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Heart failure in congenital heart disease: management options and clinical challenges

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Abstract

Introduction: The population of adults with congenital heart disease (ACHD) is rapidly expanding and one of the major complications is heart failure. Timely diagnosis and treatment are crucial, but strong evidence for effectiveness of heart failure treatment in ACHD is currently lacking. Components of the medical history, physical examination and further diagnostic tests including ECG, echocardiography, cardiac magnetic resonance imaging, exercise testing, and biomarkers can identify patients at risk for early mortality or heart failure.

Areas covered: Although the number of studies guiding evidence-based treatment are expanding, many clinical questions have not been completely answered yet. Therefore, in this review we provide an overview of current available insights in epidemiology, diagnosis, risk stratification and treatment options in ACHD patients, including non-medical therapies and advanced care planning.

Expert Opinion: We strongly advocate expanding current use of biomarkers in the diagnostic process and timely initiation of discussing advanced treatment options and advanced care planning with patients and their loved ones. More research in multi-center collaborations is needed to study all aspects of care of adult congenital heart disease patients.

Keywords: Risk stratification; Prognosis; Diagnosis; Biomarkers; Heart failure; Treatment; Congenital Heart Defects; Predictors.

Article highlights

- Nowadays, most CHD patients will survive into adulthood due to the astonishing improvement in care.
- Heart failure is an important and increasingly prevalent clinical issue in ACHD patients.
- Biomarkers are the cornerstone of heart failure diagnosis.
- There are currently no large clinical trials guiding clinical treatment of heart failure, so multicenter collaboration is essential.
- Advanced care planning is essential and should be discussed early with our patients and their loved ones.

1. Introduction and epidemiology

Congenital heart disease (CHD) is the most common congenital abnormality diagnosed in newborns and lifelong specialist follow-up and often repeated surgical or interventional procedures are required [1]. There has been a substantial increase in the reported birth prevalence of CHD over time, with a reported incidence of 9.1 per 1.000 live births after 1995 [2]. There are significant geographical differences, with Europe having the second highest incidence (8.2 per 1.000 live births). Worldwide, 1.5 million children with CHD are born each year. Among them, 55% will have a simple heart defect, the remaining 45% having a defect of moderate or great complexity [3].

Due to the major advances in cardiothoracic surgery, pediatric cardiology and intensive care medicine in the past decades, most patients born with a CHD defect will survive into adulthood. In 2014, an estimated 1 million adults with CHD were living in the European Union [4], an estimated prevalence of 3 per 1000 [5]. Importantly, there has been an increase in the prevalence of CHD in patients beyond 60 years of age from 0.5% in 2000 to 5.1% in 2012 [4], to an estimated 11% when extrapolated to 2030 (figure 1). Since there is a high morbidity and mortality in this specific patient group, this will have a major impact upon organization of care and health care costs [6].

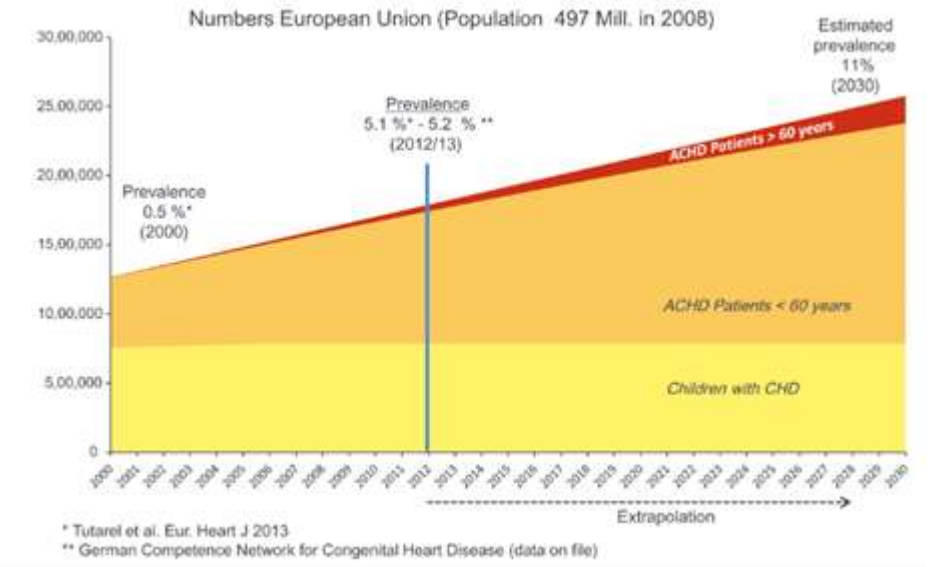

Figure 1. *Changing prevalence of Congenital Heart Disease (CHD) in the European Union by age group. The rough estimates of the total population of children, adult patients 18-60 and adult patients >60 years with CHD are based on published birth rates (in 2008) and consider only patients born after 1970, ignoring adult mortality. Assumptions are based on currently reported survival into adulthood[8], reported*

rates of patients >60 years and records of the German Competence Network for Congenital Heart Disease. ACHD: Adult Congenital Heart Disease. **Reproduced with permission.** [4]

Despite this spectacular increase in life expectancy complications occur often including heart failure, arrhythmias and stroke, necessitating lifelong specialized care and follow-up [7].

There are many potential factors contributing to the development of heart failure in CHD patients. Valvar abnormalities, shunt lesions, inflow or outflow tract obstruction, arrhythmia, persistent anatomical defects, abnormal loading conditions or cyanosis all have the potential to compromise cardiac function. Subsequent neurohumoral activation, myocardial fibrosis and adverse remodeling will lead to a progressive deterioration of cardiac function and the clinical syndrome of heart failure [8, 9].

The prevalence of heart failure in patients with adult congenital heart disease (ACHD) varies according to the underlying structural anomaly. In adults with a repaired Tetralogy of Fallot (ToF), there is a marked increase in prevalence of heart failure, ranging from 31.7% in patients aged 20-29 years old to 52.9% in patients over 50 [10]. There is also a clear increase with age of the prevalence of heart failure in patients with a transposition of the great arteries after atrial switch procedure. The probability of developing heart failure is about 25% in patients aged 20, 40% in patients aged 30 to almost 60% in patients aged 40 [11]. However, other studies report a lower prevalence of 23% during a median follow-up period of up to 35 years [12, 13]. Nevertheless, this number might increase even further in the near future, since a progressive deterioration of the systemic right ventricle in these patients is a well-known and unavoidable phenomenon [14]. In patients with a congenitally corrected transposition of the great arteries (ccTGA), the reported prevalence of heart failure by age 45 is 25% in patients without associated lesions and 76% in patients with associated lesions [15]. In patients with a single ventricle morphology after Fontan palliation, a prevalence of up to 40% is described during a mean post-operative follow-up period of 16 years, with patients having right ventricular morphology being especially at risk [16, 17]. Fortunately, in patients with less complex defects and systemic left ventricle morphology, a much lower prevalence is described, ranging from 2% in patients aged 30 with a repaired coarctation to 11% in patients with left to right shunt lesions [11].

Heart failure comprises a substantial burden of morbidity and utilization of resources. The reported incidence of first hospital admission for heart failure in ACHD patients was 1.2 per 1000 patient years in the Dutch national CONCOR registry [17]. In another study, heart failure accounted for 20% of all ACHD related hospital admissions [18]. Patients admitted for heart failure tend to have a longer hospital stay (12.2 days), are frequently admitted at the intensive care unit (25%) and more frequently readmitted (18%) [19]. Burchill et al described an increase in ACHD hospitalization rate of 91% between 1998 and

2001 with a 258% increase in ACHD heart failure hospitalization rate, which is twice as much as for non-ACHD heart failure admissions[20].

Finally, heart failure has become the leading cause of death in patients with ACHD, with a reported relative contribution ranging between 17% - 42%[17, 21, 22, 23, 24, 25, 26]. In figure 2, we summarized a number of trials investigating the mechanism of death in patients with ACHD. In 24.694 patients with ACHD, 1573 patients died. In 28.6%, heart failure was the mechanism of death [17, 21, 22, 24, 26].

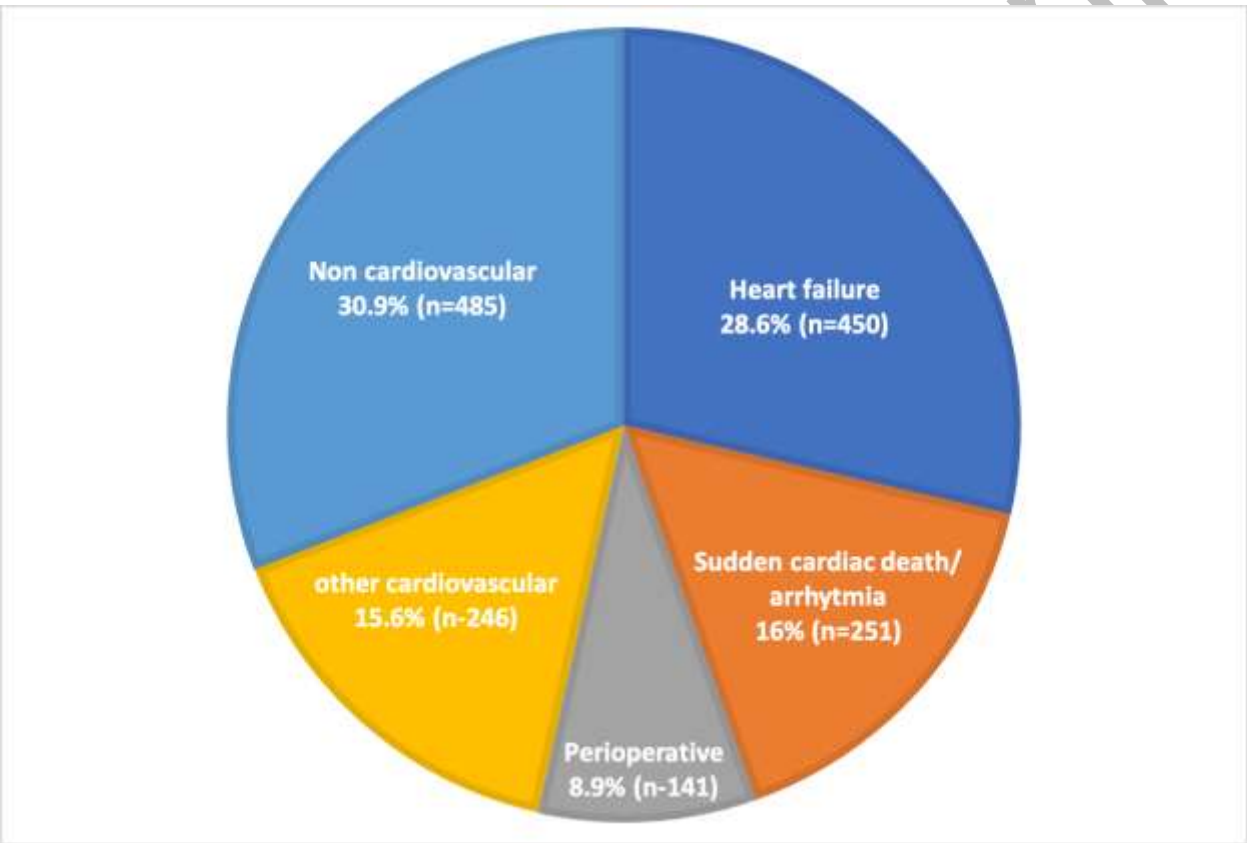

***Figure** 2. Mechanism of death in 1573 adult patients with congenital heart disease. See text for references.*

The abovementioned data emphasize the emerging importance of the clinical syndrome of heart failure amongst patients with ACHD. However, due to the significant heterogeneity in underlying cardiac anatomy, but also surgical and interventional history, clinical presentation varies widely, and the full scope of heart failure is likely to be underestimated. This is confirmed in multiple studies that have demonstrated VO2 max in ACHD patients to be diminished, regardless of NYHA class and underlying

cardiac anomaly[27, 28]. Subsequently we may greatly underestimate the true prevalence of (sub-clinical) heart failure and substantial efforts should be made to identify those patients at risk and those in the early stages of heart failure.

2. Diagnosis of heart failure in ACHD

Defining heart failure in ACHD can be challenging and might be influenced by patient and physician factors. The definition in the 2016 ESC Guidelines is as follows: " a clinical syndrome characterized by typical symptoms (…) that may be accompanied by signs (…) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress [9]." It can be easily appreciated that ACHD patients all have a structural abnormality which is often accompanied by elevated cardiac pressures [29]. Also, many patients have been adapting to their condition since birth. This lifelong adaptation may lead to a patient-specific adjustment and may mask their awareness of heart failure symptoms. As a result, signs and symptoms indicative of heart failure may not be reported to their physician. The guidelines differentiate between heart failure with reduced ejection fraction (HFREF) and heart failure with preserved ejection fraction (HFPEF), also known as diastolic dysfunction. The presence of HFPEF and its role in ACHD patients is not well investigated, although in specific cohorts such as Fontan patients some research is becoming available [30].

Diagnosis of heart failure in ACHD should consist of a comprehensive evaluation of signs and symptoms, diagnostic testing and medical history, as advised by the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. In ACHD patients, the guidelines do not offer any specific recommendations, but, as always, a patient-tailored approach is essential. Consultation with both ACHD and heart failure specialists is often helpful and constructive to evaluate the complex situation of these patients and to optimize diagnosis and treatment.

Symptoms and signs are often nonspecific and can be different from heart failure symptoms in the general population due to the relatively younger age and more complex (cardiac) history of the ACHD population, including a higher percentage of right heart failure [31]. Symptoms of heart failure include, but are not limited to, shortness of breath, fatigue, loss of energy, orthopnea, palpitations, postural nocturnal dyspnea, diminished exercise capacity, loss of appetite, weight gain, swollen ankles or abdomen and chest discomfort. A thorough history should be taken to elucidate the nature of the symptoms, time frame, provoking factors, such as anemia, arrhythmias or substance abuse, and

alternative explanations. The aim of the physical examination should be focused on signs of congestion and should be repeated at regular intervals during follow-up and treatment.

Congenital conditions with a predominantly right-sided phenotype and heart failure often exhibit signs of systemic venous congestion, such as peripheral edema (ankles, lower legs and abdomen), raised jugular venous pressure, hepatic and splenic enlargement and pleural effusion. Conditions associated with right- sided congestion include left-to-right shunts (e.g. atrial septal defects), Ebstein's anomaly with severe tricuspid valve regurgitation and Tetralogy of Fallot (ToF) with abnormalities of the pulmonary valve, arteries and the right ventricular outflow tract. Importantly, patients with predominantly right-sided abnormalities such as ToF may also develop left ventricular dysfunction, which may in turn cause symptoms [32]. Signs of left-sided causes of heart failure include crackles on lung auscultation, third heart sound and a displaced apex beat. It is important to realize that failure of the right ventricle and tricuspid valve in systemic right ventricles (e.g. ccTGA or after atrial switch surgery) leads to symptoms and signs of pulmonary congestion. In patients after Fontan procedure with a univentricular heart systemic congestion often predominates, related to elevated pressures in the Fontan circulation.

Initial diagnostic tests include electrocardiography, transthoracic echocardiogram and laboratory testing (e.g. hemoglobin, kidney and thyroid function and natriuretic peptides). Often, additional testing will be required to assess myocardial function, valvar function, exercise tolerance and heart rhythm abnormalities [33, 34]. These include, but are not limited to, cardiac magnetic resonance imaging, computer tomography scan, transesophageal echocardiography, cardiopulmonary exercise testing, tape monitoring and other forms of heart rhythm analysis such as implantable loop recorders (see table diagnosis).

	Indications	Limitations
Electrocardiogram	Sinus rhythm; atrial arrhythmias, e.g. atrial fibrillation; conduction delay	May not show paroxysmal arrhythmias
Laboratory testing	Kidney, liver and thyroid function; hemoglobin; infection parameters; clotting function; specific heart failure biomarkers	
Transthoracic echocardiogram	Myocardial contractile function; diastolic function; valvar function; intra-cardiac pressures; pulmonary pressures; dimensions of great vessels; function of baffles and conduits; pericardial fluid	Poor acoustic windows
Chest radiography	Cardiac size; pleural effusion; hilar enlargement	
Magnetic resonance imaging	Ventricular dimensions and function; valvar function; shunt fraction (Qp:Qs); baffle and conduit function; anatomic relationships	Artefacts from implants, claustrophobia
Computer tomography	Anatomic relationships; dimensions of vessels and structures	Possible use of iodine-based contrast agent, irradiation
Transesophageal echocardiography	Anatomic relationships; valvar function; intra-cardiac shunts	Semi-invasive
Cardiopulmonary exercise testing	Exercise capacity; rhythm disturbances; blood pressure at exercise	Inability to exercise
Tape monitoring	Heart rate frequency; atrial and ventricular rhythm abnormalities such as ectopic beats; atrial tachycardia and fibrillation and (non-sustained) ventricular tachycardia	May not show paroxysmal arrhythmias
Blood pressure recording	Readings during day and night and during different activities	

Coronary angiography	Course and condition of coronary arteries	Invasive, use of iodine-based contrast agent, irradiation
Left heart catheterization	Pressures and gradients at different locations, such as mitral valve, left ventricle, aortic valve, coarctation	Invasive
Right heart catheterization	Anatomy of venous structures; pressures at different levels, such as caval veins, right atrium, right ventricle, pulmonary artery (trunk and branches) and wedge pressure; Pressure gradient across pulmonary valve and conduits	Invasive

3. Risk stratification

In ACHD patients many factors are identified as prognostic including ventricular function, the presence of pulmonary hypertension, exercise capacity and biomarkers. The systolic ventricular function is one of the most important prognostic parameters and a moderately to severely impaired systemic ventricular function is an independent predictor for sudden cardiac death in the overall ACHD population. This is also true for patients with a systemic right ventricle. In addition, higher ventricular end-diastolic volumes are independently associated with a higher mortality risk in patients with a Fontan circulation and in patients with repaired ToF [35, 36, 37]. A substantial proportion of ACHD patients develop pulmonary arterial hypertension and elevated pulmonary pressures are also strongly indicative of poor prognosis. Lower peak VO2 measured during cardiopulmonary exercise test is associated with a higher risk of hospitalization or death or the development of heart failure, and independently predicts mortality, indicating that it is a powerful prognostic tool within the entire ACHD population [27, 38].

In patients with heart failure, natriuretic peptides are firmly established prognostic tools. Neurohormonal activation of the natriuretic, endothelin, sympatho-adrenergic, and renin-aldosterone systems also occurs in all types of congenital heart disease [39]. Accumulating evidence shows that N-terminal pro-B-type natriuretic peptide (NT-proBNP) is related to disease severity and that it is useful for risk stratification in patients with clinically stable ACHD, even beyond conventional risk markers [40, 41]. Interestingly, normal levels of NT-proBNP (<14 pmol/L) can accurately rule out the risk of death and heart failure with a high negative predictive value [42]. A position paper from the working group of grown-up congenital heart disease and the heart failure association of the European Society of Cardiology has therefore suggested that a two-fold increase of baseline NT-proBNP within 6 months is regarded as a significant increase which indicates the need for optimization of heart failure medical therapy [43]. In the literature different results have been described for the association between NT-proBNP levels and outcome in patients with a Fontan circulation. Higher levels of NT-proBNP are reported, especially in patients with an older Fontan modification (atriopulmonary connection and atrioventricular connection) compared to total cavopulmonary connection, independently from cardiac status [44, 45], while others found significant higher levels of NT-proBNP in Fontan patients with moderate to severely impaired ventricular function [46]. Furthermore, since there are several modes of Fontan failure and NT-proBNP reflects a high volume load and myocardial stress, biomarkers discriminating between the modes of Fontan failure are needed and in many patients the NT-proBNP levels are relatively low.

Biomarkers that reflect other pathophysiological mechanisms which are involved in the heart failure syndrome, such as high-sensitive troponin-T (hs-TnT) and growth-differentiation factor 15 (GDF-15) are also related to the occurrence of heart failure in ACHD patients. In a prospective cohort of 595 patients with moderate and complex ACHD, elevated levels of hs-TnT (>14 ng/L, 8% of patients) and GDF-15 (>1109 ng/L, 15% of patients) could predict outcomes in ACHD patients with elevated levels of NT-proBNP, suggesting a potential benefit of a multi-marker approach [42]. Other promising novel cardiac markers are red cell distribution width, galectin-3 and ST-2[47]. Some studies have focused on specific patient groups such as patients with a systemic right ventricle[47]. In Figures 3 and 4 these findings are summarized. Few studies have attempted to develop risk prediction models specifically for patients with ACHD [38, 48, 49].

(Figures 3 and 4)

An integral perspective of the patients' clinical prospects should always be based on a combination of all available information, that is composed of the medical history, physical examination, imaging, exercise testing and biomarkers. The frequency at which individual patients should be monitored at the outpatient clinic and the type and frequency of additional investigations is based on expert opinion in specialist centers.

Although many women with heart disease may be in a stable clinical condition, pregnancy is associated with substantial hemodynamic changes that carry an increased risk of cardiac complications, especially heart failure. The risk of developing heart failure during pregnancy is strongly influenced by the type of heart defect and presence of residual lesions. The modified World Health Organization (mWHO) classification seems to be the most accurate tool in predicting these risks [50]. It stratifies patients based on their underlying diagnosis into four groups from very low risk patients (mWHO I), to high risk patients in whom a pregnancy is thought to be life threatening and therefore contraindicated (mWHO IV) [51]. Pregnancy is contraindicated (mWHO IV) in women with pulmonary hypertension, severe cyanosis, significantly reduced left ventricular function, previous peripartum cardiomyopathy with incomplete recovery, symptomatic left ventricular outflow tract obstruction, and patients with a severely dilated aorta [52].

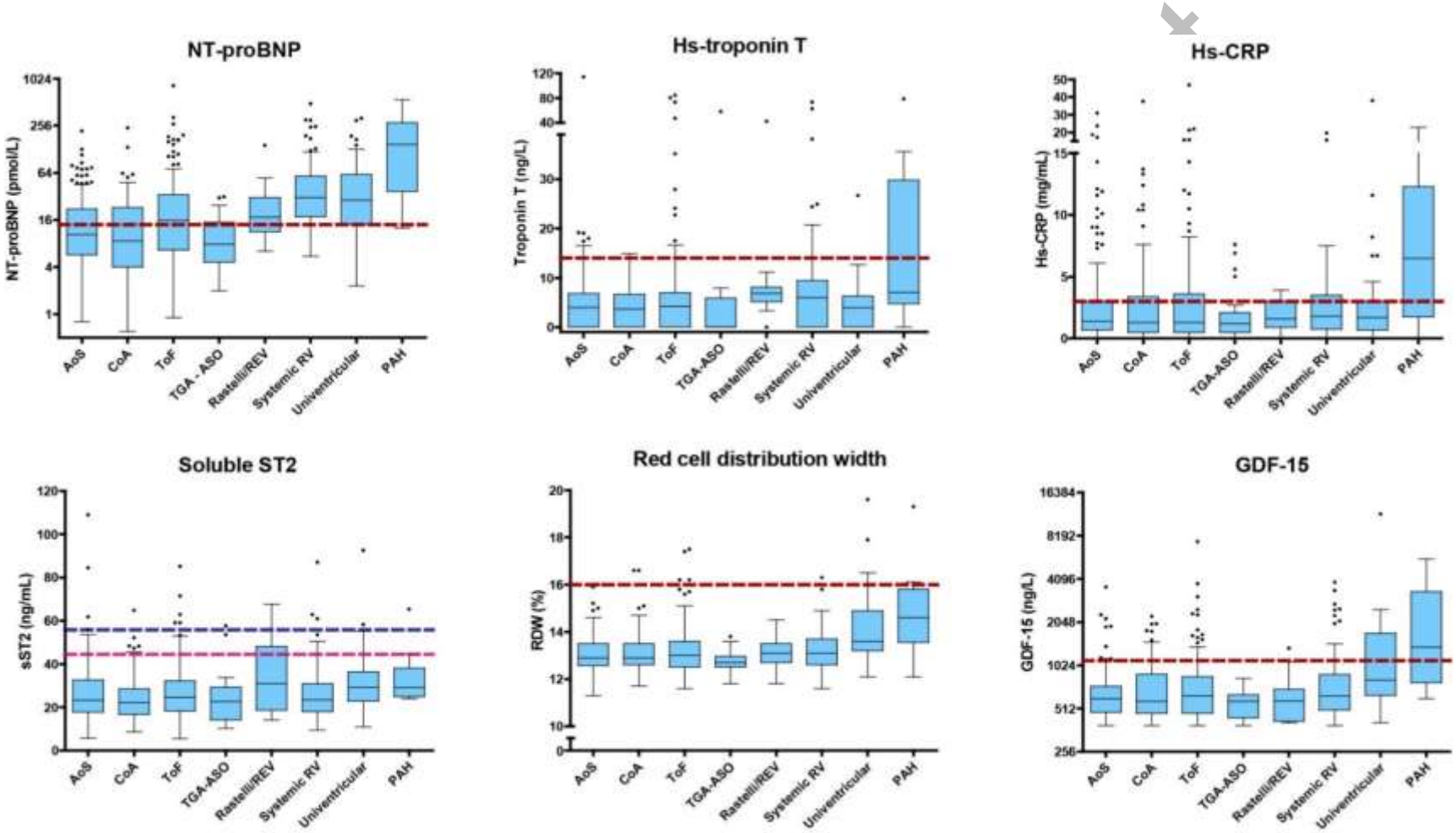

Figure 3. Biomarker levels in adults with congenital heart disease according to the type of congenital heart disease. Combined data previously published by Baggen 2017, Baggen 2018, Eindhoven 2015, Geenen 2019 [42, 53, 54, 55]

Figure legend: For NT-proBNP and GDF-15 the x-axis is on the 2log scale.

Abbreviations: AoS= aortic stenosis, CoA= coarctation of the aorta, ToF= Tetralogy of Fallot, TGA-ASO= transposition of the great arteries

corrected by the arterials witch operation, RV= right ventricle, Univentricular= functionally univentricular hearts , PAH= pulmonary arterial hypertension, NT-proBNP= N-terminal pro B-type natriuretic peptide, Hs=high sensitivity, CRP= C-reactive protein, ST2= suppression of tumorigenicity-2, GDF-15= growth differentiation factor-15

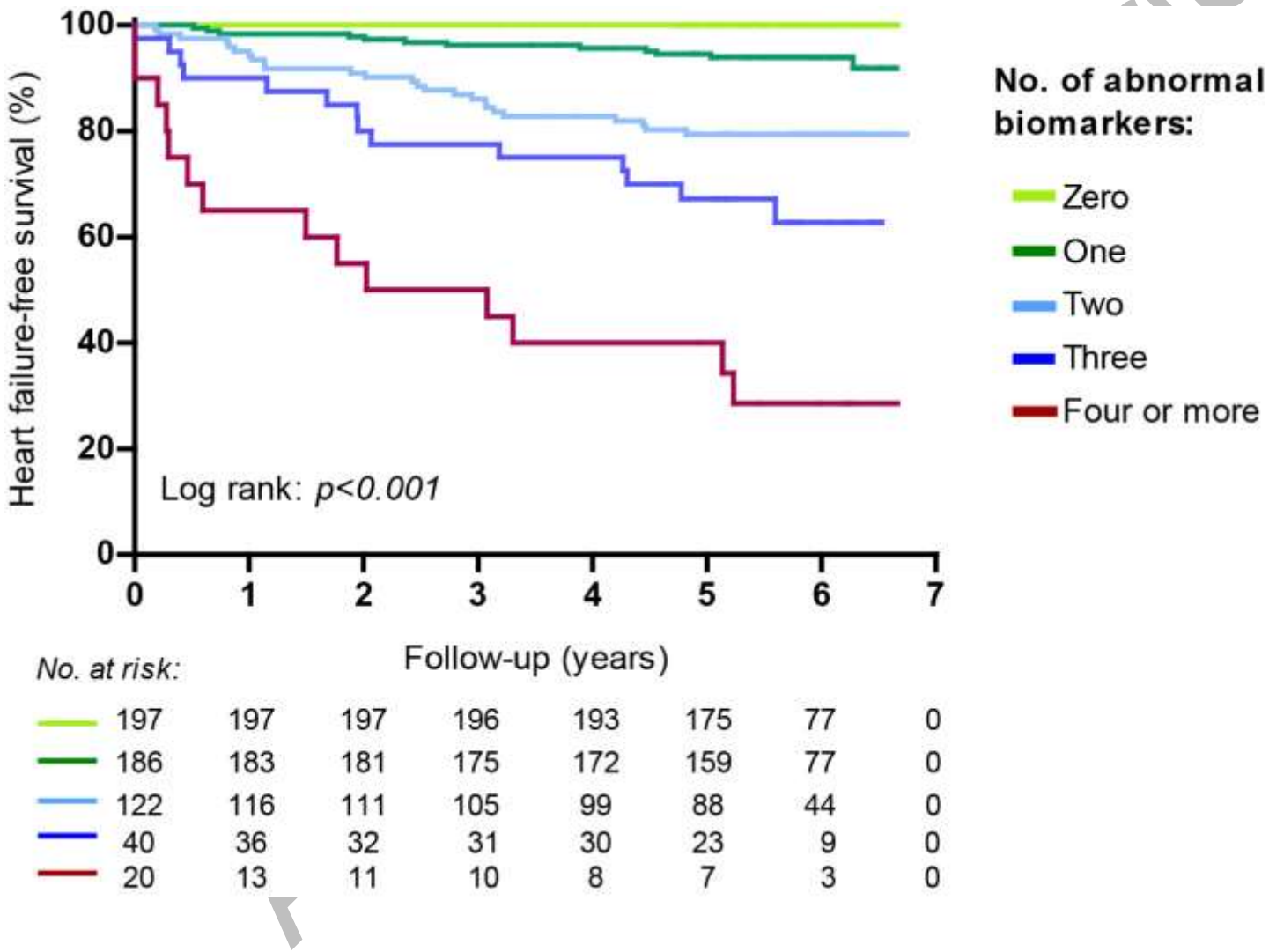

Figure 4. Heart-failure free survival according to the number of abnormal biomarker levels in adults with congenital heart disease. Combined data previously published by Baggen 2017, Baggen 2018, Eindhoven 2015, Geenen 2019 [42, 53, 54, 55]

Figure legend: Included biomarkers and definitions of abnormal levels: NT-proBNP (>14 pmol/L), hs-troponin T (>14 ng/L), hs-CRP (>3 mg/mL), sST2 (♂> 55.85 ng/mL, ♀> 44.50 ng/mL), RDW (>16 %), and GDF-15 (>1109 ng/L)

4. Treatment

4.1 General considerations

So far, no clinical trials on heart failure medication in ACHD patients have demonstrated survival benefit. In the most recent ESC guidelines for the treatment of acute and chronic heart failure, no specific recommendations regarding patients with ACHD are given [9]. A recently published position paper on behalf of the Working Group of Adult Congenital Heart Disease suggests that in the setting of increased neurohumoral and cardiac autonomic activity, the use of diuretics, renin-angiotensin-aldosterone system (RAAS) blockers, betablockers and mineralocorticoid receptor antagonists might be considered [43].

Since similarities in the pathophysiological process of heart failure in ACHD patients and various forms of acquired ventricular systolic dysfunction have been described, therapies that improve the prognosis in acquired systolic dysfunction might also be beneficial in selected ACHD patients [39, 56]. Most profound benefit is expected in patients with a two-ventricle physiology with anatomical left ventricular systolic dysfunction [8]. Unfortunately, this is not supported by evidence from randomized clinical trials. However, we have to highlight that most studies were small and probably underpowered to show an effect. Furthermore, the risk of poor tolerance might be increased in patients with ACHD, particularly in those with a systemic right ventricle or in patients with a Fontan circulation/univentricular heart. At present, there is no medical treatment with proven benefit for HFPEF in the general cardiology population nor in ACHD patients.

Before initiation of heart failure medication, all patients should undergo an extensive evaluation, including a thorough clinical evaluation, electrocardiography, transthoracic echocardiogram and laboratory testing, including biomarkers (table 1). Relevant medical comorbidities should be treated, common interventions for cardiovascular risk factor modulation, e.g. weight reduction, smoking cessation and iron supplementation should be offered [8, 9, 43]. If significant hemodynamic lesions still exist, they should be corrected or repaired according to current guidelines [3, 57]. In figure 5, a diagnostic and treatment algorithm is suggested.

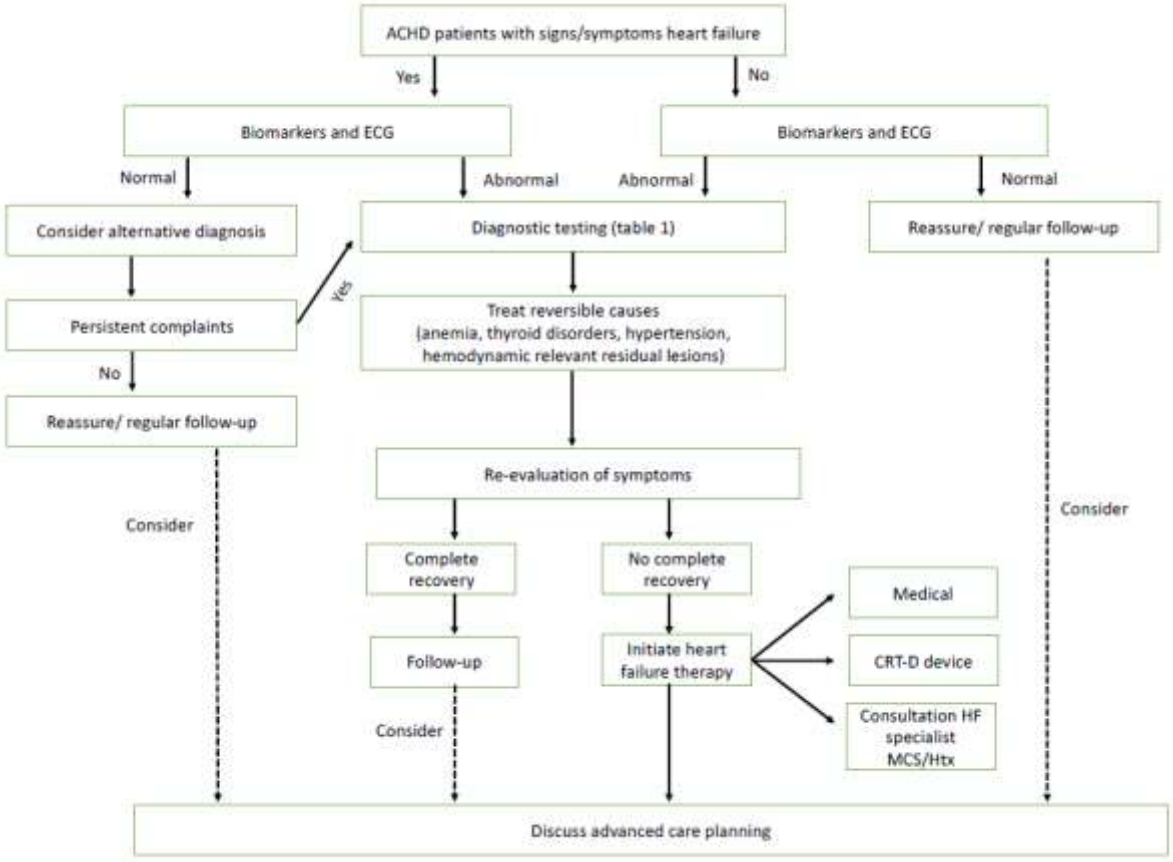

Figure 5: *proposed diagnostic and treatment algorithm in ACHD patients with signs/symptoms of heart failure.*

Abbreviations: ACHD= Adult Congenital Heart Disease, CRT-D=cardiac resynchronization therapy-defibrillator, MCS= mechanical support, HTx= heart transplantation

4.2 Medical therapy

Betablockers

A limited number of studies describe the potential beneficial effects of betablockers for heart failure in CHD. In children and adolescents with symptomatic systemic ventricular dysfunction, carvedilol showed no significant difference in clinical heart failure outcome, although a beneficial trend in patients with a systemic left ventricle was observed [58]. In a small study evaluating patients admitted because of heart failure with dilated cardiomyopathy and various types of CHD, carvedilol treatment increased left ventricular ejection fraction (LVEF) and led to a decrease in human atrial natriuretic peptide (hANP)/ b-type natriuretic peptide (BNP) blood levels [59].

The only prospective randomized, double-blind, placebo-controlled trial evaluating beta-blockers in ACHD patients with heart failure was performed in patients after surgical correction of ToF with right ventricular failure who were in NYHA class I or II. No difference in blood levels of BNP, peak uptake of oxygen, NYHA class or effect on right and left ventricular volumes and ejection fractions as determined by magnetic resonance imaging was observed [60]. In contrast, a meta-analysis evaluating beta-blockers in pediatric and CHD patients with heart failure demonstrated a positive effect on echocardiographic parameters in patients with systemic left ventricular failure [61].

In conclusion, there is currently insufficient data to give firm recommendations regarding the use of beta-blockers in ACHD patients with heart failure, although it might be considered in ACHD patients with aortic or mitral valve stenosis, especially when arrhythmias are also present [43].

Renin-angiotensin-aldosterone system blockers and mineralocorticoid receptor antagonists

Since angiotensin receptor enzyme (ACE) inhibitors reduce mortality and morbidity in patients with HFREF, they are recommended unless contraindicated in all symptomatic patients with heart failure [9]. Nonetheless, robust evidence for the implementation of ACE inhibitors in ACHD patients is lacking. Two studies described the use of ACE inhibitors in patients with repaired ToF. In the APPROPRIATE trial, ramipril had no effect on ventricular volume, functional class, severity of pulmonary regurgitation or peak oxygen uptake [62] in ToF patients with moderate to severe pulmonary regurgitation. Nevertheless, an improvement in LVEF and decrease in progression of diastolic function was demonstrated [63]. In another study of 95 ToF patients with a right ventricular ejection fraction <50% but without important pulmonary valvar disease, the angiotensin receptor blocker (ARB) losartan had no effect on right ventricular ejection fraction[64]. In patients with a systemic right ventricle no clear evidence supporting the use of ACE/ARB/MRAs is available yet. This is discussed in more detail below.

Mineralocorticoid/aldosterone receptor antagonists (MRA) are recommended in all HFREF patients already treated with ACE inhibitor and betablockers with a LVEF <35% who remain symptomatic [9]. Although studies in ACHD patients are lacking, in our opinion its use should be considered in heart failure patients with bi-ventricular physiology and a failing systemic left ventricle.

Diuretics

Currently, there are no randomized clinical trials available demonstrating an effect of diuretics on morbidity or mortality in ACHD patients [42]. Still, these drugs are routinely used to treat the signs and symptoms of congestive heart failure in ACHD patients. A meta-analysis amongst non-ACHD heart failure patients, showed a significant increase in exercise capacity and reduction of the risk of death and worsening heart failure, supporting its use also in ACHD patients showing signs of congestion [65].

Digoxin

Digoxin has a limited role in the treatment of heart failure in ACHD and non-ACHD patients, since no effect on mortality has been demonstrated [9, 42]. In a pediatric study among patients with left to right shunting and a preserved LVEF, digoxin showed no incremental decrease in proBNP on top of treatment with diuretics and ACE inhibitors [66]. Nonetheless, in our opinion it can still be considered in selected patients remaining symptomatic despite regular heart failure treatment, especially in those with atrial fibrillation, although there are studies describing an increased mortality in patients using digoxin [67]. However, this was not confirmed in other studies and more research is clearly needed [68].

Novel therapies: Angiotensin receptor neprilysin inhibitors

Angiotensin receptor neprilysin inhibitors (ARNIs) are a new class of therapeutic agents acting on the renin-angiotensin aldosterone system and the neutral endopeptidase system. In the most recent ESC guideline on heart failure, ARNIs have a class I recommendation in ambulatory patients with HFREF who remain symptomatic despite optimal treatment with an ACE-inhibitor, a beta-blocker and an MRA [9]. In the PARADIGM-HF trial, sacubitril/valsartan was superior to enalapril in reducing the risk of death and hospitalization for heart failure in patients with a reduced ejection fraction and NYHA class ≥ 2 [69]. Although large prospective studies in ACHD patients are lacking, first study results were recently reported. In 15 patients with refractory heart failure despite guideline guided therapy, sacubitril/valsartan was initiated. No clinical deterioration was reported. In four patients in NYHA class III with complex ACHD, pulmonary hypertension and cyanosis, a significant improvement to NYHA class II was reported [70]. In a study of 23 patients with moderate/severe complexity ACHD, no improvement in functional class or systemic ventricular function, nor decrease in proBNP was described. In four patients, treatment was discontinued due to side effects [71].

Finally, in a small prospective study in patients with complex ACHD, 5 patients with severe systemic ventricular dysfunction in NYHA class II and III showed an improvement of one functional class after six months. Sacubitril/valsartan therapy was well tolerated [72].
Since data from the first studies evaluating the use of sacubitril/valsartan in heart failure patients with ACHD are conflicting, further studies in larger cohorts are necessary to further evaluate the potential role of this novel therapy.

Novel therapies: Sodium-glucose cotransporter 2 (SGLT2) inhibitors
SGLT2 inhibitors including dapaglifozin have shown to reduce death and hospitalization and improve quality of life in patients with HFREF in patients with and without diabetes [73]. However, to our knowledge, no clinical trials evaluating its use in patients with ACHD have been conducted or are being conducted at present [74].

4.3 Specific conditions

Heart failure in systemic right ventricle
Patients with a systemic right ventricle are especially at risk for developing heart failure. Cuypers et al described an incidence of 23% in patients with Mustard correction of TGA during a median follow-up period of 35 years [13]. In patients with ccTGA, the prognosis might be slightly better. Nevertheless, by age 45, 76% of patients with ccTGA with associated lesions had congestive heart failure, while this was the case in 25% of ccTGA patients without associated lesions [15].
In symptomatic patients with neurohumoral and cardiac autonomous nervous system activation, initiation of standard heart failure treatment is currently recommended. The efficacy of this treatment was recently described in a systematic review and meta-analysis [75]. Six studies with a total of 187 patients were included. Because of the small numbers, betablockers could not be analyzed. After at least 3 months of treatment with ACE inhibitors, ARBs and MRAs, no significant change in mean ejection fraction, ventricular dimensions or peak ventilatory equivalent of oxygen was described. Recently, the long-term clinical outcome of a cohort of patients with a systemic right ventricle who were treated with valsartan was reported [76]. During a median follow-up period of 8.3 years, no improvement in survival was observed. However, there was a significant reduction in the risk for events, including heart failure (HR 0.37). Although the latter might underline the importance of the initiation of larger RCTs with longer follow-up, there is currently no robust evidence supporting the initiation of classic heart failure medication in patients with a systemic right ventricle. Therefore, in our opinion this should be reserved

for selected patients with signs and symptoms of heart failure and should not be routinely initiated in asymptomatic patients with an impaired systemic right ventricular function, although it might be difficult to accurately define “asymptomatic”.

Trials evaluating the use of novel drugs in systemic right ventricles are currently ongoing. In 2017, the SERVE trial evaluating the effect of phosphodiesterase-5 inhibition was initiated, but no results were reported so far [77]. Although large trials evaluating the effect of sacubitril/valsartan in the systemic right ventricle are lacking, recently a small study in 23 patients with ACHD of moderate and severe complexity, including 12 patients with a systemic right ventricle, was reported. During a median follow-up of 221 days, there was no improvement in systemic ventricular function or functional status [71].

Fontan patients

Similar to heart failure, in the failing Fontan circulation, the circulation can no longer meet the metabolic demands of the body. Clinically, mostly symptoms of right sided heart failure, including hepatic congestion, edema and ascites are present[78]. Although usually poorly tolerated, systolic or diastolic dysfunction might also be present.

So far, no trials showed a beneficial effect on survival or exercise capacity using ACE inhibitors or MRAs[79, 80, 81]. Given the pre-load dependency of the Fontan patients, diuretics should be used with caution. In a cohort of 51 patients with an univentricular circulation, a potential beneficial effect of carvedilol on furosemide dosage and ejection fraction was described, although there are no other studies confirming these results yet [82].

Since the Fontan circulation is greatly influenced by preload, the reduction of pulmonary vascular resistance might be beneficial in improving cardiac capacity and exercise capacity in Fontan patients. In a recently published meta-analysis, no beneficial effect of pulmonary vasodilators on mortality or NT-proBNP levels was observed. However, a significant improvement in NYHA class, 6-minute walking distance and peak VO2 was described, as well as a small but significant reduction in mean pulmonary artery pressure [83]. The recently published FUEL trial exploring the use of udenafil versus placebo in 400 Fontan patients (mean age 15,5 ±2 years) showed no significant effect on improvement in oxygen consumption at peak exercise [84]. However, in the udenafil group a significant improvement in the oxygen consumption, work rate, and ventilatory efficiency at the anaerobic threshold was observed. In conclusion, although no effect on mortality has been described yet, the use of pulmonary vasodilators in patients with a failing Fontan might be considered.

5. Non-medical treatment options

5.1 Rehabilitation and lifestyle

In acquired heart disease there is extensive evidence to encourage patients to pursue a healthy lifestyle [85, 86]. The role of cardiac rehabilitation programs in heart failure is instrumental in optimizing habits in nutrition, activity and smoking cessation, increasing physical fitness and improving quality of life and symptoms [87, 88]. In CHD evidence is less extensive, but several centers have shown the beneficial effects of exercise programs in different congenital conditions [89, 90]. Cardiopulmonary exercise testing can be a useful tool in assessing both baseline functional capacity and improvement after a rehabilitation program. Comparing an individual's exercise capacity to peers with a similar congenital heart condition, gender and age is helpful in discussing a patient's progress and daily life activities [91]. Different types of exercise training, such as endurance training or higher intensity interval training, can be used, tailored to the patient's underlying pathology, capabilities and preference [92, 93]. Special consideration should be given to frequent arrhythmic events, systemic outflow tract obstruction and aortic dilatation [94]. A thorough and complete referral from the clinician to the rehabilitation team is essential in providing a safe and effective rehabilitation program, not only focusing on exercise capabilities, but also on nutrition, substance misuse and psychological factors. Currently, it is unclear what type of exercise-based cardiac rehabilitation is most suitable for heart failure patients with CHD [95]. However, in most cases the benefits of regular moderate exercise outweigh possible disadvantages and it is therefore important to discuss exercise options and offer high-quality rehabilitation programs. The risks of exercise seems low. A recently published position paper advocates an individualized exercise prescription for all adults with CHD [96].

5.2 Cardiac resynchronization and implantable defibrillator therapy

The benefits of cardiac resynchronization therapy (CRT) in patients with heart failure with reduced ejection fraction and left bundle branch block (LBBB) are well established, aiming to reduce dyssynchrony of myocardial contraction and as such improving morbidity. It is a class IA recommendation for symptomatic patients in current heart failure guidelines of the European Society of Cardiology [9]. However, there are no specific recommendations related to CHD patients, and in clinical practice recommendations are often extrapolated to this specific patient group. The wide spectrum of

causes of dyssynchrony in the various underlying congenital conditions are one of the reasons that robust recommendations are lacking [97].

The role of CRT in patients with right bundle branch block (RBBB) or indeterminate interventricular conduction delay, so called non-LBBB, is less clearly defined compared to LBBB. A recent review [98] stated the high rate of non-responders for CRT in RBBB, although some subpopulations might benefit from CRT, specifically by using mapping techniques. In ACHD patients heart failure is often related to right ventricular dysfunction whether it serves as the subpulmonic or the systemic ventricle (e.g. in ccTGA, or after atrial switch of TGA), and may also include RBBB or other interventricular conduction abnormalities. At present, specific benefits for these situations are being elucidated in smaller studies [99].

A further indication for CRT in non-LBBB setting is the chance of developing heart failure due to permanent right ventricular pacing. Flugge et al showed that this is the most common indication for CRT in CHD patients in the German National Register for Congenital Heart defects [100].

When considering device implantation, it is important to pay diligent attention to the patient's medical and surgical history before implantation. In patients with complex congenital conditions anatomical obstacles may hamper implantation. This may be related to previous surgeries such as atrial switch operations or Fontan procedures, to vascular access either congenital or due to previous endovascular procedures and to options for endo- or epicardial lead placement [101]. In patients with single ventricle physiology after the modified Fontan procedure, the role of CRT in significant ventricular dysfunction is not well studied. Demetriades et al highlight the anatomical difficulties in implantation of CRT in this patient group [102].

In recent years, His bundle pacing is being explored as a more physiological mode of ventricular pacing in heart failure [103]. Its role in congenital heart disease is presently unclear and may be technically difficult due to anatomical variation and post-surgical changes of the His bundle and surrounding tissues in different congenital conditions [104].

The current lack of knowledge on the role of CRT in ACHD patients with heart failure highlights the need for more research in this particular area, as addressed in the 2018 AHA/ACC Guidelines on ACHD, in the section on "Evidence Gaps and Future Directions" [3].

Implantable cardiac defibrillators (ICD) are used to reduce the detrimental effects of ventricular arrhythmias and can be implanted for primary or secondary prevention. In the case of secondary prevention, there is a well-established indication to prevent recurrence of life-threatening ventricular tachycardia and/or fibrillation which also applies to ACHD patients. Primary prevention of ventricular arrhythmias in ACHD is more complex with higher risk conditions which often do not coincide with clinical heart failure, contrary to non-congenital causes of heart failure [105, 106]. There is consistent evidence about the risk of sudden cardiac death in a subset of ToF patients. Khairy et al proposed a risk score based on 6 variables: prior palliative shunt, inducible sustained VT, QRS duration > 180ms, ventriculotomy incision, non-sustained VT and left ventricular end diastolic pressure > 12mmHg [107]. In patients with significant impairment of the systemic right ventricle it is as yet uncertain whether they benefit from primary ICD placement. At the moment, it is not routinely recommended. Further clinical research is required to refine risk stratification for ventricular arrhythmias [108, 109] and to minimize the occurrence of inappropriate ICD shocks [110, 111]. In a considerable proportion of ACHD patients subcutaneous ICD implantation seems suitable [112]. In addition to risk assessment and technical considerations, special care should be given to the psychological impact of ICDs and the effect it may have on quality of life and mental health, with higher anxiety levels and diminished general health perception and physical functioning reported [113, 114].

6. Advanced therapy

Heart transplantation (HT) is possible in ACHD patients. However, meticulous planning before transplantation, including evaluation using multiple imaging modalities, decisions regarding cannulation strategy and correction of residual anatomic lesions, is crucial. The 30-day mortality has improved from 14,3% before 2010 to 6.8% between 2010 and 2014 [115]. However, early mortality after heart transplant is higher in ACHD than in non-CHD patients (18.9% vs. 9.6%)[116]. After the initial 30 days patients with ACHD have a superior long-term survival compared with non-CHD adults [117]. In the Fontan population mortality remains high [118]. Identifying the appropriate time for successful heart transplant is one of the most difficult aspects of caring for adults with CHD. Adults with CHD who have

end-organ dysfunction or elevated PVR that precludes HT may improve with mechanical unloading and later become eligible for HT. Increased attention has thus turned to using mechanical circulatory support (MCS), such as ventricular assist devices (VADs) as a bridge-to-transplant, bridge-to-decision, or destination therapy. Adults with CHD had similar improvement in functional status and quality of life compared with non-CHD patients [119]. Furthermore, adults with CHD bridged to HT with a ventricular assist device (VAD) had survival comparable to those transplanted directly, despite worse baseline functional status and more co-morbidities. Taken together, these studies indicate that MCS is appropriate in selected patients. Patients with d-TGA corrected by atrial switch and l-TGA frequently develop systemic right ventricular failure as adults and may require VADs, which is more difficult but possible [120]. Surgically, the pyramidal geometry of a morphological right ventricle frequently necessitates resection of trabeculae and/or alternate positioning of the inflow cannula, often on the diaphragmatic surface or free wall [121]. Patients with baffles may require higher central venous pressures due to their inherent diastolic dysfunction from baffle stiffness, and they are at risk of obstruction from pulmonary artery catheters.

7. Advanced care planning

Advanced care planning (ACP) is a process that supports and empowers individuals, at any stage of their lives or the disease process, to consider and communicate preferences for future health care to their loved ones and health care providers . During this process, individuals have the opportunity to make decisions in advance about treatment they would and would not want, should they be unable to express their wishes at that time. This process benefits patients by increasing the likelihood that their wishes be followed but also health care providers by providing information sufficient to align treatment plans with patient goals and preferences. The majority of ACHD patients report interest in ACP independent of the underlying defect severity and prefer that such discussions be initiated early in the disease course, before life-threatening complications occur. In one study, 18 years of age was identified as the most appropriate age to initiate an ACP dialogue [122]. Although most adults with CHD report interest in ACP and in receiving information about the life expectancy of individuals with their type of CHD, some may not. Ideally, ACP is a gradual process that is initiated by exploring a person's understanding of the aims and potential benefits of ACP and discussion of their personal readiness [123]. Information about health-related experiences, values, psycho-social resources, concerns and expectations should be sought. Open and sensitive communication concordant with personal needs and values should include an explanation

of how the CHD diagnosis impacts longer term health expectations as well as anticipated disease progression, prognosis, and the advantages and disadvantages of potential treatment options. Should their condition deteriorate further, and the estimated life-expectancy decline to 1-2 years, discussions can be extended with specific questions related to wishes at the end-of-life, including issues related to the modification of cardiac devices (e.g. deactivation of ICD shock function) and other management choices at end of life, including palliative care measures. Some patients have a reduced life expectancy, such as adults with Fontan procedure, adults with cyanotic heart disease and adults with a systemic right ventricle approaching 40 years of age. It is very important to provide written documentation in medical records of elements discussed and share this information with the general practitioner and other healthcare professionals. If necessary social care, palliative care teams and/or psychological and religious support services should be involved [124]. A position paper discussing this topic from the ESC Working Group of Adult Congenital Heart will soon be published [125].

8. Conclusion

The growing number of patients with congenital heart disease who develop heart failure poses an important challenge in terms of diagnosis and treatment, both medical and non-medical. It requires a comprehensive evaluation of the clinical status by different diagnostic techniques. Knowledge and interpretation of evolving diagnostic and therapeutic options is paramount in delivering the best available care. More attention for implementing biomarkers is necessary. Evidence for a positive effect of medical treatment is absent and more research is clearly needed.

9. Expert opinion

The astonishing advances in the care and treatment of congenital heart disease (CHD) in the recent decades have undoubtedly had a positive impact on both life expectancy and morbidity. Nowadays most patients survive into adulthood and present adult cardiologists with distinct and challenging issues. Among these, heart failure occurs often and has a significant impact on mortality, morbidity and quality of life. There is a need for medical research to guide physicians and to deliver the best possible care in these patients. This need was highlighted in the 2018 American guidelines on adult congenital heart disease and is recognized by adult cardiologists in CHD worldwide.

It is important to establish a well-rounded diagnostic process for the individual patient with any signs of heart failure or reduced exercise capacity, comprising of several tests including imaging, laboratory tests and invasive techniques. The diagnosis might be difficult because all patients have an underlying structural heart abnormality and many have had subnormal exercise capacity for years. There is emerging evidence that the use of biomarkers is helpful for the clinician. Markers that are well-established in general cardiology practice, such as high-sensitive troponin and NT-proBNP, have shown to also improve the accuracy of heart failure diagnosis in CHD. In our opinion, biomarkers ought to be one of the cornerstones of evaluating heart failure and possibly guiding treatment. Therefore, the implementation of biomarkers needs more attention and more research demonstrating the value of this diagnosticon is warranted.

Research in the field of treatment of ACHD is challenging and has several obstacles, related to the heterogenic nature of the population due to multiple factors including the underlying pathology, interventions in childhood, relevant co-morbidities, psychosocial factors and geographical and historical differences in treatment. Currently, no clear evidence supporting medical treatment is available. This can be explained by the fact that most available research and clinical guidelines are based on single center, non-randomized studies in small patient groups. This has been recognized by the ACHD community and more centers are now working together internationally in setting up collaborations to study the important questions in diagnosis and treatment at this moment. These multicenter collaborations will also facilitate future research on emerging issues, such as new drug treatments and non-medical treatment options. This is also relevant when more effective options become available, especially the promising recently developed medications, such as the angiotensin-receptor-neprilysin-inhibitors or the sodium-glucose transport protein 2- inhibitors. We therefore urge our colleagues in the

field of ACHD worldwide to expand current collaborations in order to perform large prospective studies or registries in specific patient groups to better understand what treatments are effective.

In this relatively young patient group, it is essential to consider and discuss, despite their age, advanced treatment options and advanced care planning when a heart failure diagnosis is made. Patients deserve to be fully informed about prognosis and treatment options, such as implantable devices, mechanical support and heart transplantation, and whether these options apply to their specific situation. Compassionate and repeated conversations about advanced care planning will help our patients, and their families, in dealing with grief, loss and end-of-life issues. Furthermore, it will help physicians and nurses involved in the care of the patient. These important conversations should not be neglected or left to the last moment. Consultation with heart failure specialist and palliative care specialists is essential in these issues.

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Heart failure is an increasing clinical entity in ACHD patients, urging the medical community to timely discuss advanced care planning in this rapidly expanding patient category. Some important insight regarding this topic will be discussed in this paper.