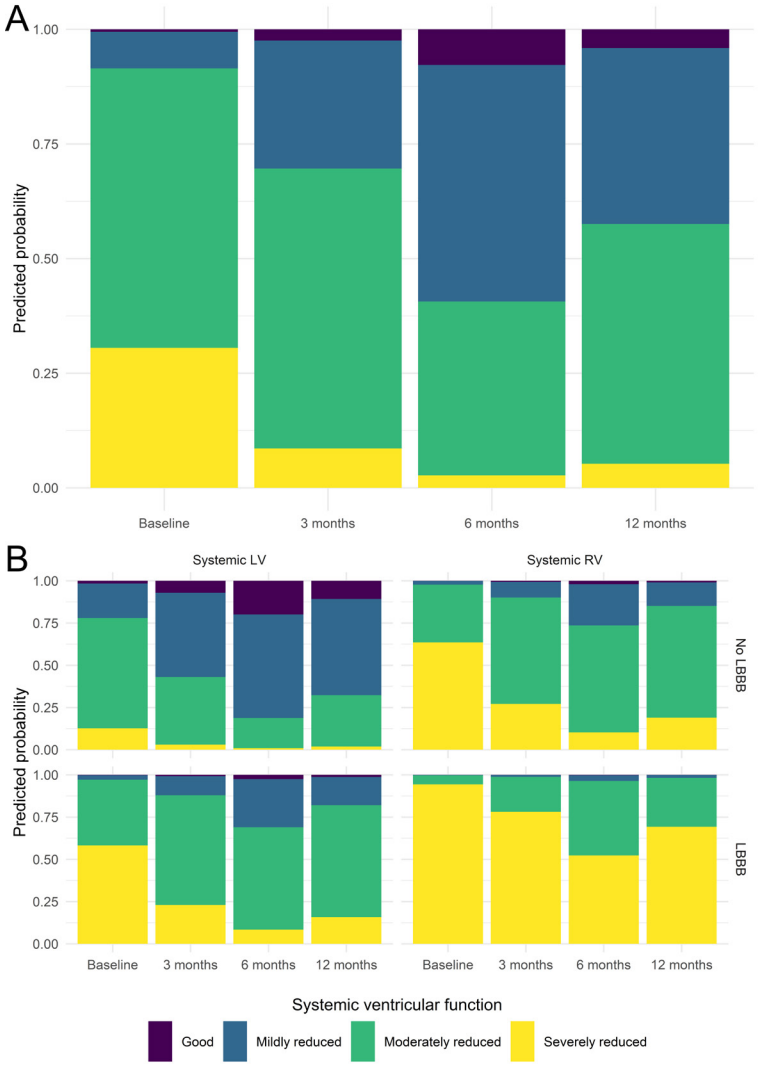


Figure 2. Change in SVF after CRT implantation

The model-estimated (predicted) probabilities for each class of systemic ventricular function are presented, calculated from the fixed effects of the cumulative link mixed model. There is a significant improvement in SVF at each follow-up moment. The presence of an LBBB at baseline and a sRV is associated with significantly worse overall SVF, but the longitudinal improvements remain significant in all groups. *CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; LV, left ventricle; (s)RV, (systemic) right ventricle; SVF, systemic ventricular function.*

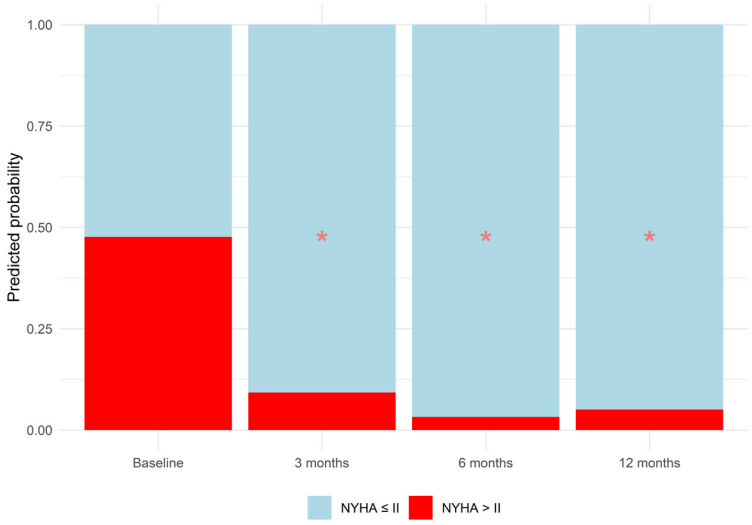
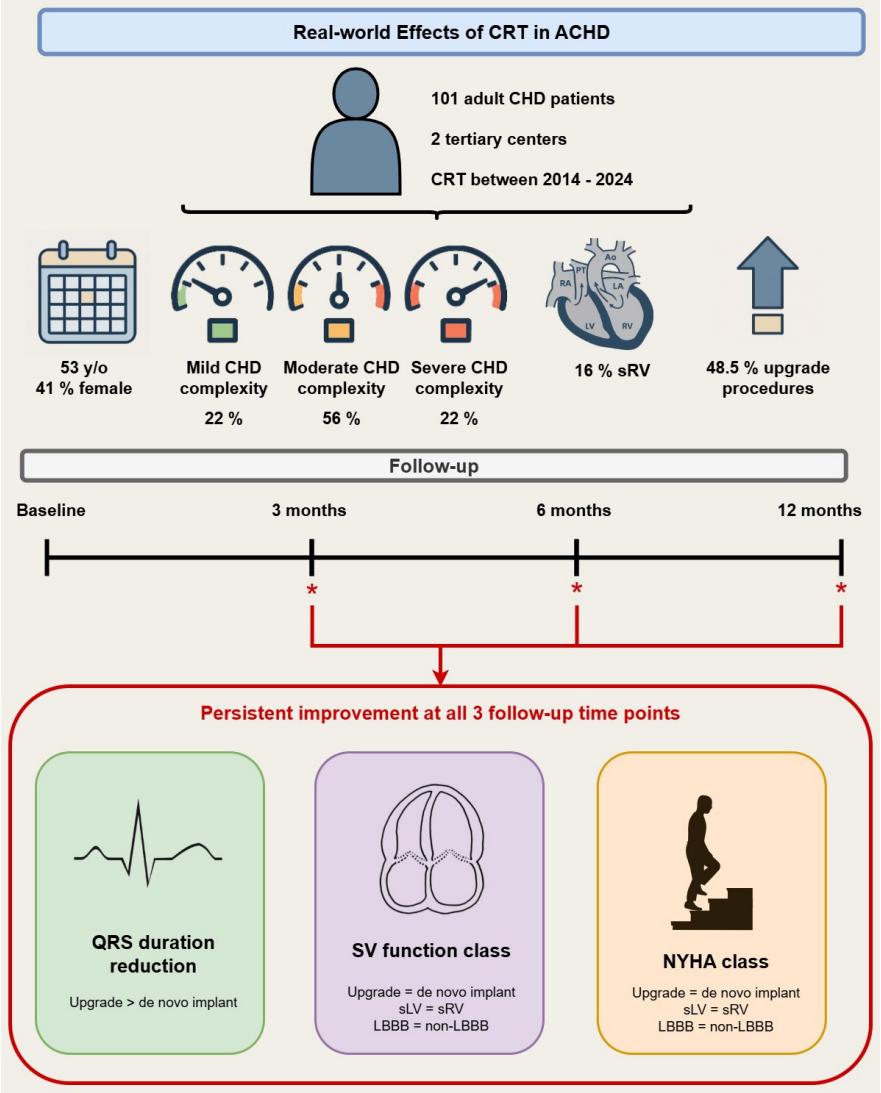


Figure 3. Change in NYHA class after CRT implantation
Model-estimated (predicted) probabilities of having NYHA class ≤ II (light blue) or > II (red) at each follow-up moment are presented, derived from the fixed effects of the generalized linear mixed model. At baseline, there is an even distribution between groups. After CRT implantation, there is a significant improvement in NYHA class, with a reduction in the probability of having NYHA class > II at each follow-up moment. The asterisks (*) indicate statistically significant changes. *CRT, cardiac resynchronization therapy; NYHA, New York Heart Association.*

Graphical Abstract. Effects of CRT in ACHD



In this real-world retrospective multicenter cohort study, the effects of CRT were investigated in 101 ACHD patients. CRT was associated with significant improvements in QRS duration, SVF, and NYHA class at 3, 6, and 12 months after implantation ($p<0.05$ for all). While QRS reduction was more pronounced after upgrade procedures than in de novo implants, both groups showed significant improvements in SVF and NYHA class. Moreover, improvements in QRS, SVF, and NYHA class extended to sRV and non-LBBB patients, supporting CRT as a safe and effective therapy in ACHD patients and emphasizing the need for individualized decision-making beyond standard guidelines. *(A)CHD, (adult) congenital heart disease; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; NYHA, New York Heart Association; sLV, systemic left ventricle; sRV, systemic right ventricle; SVF, systemic ventricular function.*

Discussion

In this real-world cohort of 101 ACHD patients, a significant reduction in QRS duration, improvement in SVF, and improvement in NYHA functional class were observed in the first year after CRT implantation. These benefits were observed across the spectrum of ACHD complexity and extended to patients with a sRV and non-LBBB QRS morphology. Patients undergoing an upgrade from a pre-existing pacing system experienced a more pronounced reduction in QRS duration compared to those receiving a de novo implant. The overall complication rate was low, underscoring the safety and feasibility of CRT in this anatomically complex and clinically heterogeneous population.

Impact on QRS duration

CRT implantation was associated with a significant reduction in QRS duration, particularly among patients undergoing upgrade from a pre-existing CIED. A likely explanation for this finding is that patients with a pre-existing device often had a paced baseline QRS complex, which could account for the more substantial reduction in QRS duration after CRT implantation by mitigating the subpulmonary pacing-induced QRS broadening and dyssynchrony. This difference between upgrade and de novo patients is in line with the previous observations of *Dubin et al*.[16] However, the clinical significance of QRS narrowing as a surrogate for CRT response remains uncertain in this population. *Yin et al*. identified baseline QRS duration as the only significant independent predictor of CRT response in a cohort of 70 ACHD patients.[8] In contrast, *Thompson et al*. found no significant difference in baseline QRS duration between responders and non-responders, and paradoxically, post-procedure QRS duration was even shorter in non-responders than in responders, with response defined as a ≥1-class improvement in NYHA and/or SVF.[10] These seemingly contradictory findings may be explained by the complex nature of electromechanical coupling in ACHD, where improvements in electrical synchrony on the intra- and interventricular level may not necessarily translate into mechanical synchrony.[10]

Impact of QRS morphology on the response to CRT

In patients with structurally normal hearts, LBBB morphology predicts better CRT response compared to non-LBBB.[17] In our cohort, however, 66.3% had non-LBBB QRS morphology at baseline. Bundle branch block, especially RBBB, is more complex in ACHD and should not be perceived in an identical manner to non-congenital populations. RBBB in ACHD can be the result of surgical incision and scarring, but also from hemodynamic (volume and/or pressure) overload of the RV, either impacting the RV or directly damaging the conduction system.[18] It is therefore not surprising that *Yin et al*. showed that stratification according to conventional QRS morphology criteria was not related to echocardiographic response

to CRT in ACHD patients.[8] Our findings support this conclusion, as patients with a non-LBBB pattern on baseline ECG demonstrate similar improvements in QRS duration, SVF class, and NYHA functional class compared to those with a LBBB morphology at baseline. Current guidelines for patients with structurally normal hearts and non-LBBB may thus not be directly applicable to the ACHD population. This is also reflected by the significant proportion of patients in our cohort (n=15, 14.9%) who received CRT, despite not meeting conventional guideline-based indications, where the decision was made on expert consensus. In the vast majority of these cases (n=14, 93.3%), the indication was a (perceived) high pacing requirement in the context of a good or only mildly reduced SVF. The expert panel opted for early CRT implantation rather than waiting for further ventricular function decline. Notably, our analysis showed improvement in SVF across all baseline SVF classes, suggesting that this approach may be beneficial, although it warrants further investigation.

Impact of systemic ventricular morphology on the response to CRT

Experience with CRT in patients with a sRV is limited, and results are variable. Some studies reported less favorable results, especially when compared to CRT in patients with sLV,[8, 19-21] while others report favorable outcomes.[16, 22] One of the largest retrospective studies to date included 80 patients with sRV and showed a significant improvement in functional class and QRS duration only after upgrade to CRT, and not after a de novo implantation.[23] Nonetheless, a recent retrospective multicenter study including 105 adult sRV patients undergoing CRT found no improvement in overall survival and reported that CRT was, in fact, associated with worse survival compared with matched controls.[24] Although the authors used propensity-score matching to adjust for baseline differences, this association may still reflect residual confounding, as in current practice, CRT is more likely to be offered to higher-risk patients with more advanced disease. In our cohort, we observed a significant reduction in QRS duration in patients with sRV following CRT, as well as an improvement in NYHA functional class and SVF. While sRV patients had worse overall SVF compared to sLV patients, and patients with a combination of an sRV and LBBB morphology exhibited the most advanced SVF impairment, the observed longitudinal improvements were statistically significant across all groups. These findings suggest that CRT should not be dismissed based on systemic ventricular anatomy and/or LBBB morphology. Due to the relatively low number of sRV patients in the current cohort and the lack of hard clinical endpoints, no definitive conclusions can be drawn about whether there is a difference in response between sRV patients undergoing upgrade or de novo CRT implantation, nor between ccTGA patients and TGA patients after Mustard. Interestingly, no patients with a single ventricle physiology who received CRT with multi-site ventricular pacing were identified at our centers, likely reflecting the anatomical and physiological complexity inherent to single ventricle anatomies, although early findings seem encouraging.[25]

Adverse events

The early implant-related complication rate in our cohort was relatively low, with only 6 patients (5.9%) requiring re-intervention within the first year. This is lower than the 11% reported in the recent retrospective cohort study by *Yin et al.*, although their mean follow-up of 4.7 years was considerably longer.[8] Earlier studies documented adverse event rates as high as 29%.[16] This discrepancy likely reflects advancements in device technology and procedural techniques over the past decades rather than differences in operator performance. Given the low complication rates with contemporary technology and the availability of a wide range of catheters, leads, and implantation techniques, CRT for ACHD appears to be a relatively safe procedure. Considering the heterogeneous anatomy in this population, referral to experienced centers may be advisable, though ACHD should not be seen as a contraindication per se for CRT implantation by skilled operators. Conduction system pacing may offer a promising alternative in selected ACHD patients, particularly when conventional CRT delivery is challenging. While early data on His bundle pacing and left bundle branch area pacing are encouraging, there is limited available data and their broader applicability in the anatomically diverse ACHD population remains uncertain and warrants further prospective evaluation.[26-29]

Study limitations

First, this study is inherently limited by the retrospective, single-arm design with limited follow-up duration. Lack of a control group that did not receive CRT prevents us from making direct comparisons, and lack of data on hard endpoints limits the ability to draw conclusions regarding the long-term benefit of CRT in the course of ACHD-related HF. Second, selection bias is inherent, as some ACHD patients with an indication for CRT may not have undergone the procedure due to various factors, and patients in whom CRT implantation was initially deemed unfeasible or unsuccessful were not captured in this study. Third, the indications for CRT were determined on a case-by-case basis, leading to a heterogeneous cohort with a range of congenital defects and variable follow-up protocols. While this introduces variability, it also reflects the real-world complexity inherent to the management of ACHD patients with HF. Fourth, assessing ventricular function in ACHD patients can be challenging, and there may be intra- and interobserver variability in these measurements. To address this, we categorized SVF based on a classification system (normal, mildly, moderately, or severely reduced) to minimize discrepancies. Fifth, follow-up data were incomplete for some participants. Mixed models were used to account for this unbalanced data by incorporating all available data and the within-patient correlation of repeated measurements, minimizing bias compared with conventional paired analyses.

Conclusions

In summary, this real-world, multicenter study of 101 ACHD patients undergoing CRT implantation demonstrates significant improvements in QRS duration, systolic SVF, and NYHA functional class in the first year following implantation. Importantly, these benefits were also observed in patients with a sRV and those with a non-LBBB QRS morphology—two patient groups outside the traditional established guidelines. Patients undergoing device upgrades experienced a more pronounced reduction in QRS duration than those receiving de novo implants, but SVF and NYHA improved significantly in both subgroups. The overall complication rate was low. These findings provide further evidence supporting the use of CRT as a safe, feasible, and effective therapy for ACHD patients with HF. ACHD patients should not be disregarded as candidates for CRT based on their intricate anatomy and ventricular morphology, and indications might extend beyond the established guidelines for patients without congenital heart disease.

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PATIENT INVOLVEMENT IN ACHD-RELATED HF

PART 3

10

Treatment Options for Heart Failure in Patients with a Systemic Right Ventricle

Behandelopties voor Hartfalen bij Patiënten met een Systemische Rechterkamer

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Sinus. June 2025.

Abstract

Hartfalen is een van de grootste problemen bij volwassenen met aangeboren hartafwijkingen. Vooral patiënten met een systemische rechterkamer lopen extra risico op het ontwikkelen van hartfalen. De laatste jaren is er een aantal behandelopties gekomen die veelbelovend zijn voor deze groep patiënten.

Hartfalen bij patiënten met een systemische rechterkamer

Hartfalen is een van de grootste problemen bij volwassenen met een aangeboren hartafwijking. Het is een levenslange aandoening, die gepaard gaat met toenemende klachten, ziekenhuisopnames, een verminderde kwaliteit van leven en een verkorte levensduur. Vooral mensen met een systemische rechterkamer lopen extra risico op het ontwikkelen van hartfalen. Op 45-jarige leeftijd heeft meer dan de helft van deze patiënten last van hartfalen. Bij deze mensen is niet de sterke linkerhartkamer, maar de rechterhartkamer verbonden aan de grote lichaamsslagader (aorta). Hierdoor moet de minder krachtige rechterkamer, die normaal alleen bloed naar de longen pompt, nu het bloed door het hele lichaam pompen. De twee meest voorkomende aangeboren hartafwijkingen die gepaard gaat met een systemische rechterkamer zijn: 1) transpositie van de grote vaten (TGA) na een Mustard of Senning operatie op jonge leeftijd, 2) congenitaal gecorrigeerde transpositie van de grote vaten (ccTGA). Helaas worden patiënten met een systemische rechterkamer zelden meegenomen in de grote onderzoeken naar behandelingen voor 'gewoon' hartfalen. Daardoor is er weinig wetenschappelijk bewijs voor de behandeling van hartfalen bij deze groep. In dit artikel bespreken we drie hedendaagse behandelopties voor hartfalen bij patiënten met een systemische rechterkamer en deelt een patiënte haar ervaringen.

Sacubitril/valsartan (Entresto®)

Sacubitril/valsartan is een combinatiemedicijn dat bestaat uit twee werkzame stoffen: sacubitril (een neprilysine remmer) en valsartan (een angiotensine receptor blokker). Dit medicijn is sinds 2016 in Nederland beschikbaar voor de behandeling van 'gewoon' hartfalen en sindsdien wordt het vaak voorgeschreven bij patiënten die klachten van hartfalen houden, ondanks andere medicatie. Het helpt het hart beter te pompen en leidt hierdoor tot minder klachten, minder ziekenhuisopnames en langere overleving. Over de afgelopen jaren heeft onze onderzoeksgroep het gebruik van sacubitril/valsartan bij patiënten met een systemische rechterkamer onderzocht. Het lijkt er op dat sacubitril/valsartan ook bij onze patiënten gepaard gaat met verbeteringen in de pompfunctie van het hart (gemeten met echo), de conditie (gemeten met een looptest) en NT-proBNP (een bloedwaarde die verhoogd is bij hartfalen).[1-3] Deze veelbelovende resultaten werden in januari 2025 ondersteund door een studie van onze onderzoeksgroep die werd gepubliceerd in het tijdschrift Open Heart.[4] In deze studie werden de veranderingen in kwaliteit van leven onderzocht, om te kijken of patiënten zich ook beter voelden met sacubitril/valsartan. In de drie jaar nadat het medicijn gestart werd, was er sprake van een verbetering in slaap, dagelijkse activiteiten, fysiek, cognitief en sociaal functioneren. Deze resultaten zijn bemoedigend en laten ze zien dat sacubitril/valsartan ook voor patiënten met hartfalen met een systemische rechterkamer waardevol zou kunnen zijn.

Dapagliflozine (Forxiga®) en empagliflozine (Jardiance®)

De medicijnen dapagliflozine en empagliflozine zijn zogenaamde Sodium-Glucose Cotransporter 2 (SGLT2) remmers. Deze medicijnen zijn oorspronkelijk ontwikkeld voor de behandeling van suikerziekte (diabetes), maar bleken juist erg effectief te zijn tegen hartfalen, ook bij patiënten zonder suikerziekte. Sinds 2021 zijn beide medicijnen beschikbaar voor de behandeling van 'gewoon' hartfalen in Nederland en in de afgelopen jaren zijn SGLT2 remmers een onmisbare standaardbehandeling geworden. We weten nog niet zo goed hoe SGLT2 remmers precies werken, maar onderzoek laat zien dat patiënten met 'gewoon' hartfalen zich beter voelen, minder vaak worden opgenomen in het ziekenhuis en langer leven als ze een SGLT2 remmer gebruiken.

In 2024 heeft onze onderzoeksgroep de behandeling van hartfalen met SGLT2 remmers bij 174 volwassenen met een aangeboren hartafwijking onderzocht.[5] In deze studie hadden 60 patiënten een systemische rechterkamer. De studie toonde aan dat SGLT2 remmers veilig zijn en goed worden verdragen bij deze groep patiënten. De bijwerkingen die we zagen waren vergelijkbaar met de bijwerkingen bij patiënten met 'gewoon' hartfalen. Opvallend was dat ook de patiënten met een aangeboren hartafwijking na het starten van een SGLT2 remmer minder vaak voor hartfalen werden opgenomen in het ziekenhuis.

Daarnaast hebben andere recente onderzoeken laten zien dat er positieve veranderingen in de klachten, de bloedwaarde NT-proBNP en de pompfunctie optraden bij patiënten met een systemische rechterkamer na het starten van een SGLT2 remmer.[6, 7] Kortom, er zijn ook hoopgevende signalen voor het gebruik van SGLT2 remmers bij patiënten met een systemische rechterkamer.

Cardiale resynchronisatie therapie (CRT)

Bij CRT zorgt een speciale soort pacemaker ervoor dat beide hartkamers worden gestimuleerd en daardoor beter samenwerken. Zo wordt geprobeerd om de pompfunctie van het hart te verbeteren. Anders dan bij het starten van medicijnen moet een patiënt een ingreep ondergaan om CRT te krijgen, omdat de pacemakerdraden in of op het hart moeten worden geplaatst. Vaak kan dit via de bloedvaten gedaan worden (katheterisatie), maar soms moeten patiënten ook een chirurgische ingreep ondergaan waarbij de pacemakerdraden op het hart geplaatst worden. Het is daarom extra belangrijk zorgvuldig te bepalen welke patiënten hier baat bij kunnen hebben. Niet iedereen komt in aanmerking voor CRT, maar voor de juiste kandidaten kan het leiden tot verbetering van het hartfalen. Net zoals bij de medicatie, wordt deze techniek al veel gebruikt bij patiënten met 'gewoon' hartfalen. Toch is het effect van CRT bij patiënten met een systemische rechterkamer nog niet genoeg onderzocht. Er zijn

steeds meer aanwijzingen dat ook zij baat kunnen hebben bij CRT, maar het is nog lastig te zeggen wie een goede kandidaat is voor CRT. Meer onderzoek is nodig om deze vragen te beantwoorden.

De ervaring van een patiënt

Vraag: Wat betekent het hebben van systemisch rechterkamer hartfalen voor u in het dagelijks leven?

Dat ik lichamelijk minder kan en minder energie heb dan een gezonde vrouw van mijn leeftijd. Het voelt een beetje als het in stand houden van een wankel evenwicht, dus op je zout- en vochtinname letten, maar wel zorgen dat je genoeg drinkt om de bloedruk een beetje op peil te houden. Iedere dag weeg ik mezelf en ik meet regelmatig mijn bloeddruk. Mijn dagelijkse energie probeer ik in balans te houden door niet te veel te doen maar wel te zorgen dat ik op een goede manier in beweging blijf. Ik ben daardoor meer met mijn lichaam bezig, dan een ander. Dat wordt een tweede natuur, maar iets spontaan ondernemen wordt dan minder makkelijk. Iets kleins als een verkoudheid of blaasontsteking kan namelijk de hele boel ontregelen, en lokt dan heel vaak een ritmestoornis uit die niet weggaat, waardoor ik voor een cardioversie naar de eerste hart hulp moet.

Vraag: In de afgelopen jaren bent u behandeld met sacubitril/valsartan, dapagliflozine en heeft u een ingreep ondergaan om CRT te kunnen krijgen. Hoe kijkt u terug op deze verschillende behandelingen en wat heeft het u opgeleverd in uw dagelijks leven?

Vooral sacubitril/valsartan verbeterde mijn conditie enorm, mijn conditie ging er echt door vooruit, daar was ik echt heel blij mee. Dapaglifozine helpt me om geen vocht meer vast te houden, maar helaas krijg ik er wel vaker blaasontstekingen door. De CRT had ik als ingreep een beetje onderschat. Ik dacht dat het een simpele ICD-vervanging 2.0 zou zijn, maar het bleek toch wel echt een operatie. Na thuiskomst had ik enorm moeite met opknappen. Gelukkig dacht mijn cardioloog enorm mee en wist zij me weer op de been te krijgen. Mijn hartritme is door de CRT veel stabieler geworden, dus ik heb zeker geen spijt van deze ingreep.

Vraag: Waar zou u graag zien dat zorgverleners hun aandacht in de toekomst meer op richten, om de zorg voor patiënten met systemisch rechterkamer hartfalen te verbeteren?

Ik vind dat jullie al heel goed bezig zijn. Het team voor volwassenen met een aangeboren hartafwijking doet goed werk. Ik voel me echt gehoord. Ik vind een eigen inbreng belangrijk, het samen met de patiënt beslissen. Het kunnen sturen van een mailtje met een vraag en daar ook antwoord op krijgen (ook al is dat door een coassistent of andere arts dan mijn eigen cardioloog) is heel veel waard en dat hoor ik ook van lotgenoten. Ook nieuwe technieken,

zoals het thuismonitor kastje voor de ICD, zijn een uitkomst. Het scheelt mij twee uur heen- en terugrijden voor een ICD-doormeting. Ook de 'The Box' voor hartfalen met een app, slimme weegschaal en horloge met hartslagmeter helpen, om zelf meer inzicht in je gezondheid te krijgen.

"Ik vind een eigen inbreng belangrijk, het samen met de patiënt beslissen."

Hoopvolle stappen in de behandeling van hartfalen

De afgelopen jaren is er meer onderzoek gedaan naar de behandeling van hartfalen bij patiënten met een systemische rechterkamer. Toch blijft het lastig om harde conclusies te trekken, omdat de studies over het algemeen klein zijn en geen controlegroep hebben. In dit artikel hebben we een paar veelbelovende behandelingen besproken:

1. Sacubitril/valsartan lijkt een veilig en effectieve medicijn voor hartfalen bij patiënten met een systemische rechterkamer, met onder andere verbeteringen in kwaliteit van leven.
2. Ook SGLT2 remmers zijn veilig en lijken op korte termijn ziekenhuisopnames voor hartfalen te kunnen verminderen.
3. CRT is een pacemaker die de pompfunctie van het hart kan verbeteren bij hartfalen. Toch is het nog lastig is om te bepalen wie het meeste baat kan hebben bij CRT.

Het blijft erg belangrijk dat er meer onderzoek specifiek gericht op volwassenen met aangeboren hartafwijkingen en hartfalen komt. Uw deelname aan wetenschappelijk onderzoek wordt enorm gewaardeerd en is van grote waarde. Juist bij zeldzame aandoeningen is elke stem belangrijk. Door onderzoek hopen we uiteindelijk patiënten met systemische rechterkamer hartfalen een betere toekomst te kunnen bieden, met minder klachten en een hogere kwaliteit van leven.

Wat kunt u als patiënt doen?

Het is belangrijk dat klachten die kunnen passen bij hartfalen op tijd herkend worden. Bespreek bij uw controleafspraken klachten die kunnen wijzen op hartfalen, zoals:

- Toenemende vermoeidheid
- Kortademigheid bij inspanning of in liggende houding
- Vocht vasthouden (dikke enkels, zwaar gevoel in de benen, bollere buik, of kortademigheid bij plat liggen).

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11

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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12

Dutch Summary

Samenvatting

Dit proefschrift heeft tot doel de onvervulde behoefte aan evidence-based behandelingsopties voor hartfalen bij volwassen patiënten met aangeboren hartafwijkingen (ACHD-gerelateerd HF) te adresseren door nieuwe farmacologische en device-gebaseerde behandelingsopties te evalueren. **Hoofdstuk 1** biedt een algemeen overzicht van de impact van ACHD-gerelateerd HF en introduceert de potentiële behandelingsopties die in dit proefschrift worden onderzocht.

Farmacologische therapieën

De doelstelling van dit proefschrift werd grotendeels gerealiseerd door de oprichting van de *Adult Congenital Heart Disease International EValuation of the Effectiveness of SGLT2i (ACHIEVE-SGLT2i) registry* (ClinicalTrials.gov NCT06932081). Het doel van deze registry is om de praktijkervaring met SGLT2i binnen de ACHD-populatie te evalueren. Eind 2025 waren reeds meer dan 400 patiënten geïncludeerd vanuit 10 deelnemende centra. In **Hoofdstuk 2** wordt het eerste bewijs voor het gebruik van SGLT2i uit deze internationale samenwerking gepresenteerd.[1] Bij een gebrek aan richtlijn-gestuurde therapeutische opties voor ACHD-gerelateerd HF weerspiegelt het toenemende voorschrijven van SGLT2i dat in deze studie wordt gerapporteerd een aanzienlijke onvervulde behandelingsbehoefte bij deze populatie. Gezien het heterogene ACHD-cohort historisch gezien wordt uitgesloten van deelname aan baanbrekende HF-studies, lijken ACHD-clinici gedwongen om te extrapoleren vanuit richtlijnaanbevelingen voor niet-ACHD-patiënten, ondanks het gebrek aan ondersteunend wetenschappelijk bewijs. Het is dan ook positief dat deze studie concludeerde dat SGLT2i veilig waren en over het algemeen goed werden verdragen bij 174 ACHD-patiënten, met een prevalentie van bijwerkingen die vergelijkbaar was met de aantallen gerapporteerd in de conventionele HF-studies. Bovendien ging het gebruik van SGLT2i gepaard met een afname van het percentage HF-gerelateerde ziekenhuisopnames over een periode van 6 maanden, wijzend op eerste tekenen van een mogelijk prognostisch voordeel van SGLT2i voor ACHD-patiënten met HF.

Zoals uiteengezet in hoofdstuk 1 lijkt de ziektelast van HF het meest urgent bij patiënten met een systemische rechterventrikel (sRV) en een univentriculaire/Fontancirculatie. Wat de eerste groep betreft, presenteert **Hoofdstuk 3** de eerste ervaring met SGLT2i dapagliflozine bij 10 volwassenen met sRV falen uit één centrum.[2] Uit het onderzoek bleek dat dapagliflozine goed werd verdragen; geen enkele patiënt stopte met de behandeling en de bloeddruk, glucose en elektrolyten bleven stabiel. Hoewel een lichte afname van de nierfunctie werd waargenomen, herstelde deze zich tijdens de follow-up tot het uitgangsniveau. Een dergelijke bevinding zou tot voorzichtigheid kunnen manen, maar deze zorg kan worden getemperd

door de inmiddels vastgestelde renoprotectieve effecten van SGLT2i.[3, 4] Bovendien werden significante verbeteringen in NT-proBNP – een belangrijke prognostische biomarker voor HF – en *New York Heart Association (NYHA)*-klasse – een classificatie voor de ernst van HF – waargenomen. Gedurende de follow-up vond slechts één ziekenhuisopname wegens HF plaats, wat aanzienlijk minder was dan de opnamefrequentie in de voorgaande maanden voor die specifieke patiënt. Dit ondersteunt het idee van een potentieel voordeel, zoals beschreven in hoofdstuk 2. De echocardiografische systolische ventrikelfunctie, dat wil zeggen de knijpkracht van de kamers van het hart gemeten met een echo via de borstwand, werd bij slechts acht patiënten geëvalueerd en toonde geen veranderingen, wat mogelijk kan worden toegeschreven aan de kleine studiepopulatie en de inherente variabiliteit in beeldvorming bij sRV patiënten.

In het verlengde van deze kleine studie werd in **Hoofdstuk 4** getracht om uitgebreidere echocardiografische gegevens systematisch te analyseren om de effecten van SGLT2i op de functie van de ventrikels te evalueren.[5] De echocardiografische beelden van 39 patiënten met sRV falen die waren geïncludeerd in de *ACHIEVE-SGLT2i registry* werden opnieuw systematisch beoordeeld. Er werd gebruikgemaakt van *linear mixed models*, een statistische techniek om herhaalde, ongebalanceerde datapunten verkregen gedurende follow-up, effectief te analyseren. Behandeling met SGLT2i was geassocieerd met een significante vroege verbeteringen in de *global longitudinal strain (GLS)* en *fractional area change (FAC)* van de sRV, twee gevalideerde parameters voor systolische sRV functie.[6] Bovendien bleek uit analyse van relevante covariabelen dat chronische subpulmonale linkerventrikel (spLV) pacing de verbetering van FAC op langere termijn afzwakte. Leeftijd bleek een negatieve invloed te hebben op de globale sRV GLS waarden, maar beïnvloedde de positieve respons op de behandeling met SGLT2i niet. Daarnaast werden verbeteringen waargenomen in de *tricuspid annular plane systolic excursion (TAPSE)* en *spLV free-wall strain (FWS)*, wat verder wijst op een mogelijk herstellend effect van SGLT2i op ventriculaire functie (reverse remodelling). Alles bij elkaar genomen levert deze studie aanwijzingen dat behandeling met SGLT2i de systolische sRV functie kan verbeteren, hoewel het belang van patiënt-specifieke factoren op de behandelingsrespons moet wordt benadrukt.

Hoofdstuk 5 gaat wederom over patiënten met sRV falen, maar verschuift de focus van de evaluatie van SGLT2i naar een andere HF medicatiegroep, angiotensine receptor-neprilysine inhibitors (ARNI).[7] In deze prospectieve studie werd de impact van de ARNI sacubitril/valsartan op veranderingen in de *quality of life* (QOL, kwaliteit van leven) op middellange termijn onderzocht. De studie vond dat sacubitril/valsartan geassocieerd was met betekenisvolle en aanhoudende verbeteringen in de QOL. Eenendertig patiënten

vulden 98 QOL-vragenlijsten in en wederom werden met behulp van *linear mixed models* significante en consistente verbeteringen aangetoond op meerdere QOL-domeinen. Deze bevindingen bevestigen de eerder gerapporteerde verbeteringen in de QOL op korte termijn en breiden deze verder uit op de middellange termijn na het starten met sacubitril/valsartan.[8] Dit versterkt het bewijs voor de therapeutische rol van sacubitril/valsartan, dat verder gaat dan functionele en op biomarkers gebaseerde voordelen, en ondersteunt de hypothese dat sRV falen kan verbeteren door gerichte farmacologische therapie.[8]

Aangaande de populatie met een univentriculaire/Fontancirculatie, had **Hoofdstuk 6** tot doel de veiligheid en werkzaamheid van SGLT2i te onderzoeken bij 33 patiënten met een Fontancirculatie en HF (*Fontan Circulatory Failure, FCF*) die waren geïncludeerd in de *ACHIEVE-SGLT2i registry.*[9] Deze studie toonde aan dat behandeling met SGLT2i in deze specifieke populatie ook veilig was en goed werd verdragen. In een poging om verschillende pathofysiologische mechanismen van FCF te verkennen en ons inzicht in de complexe onderliggende hemodynamica van FCF te verdiepen, werden verschillen in de behandelrespons tussen patiënten met verminderde en behouden ventriculaire functie onderzocht. Behandeling met SGLT2i ging gepaard met een significante afname van NT-proBNP bij FCF-patiënten, ongeacht het onderliggende FCF-fenotype.

In **Hoofdstuk 7** werden vervolgens de longitudinale veranderingen in ventriculaire functie, gemeten met transthoracale echocardiografie bij 13 patiënten met een univentriculaire circulatie en HF geëvalueerd.[11] De meerderheid van de patiënten had een Fontancirculatie en alle longitudinale echocardiogrammen werden opnieuw geanalyseerd. Uit het onderzoek bleek dat behandeling met een SGLT2i geassocieerd was met een significante afname van de end-systolic area van de ventrikel, verbetering in de systemic *ventricular FWS* en *basal lateral strain* en een vroege verbetering in de isovolumic acceleration. Patiënten met verminderde systolische ventriculaire functie vertoonden een vroege verbetering in FAC, terwijl patiënten met behouden systolische ventriculaire functie dat niet deden. Deze bevindingen suggereren dat behandeling met SGLT2i inderdaad de ventriculaire functie bij patiënten met een univentriculaire circulatie kan verbeteren, hoewel dit deels een fenotype-specifieke reactie kan zijn. Deze eerste inzichten in de effecten van SGLT2i op ventriculaire functie worden beperkt door de kleine steekproefomvang en de inherente heterogeniteit die gepaard gaat met deze complexe aangeboren hartaandoeningen. Niettemin levert deze studie het eerste gestructureerde bewijs dat behandeling met SGLT2i geassocieerd lijkt met verbeteringen in systolische ventriculaire functie bij patiënten met een univentriculaire circulatie en HF.

Device-gebaseerde therapieën

Naast de hierboven beschreven farmacologische therapieën werden in dit proefschrift twee specifieke *device*-gebaseerde therapieën voor ACHD-gerelateerd HF onderzocht. In **Hoofdstuk 8** wordt het complexe en op de patiënt afgestemde besluitvormingsproces rond de behandeling van *baffle leaks* bij volwassenen met sRV falen lang na de atriale switch procedure besproken.[10] Bij de atriale switch procedure worden chirurgisch tunnels gecreëerd in de boezems van het hart – de zogenaamde *baffles* – om het bloed naar de juist ventrikels te leiden. Naarmate de tijd vordert kunnen lekkages in deze *baffles* optreden – de *baffle leaks* – die kunnen leiden tot problemen. Er worden drie gevallen met uiteenlopende hemodynamische profielen en illustratieve behandelingsstrategieën gepresenteerd. Twee patiënten vertoonden cyanose – een daling in de zuurstofsaturatie – tijdens inspanning als gevolg van een functionele rechts-naar-links *shunt* en ondergingen een succesvolle percutane sluiting van de *shunt*, waarna de cyanose verdween. Het derde geval betrof een patiënt met volumeoverbelasting van de spLV, veroorzaakt door een significante links-naar-rechts *shunt*. Deze patiënt werd conservatief behandeld om verdere verslechtering van de sRV functie te voorkomen, omdat de links-naar-rechts *shunt* als hemodynamisch gunstig werd beschouwd aangezien deze shunt de falende sRV met zijn verhoogde eind-diastolische druk effectief ontlastte. Tezamen genomen onderstrepen deze gevallen het belang van geïndividualiseerde, patiëntgerichte besluitvorming die gebaseerd is op multimodale beeldvorming en invasieve hemodynamische beoordeling.

Hoofdstuk 9 had tot doel de effecten van cardiale resynchronisatietherapie (CRT), een integraal onderdeel van de behandeling van geselecteerde patiënten met 'conventioneel HF', te onderzoeken in een retrospectief *multicentre* cohort van 101 ACHD-patiënten.[12] Deze studie toonde aan dat CRT, wanneer uitgevoerd in gespecialiseerde centra en wanneer technisch haalbaar, geassocieerd was met significante verbeteringen in QRS-duur, systemische ventriculaire functie en NYHA-klasse in het eerste jaar na implantatie. Hoewel de reductie van de QRS-duur meer uitgesproken was bij patiënten die een upgrade-procedure ondergingen (dat wil zeggen patiënten die al een conventionele pacemaker hadden en een upgrade naar een CRT-device ondergingen), werd er ook een significante reductie in QRS-duur geobserveerd bij patiënten met een sRV en patiënten met een QRS-morfologie zonder linkerbundeltakblok (LBTB), waarbij deze laatste morfologie doorgaans in verband wordt gebracht met een slechtere respons op CRT in de 'conventionele HF'-populatie.[13] Concluderend ondersteunt deze studie CRT als een veilige en effectieve therapie bij geselecteerde ACHD-patiënten, waarbij bij meer dan 70% van de patiënten na 12 maanden een gunstige respons werd waargenomen.

Patiëntbetrokkenheid

Ten slotte culmineren de bevindingen van dit proefschrift in **Hoofdstuk 10**. Dit hoofdstuk is geschreven in samenwerking met een ervaringsdeskundige met sRV falen, die heeft deelgenomen aan meerdere onderzoeken die in dit proefschrift zijn opgenomen. Het artikel is gepubliceerd in het kwartaalblad Sinus van de Patiëntenvereniging Aangeboren Hartafwijkingen.[14] Het artikel heeft tot doel de recente ontwikkelingen in de behandeling van ACHD-gerelateerd hartfalen te vertalen naar toegankelijke, patiëntgerichte taal, en benadrukt het belang van patiëntbetrokkenheid bij onderzoek en zorg voor ACHD-patiënten. Het versterken van patiëntbetrokkenheid is van cruciaal belang voor de toekomst van de ACHD-zorg, met name in een tijdperk van overvloedige en steeds complexere medische informatie en behandelmogelijkheden. Uiteindelijk moeten onze wetenschappelijke activiteiten worden geleid door de behoeften van onze patiënten.

Context en toekomstperspectieven

De afgelopen jaren zijn er aanzienlijke inspanningen geleverd om potentiële farmacologische en *device*-gebaseerde therapieën te evalueren om de last van HF bij de ACHD-populatie te verminderen. Het bewijs ter ondersteuning van deze behandelingsopties is gestaag toegenomen en de studies die in dit proefschrift worden gepresenteerd leveren een zinvolle bijdrage aan dit dynamische vakgebied. Naast het werk dat in dit proefschrift wordt gepresenteerd, zijn er verschillende belangrijke studies gepubliceerd door andere onderzoeksgroepen die context bieden voor de in dit proefschrift gepresenteerde bevindingen.

Het gebruik van SGLT2i in de ACHD-populatie is samengevat in een systematische review door *Marshall et al*. (2024) en een meta-analyse door *Das et al*. (2025). Beide studies bevestigden dat SGLT2i veilig zijn en goed worden verdragen bij ACHD-gerelateerd HF.[15, 16] Hoewel een directe vergelijkingen met betrekking tot de veiligheid en verdraagbaarheid tussen deze studies en de baanbrekende SGLT2i-onderzoeken bij “conventionele HF patiënten” niet haalbaar is, lijken de gerapporteerde percentages van patiënten die bijwerkingen ervaren en het bijwerkingenprofiel wel vergelijkbaar.[17] Door de resultaten van 8 studies met in totaal 287 patiënten te combineren, toonde de analyse van *Das et al*. aan dat SGLT2i ook de klinische symptomen en NT-proBNP waarden leken te verbeteren, bevindingen die in lijn zijn met de resultaten die in Hoofdstukken 3 en 6 van dit proefschrift worden gerapporteerd. Het is wel belangrijk op te merken dat Hoofdstuk 2 van dit proefschrift de meerderheid van de onderliggende gegevens bevat die in de meta-analyse zijn geanalyseerd. Toch moet ook nadrukkelijk worden verwezen naar de DAPA-SERVE-studie; tot op heden de enige *open-label*, gerandomiseerde studie over dit onderwerp. De auteurs onderzochten 50 patiënten met sRV falen, van wie er 25 werden behandeld met SGLT2i. Ze concludeerden

dat behandeling met SGLT2i veilig was en gepaard ging met verbeteringen in de systolische sRV functie.[18] De prospectieve DAPA-SRV studie ondersteunt ook het gebruik van SGLT2i bij sRV falen, door verbeteringen vast te stellen in de afgelegde afstand bij de 6-minuten-looptest, QOL en de echocardiografische sRV functie na het starten van SGLT2i bij 32 patiënten.[19] De afgelopen jaren is er daarnaast bewijs naar voren gekomen dat het gebruik van ARNI ondersteunt. Observationele studies richtten zich voornamelijk op sRV falen en toonden over het algemeen bevredigende veiligheid en verdraagbaarheid aan. Er worden veelbelovende verbeteringen beschreven in klinische uitkomsten, beeldvormingsparameters en metingen van natriuretische peptiden, hoewel er ook een risico lijkt te bestaan op hypotensie en achteruitgang van de nierfunctie, hetgeen zorgvuldige monitoring vereist.[8, 20-23]

Ondanks dat het bewijs voor de effectiviteit van nieuwe farmacologische middelen bij de behandeling van ACHD-gerelateerd HF dus beperkt blijft en is gebaseerd op kleine, voornamelijk observationele studies, lijken zowel SGLT2i als ARNI veilig, worden ze goed verdragen en vertonen ze veelbelovende tekenen van vroege effectiviteit. Desalniettemin blijft een verschil in ziekte- en fenotype-specifieke respons op de behandeling met SGLT2i mogelijk. Dit vereist verdere evaluatie, met name in relevante subgroepen zoals sRV of univentriculaire/Fontancirculatie patiënten en in HF met verminderde versus behouden ejectiefractie.

Er kunnen parallellen worden getrokken tussen de stand van zaken met betrekking tot het bewijs voor SGLT2i, ARNI en CRT. Tot op heden is er slechts één systematische review die het bewijs voor CRT binnen de sRV populatie samenvat, waarin alleen retrospectieve, observationele studies zijn opgenomen. De auteurs concludeerden dat CRT een effectieve behandeling kan zijn voor sRV-falen, met variërende CRT-responspercentages en definities.[24] Recenter onderzoek met een propensity-matched analyse van 105 sRV patiënten die een CRT-implantatie ondergingen suggereert echter dat CRT niet geassocieerd is met verbeterde overleving en trekt de effectiviteit van deze behandeling voor sRV falen in twijfel.[25] Andere observationele studies hebben veelbelovende resultaten laten zien in de algemene ACHD-populatie, hoewel er momenteel geen consensus bestaat over nauwkeurige definities van responders en studies met gegevens over harde klinische eindpunten en systematische reviews ontbreken.[26] Om de kennis over dit onderwerp verder te vergroten, heeft onze groep de *Real-World Data on the Effects of Cardiac Resynchronization Therapy in Adult Patients With Congenital Heart Disease (RECORD-CHD) registry* (NCT06969924) opgezet.

Uit de resultaten die in dit proefschrift worden gepresenteerd en de studies die de afgelopen jaren zijn gepubliceerd, komt een overkoepelende limitatie naar voren. Het onderzoek

naar ACHD wordt structureel belemmerd door heterogene studiepopulaties van beperkte omvang, observationele en vaak single-centre onderzoeksopzetten en een algemeen gebrek aan prospectieve studies met voldoende statistische power. Hoewel de vroege voordelen die voor deze nieuwe behandelingsopties zijn waargenomen bemoedigend zijn, is het bewijs verre van definitief en zal het in zijn huidige vorm waarschijnlijk niet leiden tot sterke aanbevelingen in ACHD- of HF-specifieke richtlijnen. Dit proefschrift biedt daarom een sterke rationale voor grote, *multicentre*, prospectieve, gerandomiseerde studies die gericht zijn op het ophelderen van de potentiële effectiviteit van deze nieuwe behandelingsopties bij de ACHD-populatie. Niettemin blijven de aanzienlijke kosten die gepaard gaan met het uitvoeren van dergelijke klinische trials een belangrijke beperkende factor in ACHD-onderzoek.

Eerdere ervaringen hebben aangetoond dat het uitvoeren van klinische *trials* in de ACHD-populatie geen sinecure is, zoals blijkt uit de recente voortijdige beëindiging van de PARACYS-RV -studie vanwege zorgen omtrent patiëntveiligheid. PARACYS-RV had tot doel de effecten van sacubitril/valsartan bij de populatie met sRV falen te evalueren via een gerandomiseerde, placebogecontroleerde, dubbelblinde, *cross-over* onderzoeksopzet. Het onderzoek werd beëindigd omdat er een toename van worsening *HF events* werd waargenomen na het staken van sacubitril/valsartan na de run-in fase en tijdens de geplande *wash-out* periode. Hoewel er bij de met sacubitril/valsartan behandelde patiënten verbeteringen werden waargenomen in de submaximale inspanningsduur en NT-proBNP, kon er door de voortijdige beëindiging geen definitieve conclusie worden getrokken over de effectiviteit. Deze ervaring toont aan dat observationele resultaten kunnen afwijken van de uitkomsten van gerandomiseerde studies en benadrukt de complexiteit van een robuuste onderzoeksopzet binnen de ACHD-populatie. De bezorgdheid over de veiligheid bij PARACYS-RV is spijtig, gezien *cross-over* trials methodologisch aantrekkelijk zijn in ACHD-onderzoek vanwege hun efficiëntie, waardoor de vereiste steekproefomvang kan worden verkleind en variabiliteit tussen proefpersonen kan worden gecontroleerd.[27]

Momenteel worden er deelnemers geworven voor een eenvoudiger single-centre onderzoek waarin ACHD-patiënten worden gerandomiseerd in een groep die sacubitril/valsartan krijgt en een placebogroep. Naar verwachting zal dit onderzoek in de toekomst waardevolle inzichten opleveren (NCT06693674). In de database van ClinicalTrials.gov zijn daarnaast nog twee gerandomiseerde klinische trials te vinden waarin de effecten van SGLT2i bij patiënten met FCF (NCT06955260) en tetralogie van Fallot (NCT06668389) worden geëvalueerd, en één waarin de effecten van CRT bij de algemene ACHD-populatie (NCT05524324) worden geëvalueerd. De resultaten van deze studies worden vol anticipatie afgewacht door de ACHD-gemeenschap, hoewel er nog steeds zorgen bestaan over de heterogeniteit van

de populatie, de balans tussen het bereiken van voldoende statistische power en haalbare inclusietermijnen en de keuze van optimale (surrogaat) eindpunten.

Om deze zorgen weg te nemen en een aanvullende strategie te bieden om de kennis over ACHD-gerelateerd HF te bevorderen, heeft dit proefschrift zich ten doel gesteld om gebruik te maken van *real-world data* door middel van de oprichting van de *ACHIEVE-SGLT2i* en *RECORD-CHD* registries. Hoewel deze *registries* beperkt blijven in omvang en alleen de verzameling van multicentre observationele gegevens faciliteren, kan mogelijk een deel van de antwoorden die we zoeken uiteindelijk worden afgeleid uit grote, prospectieve, *registry*-gebaseerde klinische onderzoeken.[28, 29] *Real-world follow-up* studies kunnen in de praktijk inzicht verschaffen in de veiligheid van behandelingsopties op lange termijn en kunnen worden gebruikt om specifieke neurohumorale biomarker- en beeldvormingsstudies uit te voeren. Bovendien zijn *real-world registries* en *registry*-gebaseerde studies krachtige instrumenten om harde klinische eindpunten te meten, wat mogelijk patiëntselectie kan verbeteren, besluitvorming kan sturen en aanbevelingen in richtlijnen kan beïnvloeden.

Om deze infrastructuur op te zetten zou de ACHD-gemeenschap inspiratie kunnen putten uit succesvolle initiatieven zoals de Zweedse nationale HF *registry* (SwedeHF) en de koppeling van gegevens tussen deze ziektespecifieke *registry* en de nationale sterfte- en ziekenhuisopnamedatabases.[30] Specifiek voor de Nederlandse situatie zou dit kunnen worden bereikt via de Nederlandse database voor aangeboren hartafwijkingen (CONCOR), die gedeeltelijk is samengevoegd met de Nederlandse Hart Registratie (NHR) en een platform biedt voor *data-linkage* studies. Twee componenten zijn essentieel om het volledige potentieel van deze *real-world evidence*-benadering te kunnen benutten.

Ten eerste is sterke nationale en internationale samenwerking onontbeerlijk om de vereiste schaal te bereiken. Dit kan nationaal worden gerealiseerd via netwerken zoals het "Deltaplan Hartfalen" van de *Dutch CardioVascular Alliance (DCVA)*, waarvan het werk in dit proefschrift reeds deel uitmaakt. Internationaal kunnen de *Working Group on Adult Congenital Heart Disease van de European Society of Cardiology (ESC)*, de *International Society for Adult Congenital Heart Disease (ISACHD)* en de *Alliance for Adult Research in Congenital Cardiology (AARCC)* een sleutelrol spelen bij het verwezenlijken van deze ambitie.

Ten tweede zijn methodologische ontwikkelingen in ACHD-onderzoek nodig voor een robuuste analyse van deze *real-world data*. Zoals in dit proefschrift wordt benadrukt, biedt *mixed-effects modelling* een rigoureus statistisch kader voor de data-analyse van

ongebalanceerde herhaalde metingen, hetgeen nodig is om longitudinale veranderingen in complexe datasets betrouwbaar te analyseren. Daarnaast is target *trial emulation* een opkomend kader voor het ontwerpen van observationele studies, dat de kwaliteit van observationele studies aanzienlijk kan verbeteren en het mogelijk maakt het causale effect van interventies te benaderen.[31]

Tezamen kunnen sterke (inter-)nationale samenwerking en methodologische vooruitgang enkele van de praktische obstakels van conventionele gerandomiseerde gecontroleerde trials mitigeren, waardoor een realistische en haalbare strategie ontstaat om de vele hiaten in het bewijs rond ACHD-gerelateerd HF op te vullen.

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PhD Portfolio

The PhD Trajectory – An Overview
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Dissemination, Acknowledgement, Esteem And Other Relevant Scientific Activities

The PhD Trajectory – An Overview

My PhD started in April 2022 at the Department of Cardiology of the Leiden University Medical Center and was supported by the Leiden University Medical Center research council Cardio-Vascular cluster Themes for Innovation funding obtained by Dr. Egorova. The aim was to evaluate the effects of novel HF treatments in ACHD patients. In my first year, I focused on setting up a registry infrastructure, developing study protocols, and obtaining ethical approvals. I completed an initial study evaluating SGLT2i in patients with an sRV (Chapter 3) and wrote a case series on the management of baffle leaks in this population (Chapter 8).

To expand this work, I initiated an international collaboration with Prof. Veldtman (Glasgow), Dr. Zemrak (London), and Dr. MacDonald (Cardiff). This led to three working visits, each about three weeks long, at the end of my first year. During these visits, I collected data for a first multicentre study. I wrote the manuscript at the start of my second year, and it was published in the Journal of the American College of Cardiology (Chapter 2). During this first year, I also completed several PhD courses and obtained my BROK certificate. Although my Dekker Junior Clinical Scientist grant application on this topic was unsuccessful, I received funding from Foundation 'De Drie Lichten' and an educational grant from AstraZeneca.

In my second year, I again applied for the Dekker grant but was not selected. I was awarded the KNAW Ter Meulen Grant, which supported a three-month research visit to Glasgow in December 2023. During this period, I learned and performed detailed echocardiographic analyses on patients with sRV and single ventricle physiology treated with SGLT2i (Chapters 4 and 7). In the spring of 2024, I spent two months in London to collect data on CRT in ACHD patients (Chapter 9).

In my third and fourth year, I focused on registry-based research. We established the ACHIEVE-SGLT2i registry (NCT06932081), an international multicentre registry investigating SGLT2 inhibitor use in ACHD patients. This required coordination across centres, standardised data collection, and attention to data quality. The registry now includes over 430 patients from 11 centres across Europe, the United Kingdom, and the United States. Within this framework, I conducted a study on SGLT2i therapy in patients with FCF (Chapter 6).

Building on earlier CRT work, Drs. Zwaenepoel, a cardiac implantable electronic device fellow at our centre, and I established the RECORD-CHD registry (NCT06969924). This

registry systematically collects CRT data in ACHD patients. We also conducted a systematic review and meta-analysis and a study on CRT response and predictors, which are not included in this thesis. In parallel, I published on changes in QOL following initiation of sacubitril/valsartan in sRV patients (Chapter 5), building on earlier work by my predecessor, Dr. Nederend.

To contribute to dissemination and patient engagement, I co-authored an article with a lived-experience expert for the journal of the Dutch ACHD patient association (Chapter 10). From my third year onwards, I was also involved in recruitment and data collection for the ARTORIA-R registry, focusing on outcomes in ACHD patients with end-stage HF evaluated for heart transplantation, with first results anticipated in 2026.

From a methodological perspective, I focused on improving my statistical skills, particularly in the analysis of longitudinal data using mixed-effects models. Working with repeated measurements required close collaboration with statisticians and iterative model development. Over time, I became more confident in applying these methods across projects, enabling more advanced analyses and clearer interpretation of results. During my PhD, I also started using generative artificial intelligence tools in a supportive role, for R scripting and text correction.

In addition to clinical and registry-based research, I initiated a preclinical project using an SGLT2 knock-out mouse model to investigate right ventricular fibrosis, in collaboration with Dr. Zuurbier at Dr. Weber at the Amsterdam UMC. Although not included in this thesis, this project provided translational research experience, and is being continued by my successor Drs. Tebbens.

Alongside my research, I served as a junior editor for European Heart Journal – Case Reports, reviewing over 50 manuscripts. I also contributed to teaching by giving work groups and supervising BSc and MSc students. In addition, I was involved in academic and organizational activities, including the LUMC cardiovascular research newsletter, the departmental scientific committee, writing patient information, and national initiatives within the Netherlands Society of Cardiology (Landelijke Assistentendag Cardiologie/ Juniorkamerdag). During my PhD, I remained involved in clinical care with the post-myocardial infarction outpatient clinic. In August 2025, after just over three years of full-time research, I transitioned to full-time clinical work as a resident not in training (ANIOS), and in February 2026, I was accepted into the cardiology residency program (AIOS), which I started in June 2026.

Overall, my PhD trajectory combined clinical, translational, and methodological research, with an emphasis on international collaboration and registry-based studies. Over time, I developed independence in study design, repeated measurements analyses, and multicentre collaboration. With the enthusiasm of my successor Drs. Westdorp, and the continued support of my supervision team, I aim to further develop this research line and improve care for ACHD patients with HF.

CRediT Statement For The Chapters In This Thesis

Ch.	Type*	Short Title	Conceptualization	Data Curation	Formal Analysis	Funding Acquisition	Investigation	Methodology	Project Administration	Resources	Software	Supervision	Validation	Visualization	Writing - Original Draft	Writing - Review & Editing	Preregistered	Preprinted	Published with Peer Review
1	Introduction	1: Introduction	■				■	■	■					■	■	■	☐	☐	☐
2	PhD project chapter	2: SGLT2i in 174 ACHD patients	■	■	■	▒	■	■	■	■	■	▒	■	■	■	■	☐	☐	☑
3	PhD project chapter	3: SGLT2i in sRV failure	■	■	■		■	■	■	■	■		■	■	■	■	☐	☐	☑
4	PhD project chapter	4: SGLT2i in sRV failure - imaging	■	■	■	▒	■	■	■	■	■	▒	■	■	■	■	☐	☐	☑
5	PhD project chapter	5: ARNI in sRV failure	▒	■	■		▒	■	▒	■	■	■	■	■	■	■	☐	☐	☑
6	PhD project chapter	6: SGLT2i in Fontan failure	■	■	■	▒	■	■	■	■	■	▒	■	■	■	■	☐	☐	☑
7	PhD project chapter	7: SGLT2i in SV failure - imaging	■	■	■	▒	■	■	■	■	■	▒	■	■	■	■	☐	☐	☑
8	PhD project chapter	8: Baffle leaks in sRV failure	■	■	■		■	■	■	■	■		■	■	■	■	☐	☐	☑
9	PhD project chapter	9: CRT in ACHD	■	■	▒	▒	▒	■	■	■	■	▒	■	■	■	▒	☐	☐	☑
10	PhD project chapter	10: Patient involvement article	■				■	■	■							■	☐	☐	☐
11	Discussion	11: Discussion	■				■	■	■							■	☐	☐	☐

*PhD project chapters are the direct result of the PhD project of the PhD candidate.
Some theses also include Collaboration Chapters, to which the PhD candidate has contributed but fall outside the PhD project.

Dissemination Table

PEER REVIEWED PUBLICATIONS

1. Tsang V, Haapanen H, **Neijenhuis R.** Aortic Coarctation/Arch Hypoplasia Repair: How Small Is Too Small. Seminars in Thoracic & Cardiovascular Surgery: Pediatric Cardiac Surgery Annual. 2019;22:10-3.

Chapter in this thesis	Not in this thesis
URL	https://www.semtcvspeds.com/article/S1092-9126(18)30018-8/fulltext
DOI	10.1053/j.pcsu.2019.02.011

2. Haapanen H, Tsang V, Kempny A, **Neijenhuis R**, Kennedy F, Cullen S, et al. Grown-up Congenital Heart Surgery in 1093 Consecutive Cases: A "Hidden" Burden of Early Outcome. The Annals of Thoracic Surgery. 2020;110(5):1667-76.

Chapter in this thesis	Not in this thesis
URL	https://www.annalsthoracicsurgery.org/article/S0003-4975(20)30338-6/fulltext
DOI	10.1016/j.athoracsur.2020.01.071

3. Mustafa MR*, **Neijenhuis RML***, Furci B, Tsang VT. Neck cannulation for bypass in redo sternotomy in children and adults with congenital heart disease. Interactive CardioVascular and Thoracic Surgery. 2020;31(1):108-12.

Chapter in this thesis	Not in this thesis
URL	https://academic.oup.com/icvts/article/31/1/108/5814885
DOI	10.1093/icvts/ivaa045

4. Tsang VT, **Neijenhuis RML**. Commentary: The Location of the Conduction System in Atrioventricular Septal Defect—Will It Alter the Way We Operate? Seminars in Thoracic and Cardiovascular Surgery. 2020;32(4):971-2.

Chapter in this thesis	Not in this thesis
URL	https://www.semthorcardiovascsurg.com/article/S1043-0679(20)30117-9/fulltext
DOI	10.1053/j.semtcvs.2020.04.007

5. **Neijenhuis RML**, Tsang VT, Marek J, Issitt R, Bonello B, Von Klemperer K, et al. Cone reconstruction for Ebstein anomaly: Late biventricular function and possible remodeling. J Thorac Cardiovasc Surg. 2021;161(3):1097-108.

Chapter in this thesis	Not in this thesis
Conference contributions	Oral presentation at the 100th annual meeting of the American Association for Thoracic Surgery (AATS) 2020
Pediheart podcast #164 by Dr. Robert Pass	https://open.spotify.com/episode/2MHdfIrAxMA6L3ml37dM5z?si=7877fcb723904fad
URL	https://www.jtcvs.org/article/S0022-5223(20)33049-X/fulltext
DOI	10.1016/j.jtcvs.2020.10.124

6. **Neijenhuis RML**, Regeer MV, van der Kley F, Vliegen HW, Jongbloed MRM, Kiès P, et al. Contemporary Management Strategies of Baffle Leaks in Adults with a Failing Systemic Right Ventricle Late after Atrial Switch: A Case Series and Literature Overview. J Cardiovasc Dev Dis. 2023;10(3).

Chapter in this thesis	8
URL	https://www.mdpi.com/2308-3425/10/3/129
DOI	10.3390/jcdd10030129

7. Acem I, van Praag VM, Mostert CQ, van der Wal RJ, **Neijenhuis RML**, Verhoef C, et al. Noninvasive detection of soft tissue sarcoma using volatile organic compounds in exhaled breath: a pilot study. Future Oncology. 2023;19(10):697-704.

Chapter in this thesis	Not in this thesis
URL	https://www.tandfonline.com/doi/full/10.2217/fon-2022-1122
DOI	10.2217/fon-2022-1122

8. **Neijenhuis RML**, Nederend M, Jongbloed MRM, Kiès P, Rotmans JI, Vliegen HW, et al. The potential of sodium-glucose cotransporter 2 inhibitors for the treatment of systemic right ventricular failure in adults with congenital heart disease. Front Cardiovasc Med. 2023;10:1093201.

Chapter in this thesis	3
Conference contributions	Poster presentation at EuroACHD 2023
URL	https://www.frontiersin.org/journals/cardiovascular-medicine/articles/10.3389/fcvm.2023.1093201/full
DOI	10.3389/fcvm.2023.1093201

9. **Neijenhuis RML**, MacDonald ST, Zemrak F, Mertens BJA, Dinsdale A, Hunter A, et al. Effect of Sodium-Glucose Cotransporter 2 Inhibitors in Adults With Congenital Heart Disease. Journal of the American College of Cardiology. 2024;83(15):1403-14.

Chapter in this thesis	2
Conference contributions	Oral presentation at American College of Cardiology (ACC) 73rd Annual Scientific Session & Expo 2024 • Coordinated simultaneous publication in the Journal of the American College of Cardiology (JACC) • Abstract URL: https://www.jacc.org/doi/10.1016/S0735-1097%2824%2903568-X Poster presentation at Congenital Heart Disease in the Adult (ACHD) Annual Conference - Skamania 2024 Oral presentation at the Czech Cardiovascular Research and Innovation Days 2024
Editorial Comment by Dr. Luke Burchill, Dr. Chales Jain, and Dr. William Miranda	https://www.jacc.org/doi/10.1016/j.jacc.2024.03.002
JACC podcast by Dr. Valentin Fuster	https://www.jacc.org/digital-content/podcast/effect-sodium-glucose-cotransporter-2-inhibitors-adults-congenital-heart-disease
Pediheart Podcast #293 by Dr. Robert Pass	https://open.spotify.com/episode/0mhq1ANmjlHrSwjlssUrQs?si=caacf349c9fc4107
ACC Expert Analysis by Dr. William Marshall and Dr. Curtis Daniels	https://www.acc.org/Latest-in-Cardiology/Articles/2024/06/03/12/45/An-Update-on-Sodium-Glucose-Cotransporter-2-Inhibitors-in-Adults-With-CHD
Medscape Medical News	https://www.medscape.com/viewarticle/sglt2-inhibitors-safe-hf-congenital-heart-disease-2024a10006ih
URL	https://www.jacc.org/doi/10.1016/j.jacc.2024.02.017
DOI	10.1016/j.jacc.2024.02.017

10. **Neijenhuis RML**, Nederend M, van Groningen AE, Jongbloed MRM, Vliegen HW, Jukema JW, et al. Sacubitril/valsartan is associated with improvements in quality of life in adult congenital heart disease patients with systemic right ventricular failure. Open Heart. 2025;12(1).

Chapter in this thesis	5
URL	https://openheart.bmj.com/content/12/1/e003009
DOI	10.1136/openhrt-2024-003009

11. **Neijenhuis RML**, Regeer MV, Walker NL, Mertens BJ, Hunter A, Kiès P, et al. Effect of sodium-glucose cotransporter 2 inhibitors on ventricular function in systemic right ventricular failure. Open Heart. 2025;12(2).

Chapter in this thesis	4
Conference contributions	Oral presentation at EuroACHD 2025
URL	https://openheart.bmj.com/content/12/2/e003445
DOI	10.1136/openhrt-2025-003445

12. **Neijenhuis RML**, Regeer MV, Walker NL, Hunter A, Kiès P, Holman ER, et al. Echocardiographic Effects of Sodium-Glucose Cotransporter 2 Inhibitors in Single Ventricle Circulatory Failure. International Journal of Cardiology Congenital Heart Disease. 2025:100603.

Chapter in this thesis	7
Conference contributions	Oral presentation at the 9th DCVA-NLHI Translational Cardiovascular Research Meeting and moderated poster presentation at ESC 2025
URL	https://www.sciencedirect.com/science/article/pii/S2666668525000394
DOI	10.1016/j.ijcchd.2025.100603

13. Zwaenepoel BAC, **Neijenhuis RML**, Veldtman G, Blom NA, Jukema JW, Jongbloed MRM, et al. Effectiveness of Cardiac Resynchronization Therapy in Adult Congenital Heart Disease: A Meta-Analysis of Biventricular and Conduction System Pacing Outcomes. Heart Rhythm. 2026;23(4):e624-e35.

Chapter in this thesis	Not in this thesis
URL	https://www.heartrhythmjournal.com/article/S1547-5271(26)00019-6/fulltext
DOI	10.1016/j.hrthm.2026.01.004

14. **Neijenhuis RML***, Zwaenepoel BAC*, Jansen TD, Ezzat V, van Erven L, Lowe M, et al. Effects of cardiac resynchronization therapy in adults with congenital heart disease. BMC Cardiovasc Disord. 2026;26(1).

Chapter in this thesis	*9*
Conference contributions	Poster presentation at EuroACHD 2026
URL	https://link.springer.com/article/10.1186/s12872-026-05818-5
DOI	10.1186/s12872-026-05818-5

15. **Neijenhuis RML**, Cedars AM, Zaidi A, Torres-Viera G, Mazurek R, Walker NL, et al. Real-world experience with sodium-glucose cotransporter 2 inhibitors in adults with Fontan circulatory failure. Front Cardiovasc Med. 2026;13:1771868.

Chapter in this thesis	*6*
Conference contributions	Oral presentation at the 9th DCVA-NLHI Translational Cardiovascular Research Meeting, EuroACHD 2026, and moderated poster presentation at ESC 2025
URL	https://www.frontiersin.org/journals/cardiovascular-medicine/articles/10.3389/fcvm.2026.1771868/full
DOI	10.3389/fcvm.2026.1771868

NON-PEER REVIEWED PUBLICATIONS

1. **Neijenhuis RML**. Hot Line session 3 – RESPAHE-HF2, MATTERHORN, Tri.fr. London, 31 August 2024. Netherlands Heart Journal ESC Supplement, Volume 23, Supplement 1, November 2024

Chapter in this thesis	Not in this thesis
URL	Not available
DOI	Not available
ISSN	1569-643X

2. **Neijenhuis R**, Dahlmans M, Egorova A. Behandelopties voor hartfalen bij patiënten met een systemische rechterkamer. Sinus. 2025 Juni 2025:18-20.

Chapter in this thesis	10
URL	LinkedIn post with PDF to article: https://www.linkedin.com/posts/ralph-neijenhuis_artikel-sinus-activity-7346879848063098883-CveL?utm_source=share&utm_medium=member_desktop&rcm=ACoAACut4FgBRFcShLkegyKZwnCLgWS6ZYZOruM
DOI	Not available

Overview Of Completed Courses And Other Training

Month/year	Title/description	Hours
Mandatory courses		
05/2022	Joint UL-LUMC PhD Introductory Meeting	5
07/2022	Scientific Conduct for PhDs (LUMC)	5
09/2022	Boerhaave 'Basic Methods and Reasoning in Biostatistics'	42
03/2023	Basic course for clinical investigators (BROK®)	42
Other courses		
10/2022	Dutch Heart Foundation Cardiovascular Course: Cardiac Function & Adaptation	40
06/2023	Abbott echo course 'Reis door het falende hart'	8
04/2024	ACHD Academy Echo Imaging Course: 3rd Echocardiography Imaging Course in Adult Congenital Heart Disease	8
04/2024	Hands-on course morphology of univentricular heart disease	12
06/2024	Boerhaave course 'Analysis of Repeated Measurements'	42
11/2024	Medtronic CRT training	16
10/2025	HFA clinical trials in heart failure course	16
Teaching activities		
02/2023	BSc medicine working groups on physiological concepts	4
09/2023 – 01/2024	Supervision of MSc Thesis (wetenschapsstage) Thomas Jansen	56
11/2023	BSc medicine working groups on physiological concepts	4
05/2024	BSc medicine working groups on chest pain	4
12/2024	BSc medicine working groups on cardiovascular interaction	4

Dissemination, Acknowledgement, Esteem And Other Relevant Scientific Activities

Month/year	Title/description	Linked to chapter(s)
Conference presentations		
09/2022	London ACHD 2022 Advanced Symposium, London, UK *Oral presentation*	2
11/2022	CCH Groningen 75 years symposium, Groningen, NL *Poster presentation*	2
11/2022	13th Rembrandt symposium 2022, Noordwijkerhout, NL *Oral presentation*	2
04/2023	EuroACHD 2023, Paris, France *Poster presentation*	3
05/2023	Heart Failure 2023, Prague, Czech Republic Moderated *Poster presentation*	2
11/2023	NVVC najaarscongres 2023, Papendal, NL *Oral presentation*	2
04/2024	ACC.24, Atlanta, US *Oral presentation*	2
05/2024	Skamania ACHD, Portland, US *Poster presentation*	2
11/2024	Czech Cardiovascular Research and Innovation Days 2024, Prague, Czech Republic *Oral presentation*	2
04/2025	EuroACHD 2025, Naples, Italy *Oral presentation*	4
06/2025	9th DCVA-NLHI Translational Cardiovascular Research Meeting, Utrecht, NL *Oral presentation*	6,7
08/2025	ESC 2025, Madrid, Spain *Moderated poster presentation*	6,7
04/2026	EuroACHD 2026, Madrid, Spain *Oral presentation & poster presentation*	6,9

Representing research at different type of meetings

11/2022	Netherlands Heart Institute LUMC site visit	2, 3
11/2022	SGLT2i research pitch at the ACHD work group meeting of the Dutch Society of Cardiology (NVVC)	2, 3, 4, 6, 7

Awards and prizes

10/2022	Dutch Heart Foundation Cardiovascular Course: Cardiac Function & Adaptation *Audience prize for best poster*	2
09/2022	London ACHD 2022 Advanced Symposium, London, UK *Best abstract presentation prize*	2
04/2025	EuroACHD 2025, Naples, Italy *Best abstract presentation prize*	4

Grant applications

10/2022	Stichting 'De Drie Lichten' grant € 5.500,-	2, 4, 6, 7
11/2022	AstraZeneca Educational Grant € 2.900,-	2, 4, 6, 7
06/2023	KNAW Ter Meulen Grant € 6.400,-	4, 6, 7

Unsuccessful

07/2022	Dutch Heart Foundation Dekkerbeurs Junior Clinical Scientist	
07/2023	Dutch Heart Foundation Dekkerbeurs Junior Clinical Scientist	
03/2024	Heart4data open call data-linkage	

Appendix

Acknowledgements

Curriculum Vitae

Acknowledgements

Onderzoek, zeker in het geval van zeldzame aangeboren hartafwijkingen, kan niet zonder samenwerking. Ik wil dan ook graag iedereen bedanken die direct of indirect een rol heeft gespeeld in de totstandkoming van dit proefschrift. Een aantal personen wil ik in het bijzonder bedanken.

Allereerst mijn promotoren Prof. Dr. J. Wouter Jukema, Prof. Dr. Monique R.M. Jongbloed en copromotor Dr. Anastasia D. Egorova.

Beste Wouter, ik ben enorm dankbaar voor jouw steun en betrokkenheid de afgelopen jaren. Naast het belang van sociale cohesie heb ik van je geleerd dat zo lang je er zelf vol voor gaat, alles mogelijk is.

Beste Monique, het is een eer dat ik onder jouw supervisie heb morgen werken en van jouw expertise heb kunnen leren. Jouw fundamentele interesse in de anatomie en embryologie van aangeboren hartafwijkingen vormt een inspiratie voor me.

Beste Anastasia, bedankt voor jouw eindeloze steun en enthousiasme de afgelopen jaren. Ik vind jouw motivatie bewonderenswaardig en kijk uit naar onze toekomstige samenwerkingen.

Dear Gruschen, you have been a core member of the "SGLT2i team" from the start, and this thesis would not have been possible without your dedication. You and your whole family have made me feel at home during the dark months in Glasgow, and I cannot thank you enough for that.

Dear Filip and Simon, I am truly grateful for your early support and the time I could spend at your centres in London and Cardiff. Those working visits have formed the foundation of our successful ACHIEVE-SGLT2i registry.

A huge thanks to all other collaborators in the ACHIEVE-SGLT2i and RECORD-CHD registries, from many centres in Europe, the United Kingdom, and the United States. With our work, I believe that we can make a real impact for ACHD patients suffering from HF.

Uiteindelijk gaat het om onze patiënten. Daarom wil ik ook alle patiënten die hebben bijgedragen aan het onderzoek, de Patiëntenvereniging Aangeboren Hartafwijkingen en Marianne Dahlmans, medeauteur van hoofdstuk 10, bedanken.

Philippine, Hubert, Madelien en Philippe, als congenitale vakgroep heb ik in de afgelopen jaren veel van jullie geleerd. Madelien, je hebt mijn enthousiasme voor beeldvorming echt aangewakkerd. Ook veel dank aan alle andere collega's van de afdeling hartziekten. Ik heb een hele goede tijd gehad als ANIOS en kijk er naar uit weer terug te keren in het LUMC.

Daarnaast kunnen mijn collega's uit de Tuin niet ontbreken. Van samen lunchen, religieus om 12:00 uur, tot alle congressen en uitstapjes; het was een onvergetelijke tijd. Natuurlijk verdienen 'The ACHD Kids' Marieke, Diederick, Justin, Mette, Walid en Björn en ook Bert een aparte vermelding. Als congenitale onderzoekers kunnen we altijd op elkaar rekenen. Marieke, het was niet gemakkelijk om iemand die zo gedreven is als jij op te volgen. Bert, ik heb veel van je geleerd over devices en genoten van onze samenwerking. Björn, heel veel succes met het voortzetten van de onderzoekslijn. Ik heb er het volste vertrouwen in.

Al mijn clubgenoten van Helios, door de jaren heen hebben jullie ervoor gezorgd dat het zonnetje genoeg bleef schijnen. Huisgenoten van De Lepelaer, ook jullie hebben gezorgd voor de nodige afleiding de afgelopen jaren. Boris en Tjerk, van onze eerste dagen als geneeskundestudenten tot onze start als PhD'ers aan de woonkamertafel in de Theresiastraat tijdens de lockdown hebben we onze academische carrières gedeeld. Ik ben dan ook dankbaar dat jij, Boris, naast me staat als paranimf. Boaz en Jerom, zonder dat ik bij jullie op de bank mocht bivakkeren in Londen was een deel van dit proefschrift misschien niet mogelijk geweest. Boaz, hoewel ik het niet van jouw medische kennis moet hebben, kan ik toch altijd op je rekenen. Het is een eer dat jij de oversteek vanuit Londen maakt om mijn paranimf te zijn. Ik mag me gelukkig prijzen met zoveel goede vrienden.

Mam en pap, dank jullie wel voor de onvoorwaardelijke steun. Zonder alle medische discussies met mam en de rationele blik van pap was ik niet geworden tot wie ik nu ben. Vera en Juliette, ik ben trots op jullie als mijn zusjes.

Tot slot kan mijn grootste steun en toeverlaat niet ontbreken. Liefste Maartje, dankjewel voor jouw eindeloze steun. Je onophoudelijke pogingen om te onthouden waar "SGLT2i" nu eigenlijk voor staat zijn niet onopgemerkt gebleven. We hebben flink wat tijd zij-aan-zij werkend aan één bureau in ons privékantoortje aan de gracht doorgebracht. We steunen elkaar door dik en dun en ik ben trots op alles wat we samen bereikt hebben. Door jou ben ik de beste versie van mezelf. Ik kijk uit naar de vele avonturen die we nog gaan beleven samen.

Curriculum Vitae

Ralph Mark Louis Neijenhuis werd op 9 juni 1997 geboren te Utrecht. Hij behaalde zijn voorbereidend wetenschappelijk onderwijs (VWO) diploma aan het Theresialyceum te Tilburg in 2015, waarna hij startte met de studie geneeskunde aan de Universiteit Leiden. Na zijn bachelor geneeskunde ving hij zijn master aan met een wetenschappelijke stage bij de congenitale cardiothoracale chirurgie in het Great Ormond Street Hospital en het Barts Heart Centre in Londen, onder begeleiding van Prof. Victor T. Tsang. Hij sloot zijn master cum laude af met een semi-artsstage bij de cardiologie in het HagaZiekenhuis. In mei 2022 startte hij vervolgens met zijn promotieonderzoek bij de afdeling cardiologie van het Leids Universitair Medisch Centrum (LUMC) onder begeleiding van zijn promotoren Prof. Dr. J. Wouter Jukema, Prof. Dr. Monique R.M. Jongbloed en copromotor Dr. Anastasia D. Egorova. Gedurende zijn promotie was hij visiting research fellow in het Golden Jubilee University National Hospital in Glasgow, Barts Heart Centre in Londen en University Hospital of Wales in Cardiff. Zijn werk en de internationale samenwerkingen hebben geleid tot de resultaten beschreven in dit proefschrift. Na ruim drie jaar onderzoek, startte hij in augustus 2025 als arts niet in opleiding tot specialist (ANIOS) bij de afdeling cardiologie in het LUMC. In februari werd hij aangenomen voor de opleiding tot cardioloog in het LUMC. Per 1 juni 2026 is hij gestart met zijn vooropleiding interne geneeskunde in het Onze Lieve Vrouwe Gasthuis (OLVG) te Amsterdam.