

Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology

Werner Budts¹, Jolien Roos-Hesselink², Tanja Raädle-Hurst³, Andreas Eicken⁴, Theresa A. McDonagh⁵, Ekaterini Lambrinou⁶, Maria G. Crespo-Leiro⁷, Fiona Walker⁸, and Alexandra A. Frogoudaki⁹

¹ Congenital and Structural Cardiology, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium; ² Department of Cardiology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; ³ Department of Pediatric Cardiology, Saarland University Medical Center, Homburg, Germany; ⁴ Deutsches Herzzentrum München, Munich, Germany; ⁵ Department of Cardiology, King's College Hospital, London, UK; ⁶ Department of Nursing, School of Health Sciences Cyprus University of Technology, Limassol, Cyprus; ⁷ Advanced Heart Failure and Heart Transplantation Unit, Cardiology Service, Hospital Universitario A Coruña, La Coruña, Spain; ⁸ Centre for Grown-Up Congenital Heart Disease, St Bartholomews Hospital, London, UK; and ⁹ Adult Congenital Heart Clinic, Second Cardiology Department, ATTIKON University Hospital and Athens University, Athens, Greece

Heart failure in congenital heart disease: prevalence and outcome

Improved medical care of congenital heart disease patients increased survival into adulthood from 15% in the 1960s to over 85% in the current era. As a consequence, the prevalence of adult congenital heart disease (ACHD) increased rapidly,¹ which is estimated to be >1 million ACHD patients in North America and 1.2 million in Europe. The growing number and aging of ACHD patients led to an overall increase in hospitalizations over the last decade and a substantial increase in patients presenting with heart failure (HF) (~20%).²

The incidence of first HF-admission was 1.2 per 1000 patient-years in the Dutch national 'CONCOR' registry. Patients admitted with HF had a five-fold higher risk of death than those not admitted. From the same registry, the mortality was 2.8% during a follow-up period of 24 865 patient-years. Chronic HF (26%) and sudden death (19%) were recorded most frequently. The median age at death from HF was 51.0 years (range: 20.3–91.2 years).³ In another ACHD cohort, sudden death (26%) was the most common cause of death, followed by progressive HF (21%) and perioperative death (18%).⁴ Although patients with ACHD may not readily report symptoms, clinical HF is documented in 22.2% of patients with a Mustard repair for transposition of the great arteries (TGAs), 32.3% with congenitally corrected transposition of the great arteries (ccTGA), and 40% of patients after Fontan palliation.

Pathophysiology of heart failure in adult congenital heart disease

Heart failure with impaired systolic ventricular function

The aetiology and triggers of impaired systolic ventricular function in ACHD patients are summarized in *Table 1*.

Table 1. Pathophysiology of heart failure with impaired systolic function: triggers (examples)

-
1. Systolic dysfunction of the systemic morphological left ventricle
 - Pressure overload (sub-, supra- or valvular aortic stenosis, coarctation of the aorta)
 - Volume overload (aortic valve regurgitation, VSD, patent ductus arteriosus, or mitral regurgitation)
 - Myocardial injury (limited myocardial protection during bypass, ventriculotomy)
 - Altered myocardial architecture (non-compaction)
 - Altered geometry of the sub-pulmonary ventricle interfering with diastolic filling of the systemic ventricle (severe pulmonary regurgitation in ToF)
 2. Systolic dysfunction of the sub-pulmonary morphological right ventricle
 - Volume overload (severe pulmonary regurgitation in ToF, atrial septal defect with large left-to-right shunt)
 - Pressure overload (severe RV outflow tract obstruction)
 3. Systolic dysfunction of the morphological systemic right ventricle
 - Pressure overload [congenitally corrected transposition of the great arteries, dextro-transposition of the great arteries after atrial switch repair (Mustard or Senning)]
 - Myocardial injury by functional ischaemia (single right coronary artery)
 4. Systolic dysfunction of the systemic single ventricle
 - Volume under-load after initial volume overload (Fontan repair)
 - Myocardial injury (limited myocardial protection during bypass, ventriculotomy)
 - Myocardial architecture
 5. Systolic dysfunction of the cyanotic systemic and/or sub-pulmonary ventricle with or without pulmonary hypertension
 - Myocardial injury by chronic hypoxia (VSD with pulmonary stenosis)
 - Pressure overload (Eisenmenger syndrome)
 6. Acquired ischaemic heart disease and ventricular dysfunction
 - Cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, smoking)
 - Congenital coronary artery abnormalities (anomalous origin and/or course, extrinsic compression by a dilated pulmonary artery, coronary kinking after re-implantation of coronary arteries)
 7. Systolic dysfunction of the systemic ventricle due to tachyarrhythmias
-

Heart failure with preserved systolic ventricular function

This occurs less often in ACHD patients, but is associated with specific conditions such as Shone complex and restrictive right ventricular (RV) physiology in the context of pulmonary atresia, ventricular septal defect (VSD), and major aorto-pulmonary collateral arteries.

Genetic and neurohormonal background

Heart failure in ACHD is the result not only of a structural defect but also of defective contractility or conduction. An intriguing and emerging hypothesis is that genes involved in morphogenesis during early development also play a key role in regulating myocardial function and the responses to physiological stress in both the developing and the adult heart.⁹ Adult congenital heart disease patients, rather than developing HF as a result of myocyte loss (myocardial infarction) or of intrinsic abnormalities in myocardial components (inherited cardiomyopathies), may, according to this predisposing genetic model, develop easier HF due to persistent abnormal cardiac pressure, volume, tension, and flow. Furthermore, it has been shown that all types of congenital heart disease cause neurohormonal activation of the natriuretic, endothelin, sympatho-adrenergic, and renin–aldosterone systems.⁵

Comorbidities and heart failure in adult congenital heart disease

Liver disease occurs in patients with ACHD. Elevated systemic venous pressures might lead to liver stiffness⁶ and cardiac liver cirrhosis.⁷ Liver disease is mostly associated with a failing Fontan circuit.⁸ Combined heart liver transplantation is in the end needed when a failing ventricle presents with liver cirrhosis.⁹ Also *protein losing enteropathy* (PLE) occurs in a failing Fontan. Elevated systemic venous filling pressures are considered to trigger PLE.¹⁰ Diuretics¹¹ and fenestration¹² between the systemic venous return and the pulmonary venous atrium, allowing right-to-left shunt, might reduce PLE. Also oral steroids¹² as budesonide might improve symptoms and stabilize serum albumin levels; however, its long-term effect remains unclear. *Plastic bronchitis* is a rare complication after Fontan palliation.¹³ Elevated central venous pressure and low cardiac output likely contribute to the formation of tracheobronchial casts. Haemodynamic optimization and aggressive pulmonary vasodilation might improve the clinical course. Approximately 30–50% of ACHD patients have significantly *impaired renal function*.¹⁴ The risk of chronic kidney disease is higher in cyanotic disease, but also present in non-cyanotic diseases. As such, stringent blood pressure control and reduction of proteinuria are obligatory. Finally, some *haematological disorders* might occur, mainly in ACHD patients with chronic systemic cyanosis. Haematocrit levels are increased,¹⁵ which leads to high blood viscosity and a low flow phenomenon. The latter might trigger thrombosis. In contrast, bone marrow dysfunction leads to a lower number and dysfunctional platelets and increases the bleeding risk. Elevated uric acid levels induce gout attacks and accelerate renal functional impairment.¹⁶

Diagnostic approach in heart failure

Knowing the baseline heart defect and the history of surgeries and/or percutaneous interventions is mandatory in HF ACHD patients. Diagnosing HF may be difficult as patients often fail to recognize in themselves subtle changes in functional class. Patients might have no typical HF symptoms and signs, despite reduced exercise capacity and reporting New York Heart Association (NYHA) functional class I.¹⁷ Heart failure is therefore a clinical syndrome with a diagnosis based on history, examination, and investigations. Determining the cause of HF is important, as it may be reversible due to a new or worsening residual haemodynamic lesion or an another medical problem, e.g. thyroid dysfunction (*Figure 1*).

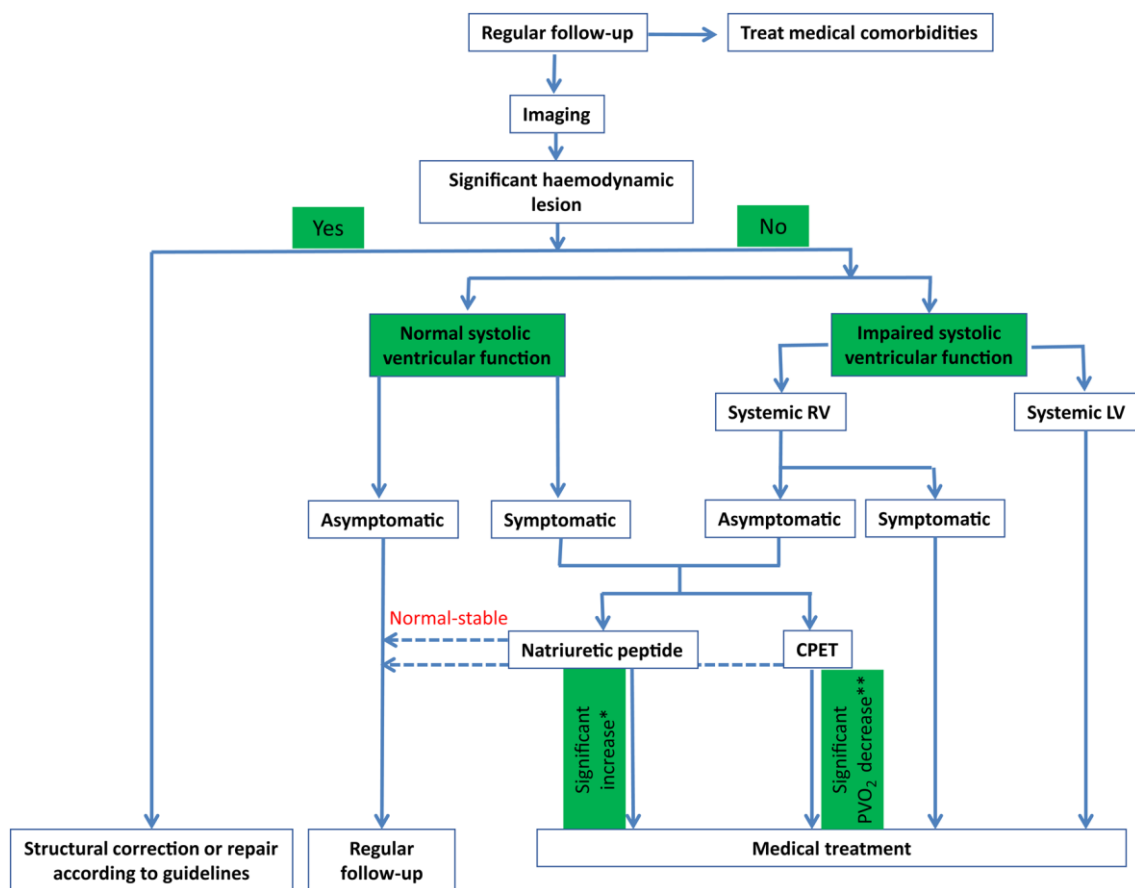


Figure 1. Diagnosis–treatment algorithm. CPET, cardiopulmonary exercise test; PVO₂, peak oxygen consumption; LV, left ventricle; RV, right ventricle. *Two-fold increase of baseline natriuretic peptide value within 6 months. **>25% decrease of peak oxygen consumption.

Clinical symptoms and signs

Heart failure symptoms and signs are described in the European Society of Cardiology (ESC) guidelines (*Table 2* adapted from ESC HF guidelines).¹⁸ Some patients with complex congenital heart disease may have worsening cyanosis in the context of intra- or extra-cardiac shunts or fenestrations. Of note, arrhythmias are closely related to HF symptoms and may be the first clinical manifestation of HF.

Table 2. Signs and symptoms of heart failure in congenital heart disease

Symptoms of systemic ventricular failure	Signs of systemic ventricular failure
Fatigue	Third or fourth heart sound (gallop)
Breathlessness	Laterally displaced apical impulse
Dry cough especially lying flat	Pulmonary crepitations
Reduced exercise tolerance	Absent BS and dull percussion lung bases due to pleural effusions
Orthopnoea	
Paroxysmal nocturnal dyspnea	
Wheezing	
Symptoms of sub-pulmonary ventricular failure	Signs of sub-pulmonary ventricular failure
Fatigue	Elevated JVP
Bloating	Hepatomegaly
Weight gain (> 2kg/week)	Ascites
Loss of appetite	Pitting leg oedema, sacral oedema, scrotal oedema
Reduced exercise tolerance	
Increased abdominal girth	
Symptoms of congestive (biventricular) failure	Signs of congestive (biventricular) failure
Combined systemic and sub-pulmonary symptoms	Combined systemic and sub-pulmonary signs

BS, breath sounds; JVP, jugular venous pressure.

Electrocardiography

Many ACHD patients have baseline abnormal electrocardiograms (ECGs) with prolonged QRS duration, other intra-ventricular conduction delay, nodal rhythm, and LV (left ventricular) or RV hypertrophy. A change in ECG morphology is therefore most relevant in the ACHD patient. However, each ECG has to be looked after atrio-ventricular (AV) conduction abnormalities (i.e. complete AV block in ccTGA) or for 'inappropriate' apparently sinus tachycardia that may mimic atypical supraventricular re-entrant tachycardia.

Imaging

A *chest X-ray* easily identifies pulmonary congestion and effusions. The position and size of the heart, size of pulmonary arteries and thoracic aorta, and concomitant lung and thorax pathology are simply obtained.

Echocardiography allows to: Recommendations have been recently published for tetralogy of Fallot (ToF) imaging.¹⁹ *Three-dimensional (3D) echocardiography* is more sensitive than 2D for the assessment of ventricular function and volumes and valves. *Transoesophageal echocardiography* may also be indicated.²⁰ *Stress echocardiography* helps assessing contractile reserve^{21,22} and diagnoses acquired heart disease such as coronary artery disease (CAD).

- Establish or confirm the underlying congenital heart disease diagnosis
- Identify concomitant/residual lesions and sequelae
- Assess ventricular function (sub-aortic–sub-pulmonary)
- Monitor disease progression
- Detect new ± acquired lesions
- Guide further interventions

Magnetic resonance imaging (MRI) is the golden standard for volumetric measurements, ventricular function, assessment of vessels, and detection of myocardial fibrosis. European Society of Cardiology recommendations for the use of MRI in ACHD patients have been published.²³

Computed tomography is particularly good for imaging stented valves and coarctation stents along with the epicardial coronary arteries, for collateral arteries, and for parenchymal lung disease.¹⁹

Cardiac catheterization provides detailed haemodynamic data for calculating pulmonary vascular resistance and for proceeding to structural interventions.²⁴ Other indications include assessment of LV and RV diastolic function, pressure gradients, and shunt quantification. Coronary angiography and the evaluation of extra-cardiac vessels such as aorto-pulmonary collateral arteries may be indicated.²⁵

Cardiopulmonary exercise and lung function test

Cardiopulmonary exercise test is a valuable tool with prognostic implications.²⁶ The exercise capacity is reduced in ACHD patients.¹⁷ The expected peak oxygen consumption varies between different types of ACHD lesions, and reference values for exercise limitations have been published.²⁷ There is a good correlation between exercise test results and mortality that seems to be increased in patients with peak oxygen consumption (VO_2) values <15 mL/min/kg. Other prognostic parameters such as ventilator response²⁸ and oscillatory patterns²⁹ provide important clinical information. *Lung function test* is needed to detect concomitant broncho-pulmonary disease.

Laboratory testing

Adult congenital heart disease patients suspected for HF should undergo basic laboratory testing including full blood count, renal function, liver function, protein and albumin, iron, and thyroid function. Laboratory testing may reveal treatable conditions. Anaemia, renal and liver dysfunction, hypoalbuminemia, hyponatremia, and iron depletion have prognostic significance.^{32–36}

Natriuretic peptides

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are related to disease severity and prognosis in HF patients with acquired heart disease.³⁰ Natriuretic peptides might be also clinically important in congenital heart disease.^{5,31,32} A recent cross-sectional study showed that BNP correlated with age was higher in women than in men, and differed per diagnosis.³³ Disease-specific correlations were also observed.^{34,35}

Septal defects

B-type natriuretic peptide levels are mildly increased in patients with unrepaired and repaired atrial septal defect or VSD.³⁴ Shunt severity and pulmonary artery pressures correlate strongly with BNP levels.^{36,37} A clear association between BNP and functional class is demonstrated.

Tetralogy of Fallot

Studies in ToF patients showed correlations between plasma BNP, RV dilation, and severity of pulmonary valve regurgitation.^{38,39} Also correlations between BNP and exercise capacity were found.^{39,40} Most studies to date present only cross-sectional data.⁴¹⁻⁵⁰ B-type natriuretic peptide levels before pulmonary valve replacement were found elevated and decrease afterwards; however, the results of individual BNP measurements differed widely so that the use of BNP changes as marker for outcome remains unclear.³⁵

Systemic morphological right ventricle

A clear correlation was found between BNP and systemic RV function.³⁵ One study showed a correlation between RV ejection fraction and atrial natriuretic peptide (ANP).⁵¹ Extensive atrial scarring in Mustard and Senning patients may contribute to elevated ANP levels. Moreover, a strong correlation was observed between plasma BNP and the severity of tricuspid regurgitation (TR).⁵²⁻⁵⁹ One longitudinal study described adult patients after atrial switch surgery for TGA.⁶⁰ They found that BNP was the most prominent predictor for HF, transplantation, and death (hazard ratio of 21). B-type natriuretic peptide might therefore be useful for risk assessment.

Hypoxia and single ventricle

Most studies found no correlation between oxygen saturation and BNP.⁶¹⁻⁶⁴ B-type natriuretic peptide levels in asymptomatic Fontan patients were comparable with those of healthy controls. However, in symptomatic patients, there was a strong correlation between BNP and the severity of HF. One study found significantly higher levels of BNP in five patients who died from HF,⁶² while another found no prognostic value of BNP.⁶⁵ B-type natriuretic peptide measurement may be useful in symptomatic patients.

Medical treatment

Systolic failure of the morphological systemic left ventricle

Trials with hard clinical endpoints have not been done in ACHD patients. The current ESC guidelines for HF¹⁸ suggest that diuretics, renin-angiotensin-aldosterone system (RAAS) blockers, β -blockers, and mineralocorticoid receptor antagonists can be used in the congenital heart disease population, mainly when neurohormonal and cardiac autonomic activity is increased.⁶⁶⁻⁶⁸

There is theoretical evidence to support the use of angiotensin-converting enzyme inhibitors (ACEIs) and, if not tolerated, angiotensin receptor blockers (ARB) in the treatment of *asymptomatic or symptomatic* HF ACHD patients. Similarly, the evidence for using β -blockers, such as carvedilol, metoprolol, bisoprolol, and nebivolol, may also be extrapolated to the ACHD population. Preliminary data suggest a favourable effect of these drugs in HF secondary to aortic^{69,70} or mitral valve disease.⁷¹

Many of these medications are prescribed for other indications, such as high blood pressure or arrhythmias, and this allows initiating drug treatment despite missing evidence in ACHD. Any treatment should serve one of two purposes: to improve prognosis or to alleviate symptoms. Loop diuretics never showed improved survival in chronic HF patients¹⁸ but relieve symptoms such as dyspnoea and peripheral oedema. Digoxin, once widely used in HF, now has a more limited role, as there is no mortality benefit when compared with placebo.

Systolic failure of the morphological systemic right ventricle

A systemic RV will gradually fail.⁷²⁻⁷⁴ Extrapolating the ESC HF guidelines¹⁸ to this ACHD group is more difficult. The cut-off of impaired ejection fraction of a systemic LV at which drug treatment has clinical benefit is well defined. However, no such data exist for the systemic RV. In most adults with a systemic RV, the systolic function is abnormal with a lower ejection fraction and lower exercise performance vs. controls.^{75,76}

For an *asymptomatic* patient without signs of HF, it is difficult to know if and when to initiate HF treatment. Patients with stable systemic RV function have not always an activated neurohormonal and cardiac autonomic nervous system. Therefore, blocking the RAAS does not result in better clinical outcome,⁷⁷⁻⁷⁹ although surrogate endpoints (exercise duration, degree of systemic AV valve regurgitation) seem to be influenced positively,^{78,80} Caution is required when using drugs that venodilate and reduce preload in Mustard or Senning patients. Ventricular filling is significantly compromised by concomitant baffle obstruction. β -Blockers might improve functional capacity and surrogate endpoints such as the severity of systemic AV valve regurgitation and RV remodelling.⁸¹⁻⁸³ However, patients with Mustard or Senning repair or with ccTGA are all susceptible to conduction abnormalities.

In *symptomatic* patients with neurohormonal and cardiac autonomous nervous system activation, standard HF treatment might offer theoretical benefit^{84,85} and is therefore suggested to be administered as in patients with a failing LV.

Systolic failure of the morphological sub-pulmonary right ventricle

No randomized controlled trials investigated which drugs to use. The beneficial effects of RAAS blockade or β -blockers have never been studied. Lack of data on the failing sub-pulmonary RV implies only few recommendations in the ESC guidelines on HF¹⁸ or pulmonary hypertension.⁸⁶ No medical treatment is indicated in *asymptomatic* patients. Diuretics are mainly the treatment of a *symptomatic* patient. Thiazides can be added in more resistant cases of oedema and act synergistically with loop diuretics, but then renal function and biochemical markers need close surveillance.⁸⁷ If RV failure is secondary to pulmonary arterial hypertension, drug therapy mainly focuses on the pulmonary circulation using endothelin receptor antagonists, phosphodiesterase inhibitors, or prostacyclines.

Systolic failure of the single ventricle

Phosphodiesterase inhibitors or endothelin receptor antagonists may improve ventricular function in a Fontan patient, when increasing pulmonary vascular resistance impairs ventricular filling. In patients treated with sildenafil, pulmonary vascular resistance decreases,⁸² exercise performance increases,⁸⁸ and myocardial performance ameliorates.⁸⁹ The effect of bosentan in the Fontan patient is less certain. Some studies suggest a beneficial effect,⁹⁰ whereas others did not.⁹¹ Perhaps, the combined increase in preload and reduction in afterload, which is more pronounced with sildenafil treatment, improves more the haemodynamics in the Fontan patient.⁹²

Primary myocardial dysfunction in Fontan requires standard HF medication for *symptom relief* in both, morphological left and right ventricles. However, in an *asymptomatic patient* with an impaired systemic right ventricle, the effect of medical treatment is unclear. Loop diuretics are frequently used if there is pulmonary fluid overload, but too high a dose can reduce preload and lead to the cardio-renal syndrome. Spironolactone appears to have an impact on PLE¹¹ and endothelial function.⁹³ One study showed that enalapril did not enhance exercise capacity in Fontan patients.⁹⁴ The indication for RAAS blockers in the Fontan is uncertain. Carvedilol has been shown to improve HF signs and symptoms.^{95,96} In summary, reducing pulmonary vascular resistance and afterload seems to have most clinical benefit, while symptomatic treatment with diuretics should be used cautiously and judiciously.

Standard HF treatment of patients with a functional univentricular heart and intra-cardiac shunt implies a difficult balance. Peripheral or pulmonary oedema can be treated with loop diuretics. However, drugs that reduce afterload may increase right-to-left shunting and lower the systemic oxygen saturation.⁹⁷

Heart failure with preserved ejection fraction

No treatment reduced morbidity and mortality in patients with preserved ejection fraction (ESC guidelines on HF¹⁸). Diuretics are used for symptom relief, and β -blockers may help by prolonging ventricular filling.

No studies in ACHD looked at ivabradine. However, in case of therapy resistance, ivabradine can be prescribed with similar indications as listed in the HF ESC guidelines.¹⁸ The same is true for hydralazine and isosorbide dinitrate. However, both agents decrease substantially the systemic vascular resistance so that systemic oxygen saturation has to be followed meticulously (see lower). Recommendations are summarized in *Table 3*.

Table 3. Medical treatment for heart failure related to intrinsic myocardial dysfunction

Systolic HF		
Systemic ventricle		
Morphological left ventricle (EF < 40%)	Asymptomatic or symptomatic	RAAS blockers β-Blockers Mineralocorticoid receptor antagonists Diuretics (loop and thiazide) Digoxin
Morphological right ventricle (EF < 40%)	Asymptomatic	No medical treatment
	Symptomatic	RAAS blockers Beta-blockers Mineralocorticoid receptor antagonists Diuretics (loop and thiazide) Digoxin
Sub-pulmonary ventricle		
Morphological left or right ventricle (EF < 40%)	Asymptomatic	No medical treatment
	Symptomatic	Diuretics (loop and thiazide) Mineralocorticoid receptor antagonists Pulmonary vasodilators (PAH)
Single ventricle		
Fontan circulation (EF < 40%)	Asymptomatic	RAAS blockers β-Blockers Mineralocorticoid receptor antagonists Digoxin
Morphological left ventricle		
Morphological right ventricle	Asymptomatic	No medical treatment
Morphological left and right ventricle	Symptomatic	RAAS blockers β-Blockers Mineralocorticoid receptor antagonists Diuretics (loop and thiazide) Digoxin
Persistent right-to-left shunt	Asymptomatic	No medical treatment
	Symptomatic	Diuretics (loop and thiazide) Agents reducing afterload
HF with preserved EF		
	Asymptomatic	No medical treatment
	Symptomatic	Diuretics (loop and thiazide) β-Blockers Rate-limiting calcium channel blocker

EF, ejection fraction; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure.

Iron deficiency has been reported in stable HF patients and in patients hospitalized for worsening HF.^{98,99} In the non-congenital population, iron replacement improves functional capacity, symptoms, and quality of life (QoL) and reduces the number of HF hospitalizations.¹⁰⁰ Although no specific trials on iron replacement exist in HF ACHD patients, a similar beneficial effect might be expected. Indeed, iron deficiency is not uncommon in ACHD patients,^{101,102} and replacement might improve functional capacity.¹⁰³ In contrast, vitamin B₁₂ and folate deficiency are relatively rare in patients with chronic HF,¹⁰⁴ and the effect of replacement on outcome, including HF ACHD patients, needs further investigation. Some data suggest that the use of anti-platelet therapy or oral anticoagulants may improve outcome in advanced HF.¹⁰⁵ This has never been investigated in HF ACHD patients, but it might be considered beneficial in HF secondary to ischaemic heart disease or atrial arrhythmia.

Acute heart failure in adult congenital heart disease patients

There are no scientific trials to guide clinicians on specifically managing ACHD patients with acute HF. Nevertheless, most of the ESC guidelines for managing acute HF¹⁸ can be applied in this context, taking into account the greater complexity and varied co-morbidities on a case-by-case basis. For example, in patients with pulmonary hypertension and/or persistent intra- or extra-cardiac shunts, the balance between pulmonary vascular resistance and systemic vascular resistance must be borne in mind and is a crucial consideration when prescribing pharmacotherapy.¹⁰⁶ Any increase in pulmonary vascular resistance will decrease cardiac output, and, in the presence of an intra-cardiac shunt, any decrease in systemic vascular resistance will increase the likelihood of right-to-left shunting and systemic desaturation. Triggers that increase pulmonary vascular resistance (hypoxia, hypercapnia, high haematocrit, positive pressure ventilation, cold, metabolic acidosis, and alpha-adrenergic stimulation) and those that decrease systemic vascular resistance (vasodilators, general anaesthesia, and hyperthermia) must therefore be avoided where possible.¹⁰⁶ Moreover, if there is a persistent right-to-left shunt, there is a risk of paradoxical air or thromboemboli and intravenous lines must be meticulously managed preferably with bubble filters attached. Patients with cyanosis have a secondary erythrocytosis and both an increased bleeding and thrombosis risk, which is generally more pronounced in the setting of acute HF. Coagulation factors and platelets should therefore be monitored, iron deficiency corrected, and venesection considered if the haematocrit exceeds 65%.

Cardiac monitoring of the ACHD patient in acute HF must also take into account the underlying congenital lesion, e.g. the patient with a subclavian flap repair of coarctation of the aorta should have blood pressure measured in the right arm as the left subclavian has been used for the repair, or placement of a central line in a Fontan patient, which sits in the pulmonary artery, and is therefore not a reliable measure of systemic venous filling pressure.¹⁰⁶

Finally, if maximal medical treatment fails to stabilize the haemodynamics, then extra-corporal membrane oxygenation (ECMO) and or ventricular assist device (VAD) therapy should be considered as bridging therapy to transplantation.

Cardiopulmonary and physical rehabilitation in adult congenital heart disease patients with heart failure

Cardiopulmonary rehabilitation is since long time recommended in patients with chronic HF.^{18,107} Indeed, exercise training is safe and tends to benefit clinical outcome.^{108,109} In HF ACHD patients, no specific studies have been conducted to evaluate clinical outcome. However, exercise training seems to improve safely exercise-related and haemodynamic variables in complex congenital heart disease.^{110–112} Moreover, cardiac rehabilitation programmes improve QoL in ACHD; however, none of them suffered from HF.¹¹³ Cardiac rehabilitation is probably safe and beneficial. However, further research is needed. A recent position paper recommends individualized exercise prescription to improve long-term health behaviour, and includes also advice for HF ACHD patients.¹¹⁴

Device therapy in adult congenital heart disease patients with heart failure

Indications for implantable cardioverter defibrillator therapy

The incidence of sudden cardiac death (SCD) in the congenital heart disease population is low (<0.1% per year) and 5–10 times lower than in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II population.¹¹⁵ However, SCD accounts for 20–25% of late deaths in ACHD patients.^{4,116} There are subgroups of congenital heart disease patients carrying a slightly higher SCD risk such as patients after surgical repair of ToF, d-TGA with Mustard or Senning repairs, ccTGA, Eisenmenger syndrome, and Ebstein anomaly of the tricuspid valve.¹¹⁶ In ACHD patients, consensus exists on

*implantable cardioverter defibrillator (ICD) therapy for secondary prevention of SCD.*¹¹⁵ Implantable cardioverter defibrillator therapy is recommended in survivors of SCD due to ventricular fibrillation (VF) or unstable ventricular tachycardia (VT) without reversible cause, patients with documented spontaneous sustained VT (sVT) that is not amenable to ablation or surgery, and syncope of unknown origin with inducible sVT/ VF at electrophysiology (EP) study or a high suspicion of ventricular arrhythmias being the cause of syncope.

Selection of *ICD candidates for primary prevention of SCD* still remains challenging. In general, prophylactic ICD therapy is also indicated in those patients who meet the same standard criteria as patients with ischaemic or non-ischaemic cardiomyopathy, i.e. the presence of biventricular physiology with a systemic LV ejection fraction <35% and NYHA class II or III symptoms.^{117–122}

Non-sVT (nsVT) in ToF patients is significantly associated with inducible sVT by programmed ventricular stimulation and that inducible sVT carries a five-fold higher rate of clinical VT or SCD.¹²³ Moreover, a weighted risk score to predict appropriate ICD shocks in ToF patients with prophylactic ICD implantation has been developed, implementing additive factors of risk stratification such as left ventricle end-diastolic pressures, nsVT, inducible sVT, prior shunt, prior ventriculotomy, and QRS duration.¹²⁴ According to this risk score, prophylactic ICD therapy should be recommended in selected adults after ToF repair classified in the high-risk category. However, the management of inappropriate shocks due to supraventricular arrhythmias is still challenging and has an important impact on the subjective QoL in these patients.¹²⁵

In contrast, the predictive value of EP testing in other ACHD subgroups is limited or not known. In patients with an atrial switch repair, inducible sVT/VF does not predict clinical events.¹²⁶ However, in this subgroup of patients, a reduced ejection fraction of the systemic right ventricle has been associated with a higher incidence of ventricular tachyarrhythmias and SCD.¹²⁷ For patients with univentricular hearts and a Fontan palliation, no recommendations for ICD indications exist. Nevertheless, ICD therapy may be reasonable in adults with an impaired single or systemic RV ejection fraction and the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II and III symptoms, long QRS duration, or severe AV valve regurgitation. Implantable cardioverter defibrillator therapy is not recommended in ACHD patients and in patients with advanced pulmonary vascular disease (Eisenmenger syndrome),^{128,129} drug-refractory NYHA class IV who are not candidates for heart transplantation (HT), significant psychiatric illness, incessant VT/VF, or a life expectancy <1 year.¹¹⁷

Indications for cardiac resynchronisation therapy

Cardiac resynchronization therapy (CRT) is an established treatment option in LV electromechanical dyssynchrony. If response to CRT is positive, reverse remodelling of the LV, functional improvement, and a reduction in HF associated morbidity and mortality can be seen.^{130,131} In ACHD patients, the morphological heterogeneity of the underlying heart defects makes it far more difficult to define the role of CRT. Most of the studies available are retrospective in nature and follow-up time in all trials is limited to a few months (4.8–8.4 months); hence, the impact of CRT on long-term morbidity and mortality is not known. Surrogate parameters such as metrics of systemic ventricular function or functional parameters such as NYHA class were used to define CRT response. Despite these limitations, the following observations were made: (i) the majority of congenital heart disease patients included (58%) were in NYHA class II when compared with NYHA class III or IV patients with ischaemic or idiopathic dilated cardiomyopathy; (ii) the presence of a systemic LV predicted a better CRT response than a systemic RV¹³²; (iii) the best CRT response was seen in patients with a systemic LV which were converted to CRT from conventional RV pacing^{133,134}; (iv) the proportion of non-responders to CRT was ~10–14% in congenital heart disease patients and lower than in patients with ischaemic or idiopathic dilated cardiomyopathy; and (v) patients with single ventricle morphology may benefit from CRT using optimized pacing sites.^{132,135} In general, CRT can be recommended in ACHD patients and patients with NYHA class II–IV symptoms, an impaired systemic ventricular ejection fraction, systemic ventricular

dilation, and prolonged QRS duration. Moreover, upgrading to CRT should be considered in congenital heart disease patients with systemic LV and permanent RV pacing resulting in LV dyssynchrony and dysfunction. Cardiac resynchronisation therapy should also be considered in NYHA class IV patients as a bridge/delay to mechanical assist device therapy or HT. Remote monitoring of devices has been shown to reduce adverse outcomes in ICD patients with acquired heart disease,¹³⁶ but may also be beneficial in ACHD patients for the early detection and treatment of tachyarrhythmias.¹³⁷

Heart transplantation and assist devices

According to the 2014 International Society for Heart Transplantation (ISHLT) Registry, ACHD represents ~10% of the HT indications in patients of 18–30 years.¹³⁸ Although short-term outcomes are worse in ACHD than to those with non-ACHD (20–30% at 30 days mortality in ACHD patients), late-term survival of ACHD is improved and survival at 10 years is similar between patients with ACHD and those with acquired heart disease.^{139,140}

The outcomes after ACHD HT can vary according to different diagnosis and may be influenced by centre's expertise.¹³⁸ Timing of assessment for HT remains challenging, as accurate prediction of prognosis is difficult. There is no single prognostic variable to be able to provide a perfect discriminatory capacity on need for or timing of HT. Serial cardiopulmonary exercise testing and other prognostic variables such as hospitalizations, clinically relevant arrhythmia, symptomatic HF, PLE, and plastic bronchitis may help to differentiate those ACHD patients from who do not deserve to be assessed for HT.

Careful pre-transplant evaluation should be specifically done to assess pulmonary vascular resistance; the presence of disease in organ systems that could affect post-HT care and can (or cannot) be reversed with HT; the presence of chronic or previous infections that could affect both pre- and post-HT management; psychosocial evaluation of the patient and caregivers; patency of major veins and arteries; human leucocyte antigen sensitization; and surgical risk (multiple cardiac redo operations, great vessels anatomy).

Ventricular assist devices (VADs) may be used as destination therapy or bridging to HT in ACHD patients.¹⁴¹ However, such patients listed for HT have less likelihood to have a VAD as a bridge to HT, longer waiting time in status 2, and higher mortality risk in the waiting list.¹⁴² Several case reports describe successful use of LV assist devices in failing systemic right ventricles.^{143,144} However, complication rates remain relatively high and are related to anatomic complexity and associated morbidities (coagulopathy, liver cirrhosis, etc.). Ventricular assist devices might be applicable in a failing Fontan circulation, however, only in these patients with systolic ventricular failure.^{145,146} In case that the sub-pulmonary ventricle (as after Fallot repair) fails, an RV assist device might be useful, but clinical outcome data are lacking.¹⁴¹

Management of care, psychological issues, and nursing management

The complexity of most heart diseases leads to a systematic follow-up in specialized ACHD centres. Less complex and stable patients are frequently followed in secondary care centres. They have to be aware of the occurrence of HF and to detect it in its early stage. Especially in complex cases or cases in which evidence-based medicine is lacking, transfer to a specialized ACHD centre is preferred. This might be important when HF becomes drug therapy resistant, and bridging to or listing for HT is needed.

Frequency of follow-up is reported in the ESC guidelines for the management of grown-up congenital heart disease.²⁵ Annual check-up of an HF ACHD patient, even asymptomatic, is recommended. This is important for optimizing health behaviour and treatment adherence. Follow-up visits and educational interventions contribute to persons' well-being and improve the level of patients' knowledge on the condition of their heart. Depending on the (proceeding) symptomatology and (in)stability of the disease process, more frequent follow-ups become obligatory. Routine follow-up implies focus on risk factors (as

palpitations, syncope), clinical examination, and electrocardiographic and echocardiographic evaluation. Depending on the symptomatology, changes in BNP levels need to be controlled, 24 h Holter/bicycle testing is indicated, and if the patient remains unstable, invasive evaluation will be preferred.

Sexual activity is not harmful for the heart, advice for pregnancy, contraception and labour in the female subgroup, and recommendations about physical activities are discussed in the ESC guidelines on pregnancy¹⁴⁷ and the ESC position paper about physical activities in ACHD.¹⁴⁸

Many patients with congenital heart disease deal with social and psychological concerns that may influence QoL.¹⁴⁹ Psychosocial condition refers to a range of issues faced by adults with congenital heart disease including the 'feeling of being different', experiences related to the living with the congenital heart disease and possible exacerbation of symptoms, emotional distress, poor illness perception, educational and behavioural issues, and compromised employability and insurability.^{149,150} Psychological condition is correlated with depression, anxiety, and impaired QoL.^{149,151} Possible interventions at improving illness perceptions may enhance patients' QoL, by increasing patients' knowledge regarding their disease and informing patients about treatment options, psychosocial support, cognitive behavioural therapies, and palliative care.¹⁴⁹

They need life-long comprehensive care to which nurses are an integral part of the health-care team.¹⁵²⁻¹⁵⁴ Nursing assessment includes physical, psychosocial, and knowledge examination.^{152,153}

Conclusions

Heart failure in adult patients with congenital heart disease overshadows more and more the outcome of this patient population. No large randomized clinical trials are available to write guidelines with a certain level of evidence. However, HF strategies, effective in ischaemic and congestive heart disease, are frequently applied to patients with congenital heart defects. This position paper intends to offer a platform to parallelize HF treatment in the congenital heart disease community abroad. However, it is clear that more research is needed to reach a certain level of evidence-based medicine.

Authors' contributions

W.B., J.R.-H., T.R.-H., A.E., T.A.M., E.L., M.C.-L., F.W., and A.A.F. drafted the manuscript. Board members of Working Group of GUCH and board members of Heart Failure Association made critical revision of the manuscript for key intellectual content.

Funding

The authors received a writing grant from the European Society of Cardiology.

Conflict of interest: none declared.

Acknowledgements

We thank Prof. Dr Gerasimos Filippatos, President of the Heart Failure Association (HFA), the board members of the HFA, and the nucleus members of the Working Group of Grown-Up Congenital Heart Disease (WG GUCH) for their support and useful suggestions to this manuscript. Board members of HFA: Gerasimos Filippatos (Greece); Stefan Anker (Germany); Frank Ruschitzka (Switzerland); Theresa McDonagh (co-author, UK); Christoph Maack (Germany); Arno Hoes (The Netherlands); Jillian Riley (UK); Alexandre Mebazaa and Andrew Coats (UK); Johan Bauersachs (Germany); Rudolf de Boer (The

Netherlands); Veli Pekka Harjola (Finland); Mitja Lainscak (Slovenia); Yury Lopatin (Russia); Giuseppe Rosano (Italy); Massimo Piepoli (Italy); Ekaterina Lambrinou (co-author, Cyprus); Stephane Heymans (The Netherlands); Marisa Crespo Leiro (co-author, Spain); Adelino Leite-Moreira (Portugal); and Piotr Ponikowski (Poland). Board members of WG GUCH: Andreas Eicken (Germany); Johan Holm (Sweden); Werner Budts (co-author, Belgium); Markus Schwerzmann (Switzerland); Jolien Roos-Hesselink (co-author, The Netherlands); Julie De Backer (Belgium); Lorna Swan (UK); Gerhard Diller (Germany); Allesandro Giamberti and Massimo Chessa (Italy); Fiona Walker (co-author, UK); and Garry Webb (USA).

References

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;58:2241–2247.
2. Kantor PF, Redington AN. Pathophysiology and management of heart failure in repaired congenital heart disease. *Heart Fail Clin* 2010;6:497–506, ix.
3. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. *Eur Heart J* 2010;31:1220–1229.
4. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol* 2000;86:1111–1116.
5. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation* 2002;106:92–99.
6. Jalal Z, Iriart X, De Lédinghen V, Barnette T, Hiriart JB, Vergniol J, Foucher J, Thambo JB. Liver stiffness measurements for evaluation of central venous pressure in congenital heart diseases. *Heart* 2015;101:1499–1504.
7. Ford RM, Book W, Spivey JR. Liver disease related to the heart. *Transplant Rev (Orlando)* 2015;29:33–37.
8. Lindsay I, Johnson J, Everitt MD, Hoffman J, Yetman AT. Impact of liver disease after the Fontan operation. *Am J Cardiol* 2015;115:249–252.
9. Bradley E, Hendrickson B, Daniels C. Fontan liver disease: review of an emerging epidemic and management options. *Curr Treat Options Cardiovasc Med* 2015;17:51.
10. Pundi KN, Johnson JN, Dearani JA, Li Z, Hinck CA, Dahl SH, Cannon BC, O'Leary PW, Driscoll DJ, Cetta F. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol* 2015;66:1700–1710.
11. Ringel RE, Peddy SB. Effect of high-dose spironolactone on protein-losing enteropathy in patients with Fontan palliation of complex congenital heart disease. *Am J Cardiol* 2003;91:1031–1032, A1039.
12. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. *J Am Coll Cardiol* 2014;64:54–62.
13. Schumacher KR, Stringer KA, Donohue JE, Yu S, Shaver A, Caruthers RL, Zikmund-Fisher BJ, Fifer C, Goldberg C, Russell MW. Fontan-associated protein-losing enteropathy and plastic bronchitis. *J Pediatr* 2015;166:970–977.
14. Saiki H, Kuwata S, Kurishima C, Iwamoto Y, Ishido H, Masutani S, Senzaki H. Prevalence, implication, and determinants of worsening renal function after surgery for congenital heart disease. *Heart Vessels* 2015; <https://doi.org/10.1007/s00380-015-0730-9>.
15. Jensen AS, Johansson PI, Idorn L, Sørensen KE, Thilén U, Nagy E, Furenäs E, Søndergaard L. The haematocrit – an important factor causing impaired haemostasis in patients with cyanotic congenital heart disease. *Int J Cardiol* 2013;167:1317–1321.
16. Budts W. Eisenmenger syndrome: medical prevention and management strategies. *Expert Opin Pharmacother* 2005;6:2047–2060.
17. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005;112:828–835.

18. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitler J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Guidelines ESCfP. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787–1847.
19. Valente AM, Cook S, Festa P, Ko HH, Krishnamurthy R, Taylor AM, Warnes CA, Kreutzer J, Geva T. Multimodality imaging guidelines for patients with repaired tetralogy of Fallot: a report from the American Society of Echocardiography: developed in collaboration with the Society for Cardiovascular Magnetic Resonance and the Society for Pediatric Radiology. *J Am Soc Echocardiogr* 2014;27:111–141.
20. Flachskampf FA, Wouters PF, Edvardsen T, Evangelista A, Habib G, Hoffman P, Hoffmann R, Lancellotti P, Pepi M, Rigo EAoCIDrEDaF. Recommendations for transoesophageal echocardiography: EACVI update 2014. *Eur Heart J Cardiovasc Imaging* 2014;15:353–365.
21. Ait-Ali L, Siciliano V, Passino C, Molinaro S, Pasanisi E, Sicari R, Pingitore A, Festa P. Role of stress echocardiography in operated Fallot: feasibility and detection of right ventricular response. *J Am Soc Echocardiogr* 2014;27:1319–1328.
22. Picano E, Pellikka PA. Stress echo applications beyond coronary artery disease. *Eur Heart J* 2014;35:1033–1040.
23. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitler J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. *Eur Heart J* 2010;31:794–805.
24. Holzer R, Beekman R, Benson L, Bergersen L, Jayaram N, Jenkins K, Kennedy K, Moore J, Ringel R, Rome J, Vincent R, Martin GR. Characteristics and safety of interventions and procedures performed during catheterisation of patients with congenital heart disease: early report from the national cardiovascular data registry. *Cardiol Young* 2015:1–11; <https://doi.org/10.1017/S1047951115002218>.
25. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, (ESC) TFotMoG-uCHDdotESoC, (AEPC) AfEPC, (CPG) ECfPG. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;31:2915–2957.
26. Inuzuka R, Diller GP, Borgia F, Benson L, Tay EL, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation* 2012;125:250–259.
27. Kempny A, Dimopoulos K, Uebing A, Mocerri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. *Eur Heart J* 2012;33:1386–1396.
28. Heiberg J, Petersen AK, Laustsen S, Hjortdal VE. Abnormal ventilatory response to exercise in young adults operated for ventricular septal defect in early childhood: a long-term follow-up. *Int J Cardiol* 2015;194:2–6.
29. Nathan AS, Loukas B, Moko L, Wu F, Rhodes J, Rathod RH, Systrom DM, Ubeda Tikkanen A, Shafer K, Lewis GD, Landzberg MJ, Opatowsky AR. Exercise oscillatory ventilation in patients with Fontan physiology. *Circ Heart Fail* 2015;8:304–311.
30. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, Pacher R. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002;105:2392–2397.
31. Giannakoulas G, Dimopoulos K, Bolger AP, Tay EL, Inuzuka R, Bedard E, Davos C, Swan L, Gatzoulis MA. Usefulness of natriuretic peptide levels to predict mortality in adults with congenital heart disease. *Am J Cardiol* 2010;105:869–873.
32. Alonso-Gonzalez R, Dimopoulos K. Biomarkers in congenital heart disease: do natriuretic peptides hold the key? *Expert Rev Cardiovasc Ther* 2013;11:773–784.
33. Eindhoven JA, van den Bosch AE, Ruys TP, Opić P, Cuypers JA, McGhie JS, Witsenburg M, Boersma E, Roos-Hesselink JW. N-terminal pro-B-type natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease. *J Am Coll Cardiol* 2013;62:1203–1212.
34. Eindhoven JA, van den Bosch AE, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in simple congenital heart disease – a systematic review. *Cardiol Young* 2013;23:315–324.

35. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. *J Am Coll Cardiol* 2012;60:2140–2149.
36. Nagaya N, Nishikimi T, Uematsu M, Kyotani S, Satoh T, Nakanishi N, Matsuo H, Kangawa K. Secretion patterns of brain natriuretic peptide and atrial natriuretic peptide in patients with or without pulmonary hypertension complicating atrial septal defect. *Am Heart J* 1998;136:297–301.
37. Schoen SP, Zimmermann T, Kittner T, Braun MU, Fuhrmann J, Schmeisser A, Strasser RH. NT-proBNP correlates with right heart haemodynamic parameters and volumes in patients with atrial septal defects. *Eur J Heart Fail* 2007;9:660–666.
38. Norozi K, Buchhorn R, Kaiser C, Hess G, Grunewald RW, Binder L, Wessel A. Plasma N-terminal pro-brain natriuretic peptide as a marker of right ventricular dysfunction in patients with tetralogy of Fallot after surgical repair. *Chest* 2005;128:2563–2570.
39. Trojnarowska O, Szyszka A, Gwizdała A, Siniawski A, Oko-Sarnowska Z, Chmara E, Katarzyński S, Cieśliński A. The BNP concentrations and exercise capacity assessment with cardiopulmonary stress test in patients after surgical repair of Fallot's tetralogy. *Int J Cardiol* 2006;110:86–92.
40. Norozi K, Buchhorn R, Bartmus D, Alpers V, Arnhold JO, Schoof S, Zoega M, Binder L, Geyer S, Wessel A. Elevated brain natriuretic peptide and reduced exercise capacity in adult patients operated on for tetralogy of Fallot is due to biventricular dysfunction as determined by the myocardial performance index. *Am J Cardiol* 2006;97:1377–1382.
41. Brili S, Alexopoulos N, Latsios G, Aggeli C, Barbetseas J, Pitsavos C, Vyssoulis G, Stefanadis C. Tissue Doppler imaging and brain natriuretic peptide levels in adults with repaired tetralogy of Fallot. *J Am Soc Echocardiogr* 2005;18:1149–1154.
42. Tatani SB, Carvalho AC, Andriolo A, Rabelo R, Campos O, Moises VA. Echocardiographic parameters and brain natriuretic peptide in patients after surgical repair of tetralogy of Fallot. *Echocardiography* 2010;27:442–447.
43. Cetin I, Tokel K, Varan B, Orün U, Aşlamaci S. Evaluation of right ventricular function by using tissue Doppler imaging in patients after repair of tetralogy of Fallot. *Echocardiography* 2009;26:950–957.
44. Apitz C, Sieverding L, Latus H, Uebing A, Schoof S, Hofbeck M. Right ventricular dysfunction and B-type natriuretic peptide in asymptomatic patients after repair for tetralogy of Fallot. *Pediatr Cardiol* 2009;30:898–904.
45. Koch AM, Zink S, Glöckler M, Seeliger T, Dittrich S. Plasma levels of B-type natriuretic peptide in patients with tetralogy of Fallot after surgical repair. *Int J Cardiol* 2010;143:130–134.
46. Cheung EW, Lam WW, Chiu CS, Chau AK, Cheung SC, Cheung YF. Plasma brain natriuretic peptide levels, right ventricular volume overload and exercise capacity in adolescents after surgical repair of tetralogy of Fallot. *Int J Cardiol* 2007;121:155–162.
47. Ishii H, Harada K, Toyono M, Tamura M, Takada G. Usefulness of exercise-induced changes in plasma levels of brain natriuretic peptide in predicting right ventricular contractile reserve after repair of tetralogy of Fallot. *Am J Cardiol* 2005;95:1338–1343.
48. van den Berg J, Strengers JL, Wielopolski PA, Hop WC, Meijboom FJ, de Rijke YB, Boomsma F, Bogers AJ, Pattynama PM, Helbing WA. Assessment of biventricular functional reserve and NT-proBNP levels in patients with RV volume overload after repair of tetralogy of Fallot at young age. *Int J Cardiol* 2009;133:364–370.
49. Khositseth A, Manop J, Khowsathit P, Siripornpitak S, Pornkul R, Lolekha P, Attanawanich S. N-terminal pro-brain natriuretic peptide as a marker in follow-up patients with tetralogy of Fallot after total correction. *Pediatr Cardiol* 2007;28:333–338.
50. Dodge-Khatami A, Büchel EV, Knirsch W, Kadner A, Rousson V, Dave HH, Bauersfeld U, Prêtre R. Brain natriuretic peptide and magnetic resonance imaging in tetralogy with right ventricular dilatation. *Ann Thorac Surg* 2006;82:983–988.
51. Garg R, Raman SV, Hoffman TM, Hayes J, Daniels CJ. Serum markers of systemic right ventricular function and exercise performance. *Pediatr Cardiol* 2008;29:641–648.
52. Chow PC, Cheung EW, Chong CY, Lun KS, Yung TC, Wong KT, Chau AK, Cheung YF. Brain natriuretic peptide as a biomarker of systemic right ventricular function in patients with transposition of great arteries after atrial switch operation. *Int J Cardiol* 2008;127:192–197.
53. Schaefer A, Tallone EM, Westhoff-Bleck M, Klein G, Drexler H, Röntgen P. Relation of diastolic and systolic function, exercise capacity and brain natriuretic peptide in adults after Mustard procedure for transposition of the great arteries. *Cardiology* 2010;117:112–117.
54. Larsson DA, Meurling CJ, Holmqvist F, Waktare JE, Thilén UJ. The diagnostic and prognostic value of brain natriuretic peptides in adults with a systemic morphologically right ventricle or Fontan-type circulation. *Int J Cardiol* 2007;114:345–351.
55. Koch AM, Zink S, Singer H. B-type natriuretic peptide in patients with systemic right ventricle. *Cardiology* 2008;110:1–7.

56. Plymen CM, Hughes ML, Picaut N, Panoulas VF, Macdonald ST, Cullen S, Deanfield JE, Walker F, Taylor AM, Lambiase PD, Bolger AP. The relationship of systemic right ventricular function to ECG parameters and NT-proBNP levels in adults with transposition of the great arteries late after Senning or Mustard surgery. *Heart* 2010;96:1569–1573.
57. Norozi K, Buchhorn R, Alpers V, Arnhold JO, Schoof S, Zoega M, Geyer S, Wessel A. Relation of systemic ventricular function quantified by myocardial performance index (TEI) to cardiopulmonary exercise capacity in adults after Mustard procedure for transposition of the great arteries. *Am J Cardiol* 2005;96:1721–1725.
58. Kozelj M, Prokselj K, Berden P, Jan M, Osredkar J, Bunc M, Tretjak M, Podnar T. The syndrome of cardiac failure in adults with congenitally corrected transposition. *Cardiol Young* 2008;18:599–607.
59. Vogt M, Kühn A, Wiese J, Eicken A, Hess J, Vogel M. Reduced contractile reserve of the systemic right ventricle under dobutamine stress is associated with increased brain natriuretic peptide levels in patients with complete transposition after atrial repair. *Eur J Echocardiogr* 2009;10:691–694.
60. Westhoff-Bleck M, Podewski E, Tutarel O, Wenzel D, Cappello C, Bertram H, Bauersachs J, Widder J. Prognostic value of NT-proBNP in patients with systemic morphological right ventricles: a single-centre experience. *Int J Cardiol* 2013;169:433–438.
61. Hsu JH, Oishi PE, Keller RL, Chikovani O, Karl TR, Azakie A, Adata I, Fineman JR. Perioperative B-type natriuretic peptide levels predict outcome after bidirectional cavopulmonary anastomosis and total cavopulmonary connection. *J Thorac Cardiovasc Surg* 2008;135:746–753.
62. Koch AM, Zink S, Singer H, Dittrich S. B-type natriuretic peptide levels in patients with functionally univentricular hearts after total cavopulmonary connection. *Eur J Heart Fail* 2008;10:60–62.
63. Holmgren D, Westerlind A, Berggren H, Lundberg PA, Wåhlander H. Increased natriuretic peptide type b level after the second palliative step in children with univentricular hearts with right ventricular morphology but not left ventricular morphology. *Pediatr Cardiol* 2008;29:786–792.
64. Ohuchi H, Takasugi H, Ohashi H, Yamada O, Watanabe K, Yagihara T, Echigo S. Abnormalities of neurohormonal and cardiac autonomic nervous activities relate poorly to functional status in Fontan patients. *Circulation* 2004;110:2601–2608.
65. Inai K, Nakanishi T, Nakazawa M. Clinical correlation and prognostic predictive value of neurohumoral factors in patients late after the Fontan operation. *Am Heart J* 2005;150:588–594.
66. Ohuchi H, Takasugi H, Ohashi H, Okada Y, Yamada O, Ono Y, Yagihara T, Echigo S. Stratification of pediatric heart failure on the basis of neurohormonal and cardiac autonomic nervous activities in patients with congenital heart disease. *Circulation* 2003;108:2368–2376.
67. Sugimoto M, Masutani S, Seki M, Kajino H, Fujieda K, Senzaki H. High serum levels of procollagen type III N-terminal amino peptide in patients with congenital heart disease. *Heart* 2009;95:2023–2028.
68. Buchhorn R, Hulpke-Wette M, Ruschewski W, Ross RD, Fielitz J, Pregla R, Hetzer R, Regitz-Zagrosek V. Effects of therapeutic beta blockade on myocardial function and cardiac remodelling in congenital cardiac disease. *Cardiol Young* 2003;13:36–43.
69. Plante E, Lachance D, Champetier S, Drolet MC, Roussel E, Arsenault M, Couet J. Benefits of long-term beta-blockade in experimental chronic aortic regurgitation. *Am J Physiol Heart Circ Physiol* 2008;294:H1888–H1895.
70. Zendaoui A, Lachance D, Roussel E, Couet J, Arsenault M. Usefulness of carvedilol in the treatment of chronic aortic valve regurgitation. *Circ Heart Fail* 2011;4:207–213.
71. Ennis DB, Rudd-Barnard GR, Li B, Fonseca CG, Young AA, Cowan BR, Stewart RA. Changes in mitral annular geometry and dynamics with β -blockade in patients with degenerative mitral valve disease. *Circ Cardiovasc Imaging* 2010;3:687–693.
72. Hornung TS, Bernard EJ, Celermajer DS, Jaeggi E, Howman-Giles RB, Chard RB, Hawker RE. Right ventricular dysfunction in congenitally corrected transposition of the great arteries. *Am J Cardiol* 1999;84:1116–1119, A1110.
73. Dobson R, Danton M, Nicola W, Hamish W. The natural and unnatural history of the systemic right ventricle in adult survivors. *J Thorac Cardiovasc Surg* 2013;145:1493–1501; discussion 1501–1493.
74. Cuyper JA, Eindhoven JA, Slager MA, Opić P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J* 2014;35:1666–1674.
75. Budts W, Scheurwegs C, Stevens A, Moons P, Van Deyk K, Vanhees L. The future of adult patients after Mustard or Senning repair for transposition of the great arteries. *Int J Cardiol* 2006;113:209–214.

76. Winter MM, Bouma BJ, van Dijk AP, Groenink M, Nieuwkerk PT, van der Plas MN, Sieswerda GT, Konings TC, Mulder BJ. Relation of physical activity, cardiac function, exercise capacity, and quality of life in patients with a systemic right ventricle. *Am J Cardiol* 2008;102:1258–1262.
77. Dore A, Houde C, Chan KL, Ducharme A, Khairy P, Juneau M, Marcotte F, Mercier LA. Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial. *Circulation* 2005;112:2411–2416.
78. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. *Circulation* 2013;127:322–330.
79. Therrien J, Provost Y, Harrison J, Connelly M, Kaemmerer H, Webb GD. Effect of angiotensin receptor blockade on systemic right ventricular function and size: a small, randomized, placebo-controlled study. *Int J Cardiol* 2008;129:187–192.
80. Lester SJ, McElhinney DB, Vilorio E, Reddy GP, Ryan E, Tworetzky W, Schiller NB, Foster E. Effects of losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries. *Am J Cardiol* 2001;88:1314–1316.
81. Doughan AR, McConnell ME, Book WM. Effect of beta blockers (carvedilol or metoprolol XL) in patients with transposition of great arteries and dysfunction of the systemic right ventricle. *Am J Cardiol* 2007;99:704–706.
82. Giardini A, Lovato L, Donti A, Formigari R, Gargiulo G, Picchio FM, Fattori R. A pilot study on the effects of carvedilol on right ventricular remodelling and exercise tolerance in patients with systemic right ventricle. *Int J Cardiol* 2007;114:241–246.
83. Bouallal R, Godart F, Francart C, Richard A, Foucher-Hosseine C, Lions C. Interest of β -blockers in patients with right ventricular systemic dysfunction. *Cardiol Young* 2010;20:615–619.
84. Tutarel O, Meyer GP, Bertram H, Wessel A, Schieffer B, Westhoff-Bleck M. Safety and efficiency of chronic ace inhibition in symptomatic heart failure patients with a systemic right ventricle. *Int J Cardiol* 2012;154:14–16.
85. Dos L, Pujadas S, Estruch M, Mas A, Ferreira-González I, Pijuan A, Serra R, Ordóñez-Llanos J, Subirana M, Pons-Lladó G, Marsal JR, García-Dorado D, Casaldàliga J. Eplerenone in systemic right ventricle: double blind randomized clinical trial. The EVEDES study. *Int J Cardiol* 2013;168:5167–5173.
86. Galiè N, Hooper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, (CPG) EC[†]PG. Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–2537.
87. Jentzer JC, De Wald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010;56:1527–1534.
88. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J* 2008;29:1681–1687.
89. Shabanian R, Shahbaznejad L, Razaghian A, Kiani A, Rahimzadeh M, Seifirad S, Kocharian A, Gilani JS, Navabi MA. Sildenafil and ventriculo-arterial coupling in Fontan-palliated patients: a noninvasive echocardiographic assessment. *Pediatr Cardiol* 2013;34:129–134.
90. Ovaert C, Thijs D, Dewolf D, Ottenkamp J, Dessy H, Moons P, Gewillig M, Mertens L. The effect of bosentan in patients with a failing Fontan circulation. *Cardiol Young* 2009;19:331–339.
91. Schuurung MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, Sieswerda GT, de Bruin-Bon RH, Mulder BJ, Bouma BJ. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. *Eur J Heart Fail* 2013;15:690–698.
92. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W. Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging* 2014;7:265–273.
93. Mahle WT, Wang A, Quyyumi AA, McConnell ME, Book WM. Impact of spironolactone on endothelial function in patients with single ventricle heart. *Congenit Heart Dis* 2009;4:12–16.
94. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. *Circulation* 1997;96:1507–1512.
95. Ishibashi N, Park IS, Takahashi Y, Nishiyama M, Murakami Y, Mori K, Mimori S, Ando M, Nakanishi T. Effectiveness of carvedilol for congestive heart failure that developed long after modified Fontan operation. *Pediatr Cardiol* 2006;27:473–475.

96. Ishibashi N, Park IS, Waragai T, Yoshikawa T, Murakami Y, Mori K, Mimori S, Ando M, Takahashi Y, Doi S, Mizutani S, Nakanishi T. Effect of carvedilol on heart failure in patients with a functionally univentricular heart. *Circ J* 2011;75:1394–1399.
97. Lee KJ, Yoo SJ, Holtby H, Grant B, Mroczek D, Wong D, Grosse-Wortmann L, Benson LN, Chaturvedi RR. Acute effects of the ace inhibitor enalaprilat on the pulmonary, cerebral and systemic blood flow and resistance after the bidirectional cavopulmonary connection. *Heart* 2011;97:1343–1348.
98. Enjuanes C, Klip IT, Bruguera J, Cladellas M, Ponikowski P, Banasiak W, van Veldhuisen DJ, van der Meer P, Jankowska EA, Comín-Colet J. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol* 2014;174:268–275.
99. Jankowska EA, Kasztura M, Sokolski M, Bronisz M, Nawrocka S, Oleśkowska-Florek W, Zymlifski R, Biegus J, Siwołowski P, Banasiak W, Anker SD, Filippatos G, Cleland JG, Ponikowski P. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure. *Eur Heart J* 2014;35:2468–2476.
100. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, Investigators C-H. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;36:657–668.
101. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R, Vachiéry JL, Paelinck B, Morissens M, Budts W. Iron deficiency is associated with adverse outcome in Eisenmenger patients. *Eur Heart J* 2011;32:2790–2799.
102. Mascitelli L, Pezzetta F, Goldstein MR. Reduced body iron stores and atherosclerosis in patients with cyanotic congenital heart disease. *Int J Cardiol* 2011;146:117.
103. Tay EL, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G, Tzifa A, Goletto S, Broberg C, Dimopoulos K, Gatzoulis MA. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. *Int J Cardiol* 2011;151:307–312.
104. van der Wal HH, Comin-Colet J, Klip IT, Enjuanes C, Grote Beverborg N, Voors AA, Banasiak W, van Veldhuisen DJ, Bruguera J, Ponikowski P, Jankowska EA, van der Meer P. Vitamin B12 and folate deficiency in chronic heart failure. *Heart* 2015;101:302–310.
105. de Boer RA, Hillege HL, Tjeerdsma G, Verheugt FW, van Veldhuisen DJ. Both antiplatelet and anticoagulant therapy may favorably affect outcome in patients with advanced heart failure. A retrospective analysis of the PRIME-II trial. *Thromb Res* 2005;116:279–285.
106. Cannesson M, Earing MG, Collange V, Kersten JR. Anesthesia for noncardiac surgery in adults with congenital heart disease. *Anesthesiology* 2009;111:432–440.
107. Corrà U, Giannuzzi P, Adamopoulos S, Bjornstad H, Bjarnason-Wehrens B, Cohen-Solal A, Dugmore D, Fioretti P, Gaita D, Hambrecht R, Hellermans I, McGee H, Mendes M, Perk J, Saner H, Vanhees L, Cardiology WGoCRaEPotESo. Executive summary of the position paper of the working group on cardiac rehabilitation and exercise physiology of the European Society of Cardiology (ESC): core components of cardiac rehabilitation in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2005;12:321–325.
108. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL, Investigators H-A. Efficacy and safety of exercise training in patients with chronic heart failure: HF-action randomized controlled trial. *JAMA* 2009;301:1439–1450.
109. Koukoui F, Desmoulin F, Lairy G, Bleinc D, Boursiquot L, Galinier M, Smih F, Rouet P. Benefits of cardiac rehabilitation in heart failure patients according to etiology: INCARD French study. *Medicine (Baltimore)* 2015;94:e544.
110. van der Bom T, Winter MM, Knaake JL, Cervi E, de Vries LS, Balducci A, Meregalli PG, Pieper PG, van Dijk AP, Bonvicini M, Mulder BJ, Bouma BJ. Long-term benefits of exercise training in patients with a systemic right ventricle. *Int J Cardiol* 2015;179:105–111.
111. Duppen N, Geerdink LM, Kuipers IM, Bossers SS, Koopman LP, van Dijk AP, Roos-Hesselink JW, De Korte CL, Helbing WA, Kapusta L. Regional ventricular performance and exercise training in children and young adults after repair of tetralogy of Fallot: randomized controlled pilot study. *Circ Cardiovasc Imaging* 2015;8: <https://doi.org/10.1161/CIRCIMAGING.114.002006>.
112. Duppen N, Kapusta L, de Rijke YB, Snoeren M, Kuipers IM, Koopman LP, Blank AC, Blom NA, Dulfer K, Utens EM, Hopman MT, Helbing WA. The effect of exercise training on cardiac remodelling in children and young adults with corrected tetralogy of Fallot or Fontan circulation: a randomized controlled trial. *Int J Cardiol* 2015;179:97–104.

113. Gierat-Haponiuk K, Haponiuk I, Szalewska D, Chojnicki M, Jaworski R, Niekoszko P, Leszczyńska K, Bakula S. Effect of complex cardiac rehabilitation on physical activity and quality of life during long-term follow-up after surgical correction of congenital heart disease. *Kardiol Pol* 2015;73:267–273.
114. Budts W, Börjesson M, Chessa M, van Buuren F, Trigo Trindade P, Corrado D, Heidbuchel H, Webb G, Holm J, Papadakis M. Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription. *Eur Heart J* 2013;34:3669–3674.
115. Triedman JK. Should patients with congenital heart disease and a systemic ventricular ejection fraction less than 30% undergo prophylactic implantation of an ICD? Implantable cardioverter defibrillator implantation guidelines based solely on left ventricular ejection fraction do not apply to adults with congenital heart disease. *Circ Arrhythm Electrophysiol* 2008;1:307–316; discussion 316.
116. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJ. Sudden cardiac death in adult congenital heart disease. *Circulation* 2012;126:1944–1954.
117. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2013;61:e6–e75.
118. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol* 2002;40:1675–1680.
119. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–237.
120. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151–2158.
121. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA* 2004;292:2874–2879.
122. Silka MJ, Bar-Cohen Y. Should patients with congenital heart disease and a systemic ventricular ejection fraction less than 30% undergo prophylactic implantation of an ICD? Patients with congenital heart disease and a systemic ventricular ejection fraction less than 30% should undergo prophylactic implantation of an implantable cardioverter defibrillator. *Circ Arrhythm Electrophysiol* 2008;1:298–306.
123. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marcon F, Alexander ME, Walsh EP. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. *Circulation* 2004;109:1994–2000.
124. Khairy P. Defibrillators and cardiac resynchronization therapy in congenital heart disease: evolving indications. *Expert Rev Med Devices* 2008;5:267–271.
125. Opić P, Utens EM, Moons P, Theuns DA, van Dijk AP, Hoendermis ES, Vliegen HW, de Groot NM, Witsenburg M, Schalij M, Roos-Hesselink JW. Psychosocial impact of implantable cardioverter defibrillators (ICD) in young adults with tetralogy of Fallot. *Clin Res Cardiol* 2012;101:509–519.
126. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A, Cecchin F. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. *Circ Arrhythm Electrophysiol* 2008;1:250–257.
127. Schwerzmann M, Salehian O, Harris L, Siu SC, Williams WG, Webb GD, Colman JM, Redington A, Silversides CK. Ventricular arrhythmias and sudden death in adults after a Mustard operation for transposition of the great arteries. *Eur Heart J* 2009;30:1873–1879.
128. Rajdev A, Garan H, Biviano A. Arrhythmias in pulmonary arterial hypertension. *Prog Cardiovasc Dis* 2012;55:180–186.

129. Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, Dweik RA. Causes and circumstances of death in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2013;188:365–369.
130. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–1549.
131. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329–1338.
132. Janousek J, Gebauer RA, Abdul-Khaliq H, Turner M, Kornyei L, Grollmuss O, Rosenthal E, Villain E, Fruh A, Paul T, Blom NA, Happonen JM, Bauersfeld U, Jacobsen JR, van den Heuvel F, Delhaas T, Papagiannis J, Trigo C. Cardiac resynchronisation therapy in paediatric and congenital heart disease: differential effects in various anatomical and functional substrates. *Heart* 2009;95:1165–1171.
133. Khairy P, Fournier A, Thibault B, Dubuc M, Therien J, Vobecky SJ. Cardiac resynchronization therapy in congenital heart disease. *Int J Cardiol* 2006;109:160–168.
134. Janousek J, Gebauer RA. Cardiac resynchronization therapy in pediatric and congenital heart disease. *Pacing Clin Electrophysiol* 2008;31(Suppl 1):S21–S23.
135. Cecchin F, Frangini PA, Brown DW, Fynn-Thompson F, Alexander ME, Triedman JK, Gauvreau K, Walsh EP, Berul CI. Cardiac resynchronization therapy (and multisite pacing) in pediatrics and congenital heart disease: five years experience in a single institution. *J Cardiovasc Electrophysiol* 2009;20:58–65.
136. Akar JG, Bao H, Jones P, Wang Y, Varosy P, Masoudi FA, Stein K, Saxon LA, Normand ST, Curtis JP. Use of remote monitoring is associated with lower risk of adverse outcomes among patients with implanted cardiac defibrillators. *Circ Arrhythm Electrophysiol* 2015;8:1173–1180.
137. Nagel B, Janousek J, Koestenberger M, Maier R, Sauseng W, Strenger V, Gamillscheg A, Zartner P. Remote monitoring leads to early recognition and treatment of critical arrhythmias in adults after atrial switch operation for transposition of the great arteries. *Circ J* 2014;78:450–456.
138. Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, Dobbels F, Goldfarb SB, Levvey BJ, Meiser B, Yusef RD, Stehlik J, Transplantation ISoHaL. The registry of the international society for heart and lung transplantation: thirty-first official adult heart transplant report—2014; focus theme: retransplantation. *J Heart Lung Transplant* 2014;33:996–1008.
139. Goldberg SW, Fisher SA, Wehman B, Mehra MR. Adults with congenital heart disease and heart transplantation: optimizing outcomes. *J Heart Lung Transplant* 2014;33:873–877.
140. Burchill LJ, Edwards LB, Dipchand AI, Stehlik J, Ross HJ. Impact of adult congenital heart disease on survival and mortality after heart transplantation. *J Heart Lung Transplant* 2014;33:1157–1163.
141. Mulukutla V, Franklin WJ, Villa CR, Morales DL. Surgical device therapy for heart failure in the adult with congenital heart disease. *Heart Fail Clin* 2014;10:197–206.
142. Gelow JM, Song HK, Weiss JB, Mudd JO, Broberg CS. Organ allocation in adults with congenital heart disease listed for heart transplant: impact of ventricular assist devices. *J Heart Lung Transplant* 2013;32:1059–1064.
143. Joyce DL, Crow SS, John R, St Louis JD, Braunlin EA, Pyles LA, Kofflin P, Joyce LD. Mechanical circulatory support in patients with heart failure secondary to transposition of the great arteries. *J Heart Lung Transplant* 2010;29:1302–1305.
144. Shah NR, Lam WW, Rodriguez FH, Ermis PR, Simpson L, Frazier OH, Franklin WJ, Parekh DR. Clinical outcomes after ventricular assist device implantation in adults with complex congenital heart disease. *J Heart Lung Transplant* 2013;32:615–620.
145. Rodefeld MD, Boyd JH, Myers CD, LaLone BJ, Bezruczko AJ, Potter AW, Brown JW. Cavopulmonary assist: circulatory support for the univentricular Fontan circulation. *Ann Thorac Surg* 2003;76:1911–1916; discussion 1916.
146. Russo P, Wheeler A, Russo J, Tobias JD. Use of a ventricular assist device as a bridge to transplantation in a patient with single ventricle physiology and total cavopulmonary anastomosis. *Paediatr Anaesth* 2008;18:320–324.
147. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, (ESG) ESOG, (AEP) AfEPC, (DGesGM) GSFGM, Guidelines ECfP. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:3147–3197.

148. Budts W, Borjesson M, Chessa M, van Buuren F, Trigo Trindade P, Corrado D, Heidbuchel H, Webb G, Holm J, Papadakis M. Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription. *Eur Heart J* 2013;34:3669–3674.
149. Schoormans D, Mulder BJ, van Melle JP, Pieper PG, van Dijk AP, Sieswerda GT, Hulsbergen-Zwarts MS, Plokker TH, Brunninkhuis LG, Vliegen HW, Sprangers MA. Illness perceptions of adults with congenital heart disease and their predictive value for quality of life two years later. *Eur J Cardiovasc Nurs* 2014;13:86–94.
150. Moons P, De Geest S, Budts W. Comprehensive care for adults with congenital heart disease: expanding roles for nurses. *Eur J Cardiovasc Nurs* 2002;1:23–28.
151. Kovacs AH, Saidi AS, Kuhl EA, Sears SF, Silversides C, Harrison JL, Ong L, Colman J, Oechslin E, Nolan RP. Depression and anxiety in adult congenital heart disease: predictors and prevalence. *Int J Cardiol* 2009;137:158–164.
152. Moons P, Scholte op Reimer W, De Geest S, Fridlund B, Heikkila J, Jaarsma T, Martensson J, Smith K, Stewart S, Stromberg A, Thompson DR, Group UNITER. Nurse specialists in adult congenital heart disease: the current status in Europe. *Eur J Cardiovasc Nurs* 2006;5:60–67.
153. Dearani JA, Connolly HM, Martinez R, Fontanet H, Webb GD. Caring for adults with congenital cardiac disease: successes and challenges for 2007 and beyond. *Cardiol Young* 2007;17(Suppl. 2):87–96.
154. Baumgartner H, Budts W, Chessa M, Deanfield J, Eicken A, Holm J, Iserin L, Meijboom F, Stein J, Szatmari A, Trindade PT, Walker F, Cardiology WGoG-uCHDotESo. Recommendations for organization of care for adults with congenital heart disease and for training in the subspecialty of 'grown-up congenital heart disease' in Europe: a position paper of the working group on grown-up congenital heart disease of the European Society of Cardiology. *Eur Heart J* 2014;35:686–690.