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POSITION STATEMENT

Management of People With a Fontan Circulation: a Cardiac Society of Australia and New Zealand Position Statement

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Abstract

The Fontan circulation describes the circulatory state resulting from an operation in congenital heart disease where systemic venous return is directed to the lungs without an intervening active pumping chamber. As survival increases, so too does recognition of the potential health challenges. This document aims to allow clinicians, people with a Fontan circulation, and their families to benefit from consensus agreement about management of the person with a Fontan circulation. The document was crafted with input from a multidisciplinary group of health care providers as well as individuals with a Fontan circulation and families. It is hoped that the shared common vision of long-term wellbeing will continue to drive improvements in care and quality of life in this patient population and eventually translate into improved survival.

Keypoints

- Lifelong quality medical care with access to multidisciplinary services, is of prime importance. Care includes regular tests for surveillance of health status.
- Transition from paediatric to adult care is an active process that should commence during early adolescence and continue until successful engagement with adult congenital cardiology care.
- Children and adults with a Fontan circulation often have reduced peak exercise capacity (on average, 60–65% of predicted values). Increasingly, evidence suggests exercise training may improve exercise capacity and cardiovascular function.

Abbreviation: ACE, angiotensin-converting enzyme; AFP, alpha-fetoprotein; AHA, American Heart Association; ANZ, Australian and New Zealand (Fontan Registry); AV, atrioventricular; BNP, B-type natriuretic peptide; CHD, congenital heart disease; CMR, cardiac magnetic resonance imaging; COCP, combined oral contraceptive pill; CSANZ, Cardiac Society of Australia and New Zealand; CT, computed tomography; DOAC, direct oral anticoagulant; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HLA, human leukocyte antigen; ICD, implantable cardioverter defibrillator; PLE, protein-losing enteropathy; V_{O_2}, oxygen uptake; VT, ventricular tachycardia

- People with a Fontan circulation have higher rates of anxiety and behavioural disorders, and there needs to be a low threshold for the provision of mental health care.
- Pregnancy has increased maternal and fetal risks, and pre-conception multidisciplinary assessment and counselling is essential.
- Atrial arrhythmias are common, often late after Fontan surgical repair and due to intra-atrial re-entry or ''flutter'' mediated by atrial stretch and scarring. Some anti-arrhythmic agents, most classically the type IC drugs, may allow haemodynamically unstable, life-threatening 1:1 AV conduction.
- Anticoagulation with warfarin is routine care in patients with atrial arrhythmias.
- In patients with recurrent atrial arrhythmias, catheter ablation or surgical conversion may be considered.
- The Fontan circulation is an ideal substrate for thrombus formation and may result in intracardiac or intravascular thrombosis, ischaemic stroke, or other embolic phenomena. Antiplatelet and anticoagulant agents are commonly prescribed for thromboprophylaxis in patients with a Fontan circulation. Evidence suggests that treatment with one of these agents is advantageous, but there is no consensus on which is optimal. Despite treatment, symptomatic thromboembolic events are associated with significant mortality.
- Heart failure is the leading cause of morbidity and mortality. Diuretics provide symptomatic relief, however standard heart failure medical therapy is not of proven benefit.
- Though not well understood, there is increasing concern regarding progressive liver disease with a long-term risk of hepatocellular carcinoma.
- Despite early higher mortality post heart transplant, these individuals have better long-term survival outcomes compared with many other heart transplant recipients.

Position Statement Development

This position statement is a consensus undertaking that aims to provide expert opinion regarding the care of people with a Fontan circulation in Australia and New Zealand. Recognising that there is limited high-level evidence for the care of these people, this document has been developed as a position statement, rather than a guideline, and it does not provide ratings regarding the level of evidence for its statements. This model has been successfully applied for other chronic conditions [1]. In the absence of high-level evidence for this population, many sections of this document describe a common, rather than a universal, approach to management. The authors recognise that different centres across Australia and New Zealand have different levels of expertise and experience in certain aspects of management, which can make important contributions to local decision making.

The concept for this document was developed during a meeting of the Australian and New Zealand (ANZ) Fontan Registry Steering Committee in September 2017. This Steering Committee oversees the ANZ Fontan Registry. The registry was created in 2009 and at the latest census date (2017) comprised 1,574 participants [2,3].

A group of clinicians (the Chair and three Co-Chairs) was established, and decisions regarding content and expert contributors were made by discussion. In early 2018, the Cardiac Society of Australia and New Zealand (CSANZ) was notified of the intention to create this document, through the Quality Standards Committee. Expert contributors were approached and asked to work on a specific aspect of the document. Representation was also sought from people with a Fontan circulation and their family members; these representatives reviewed the document as a whole, ensuring a patient- and family-centred approach. The document was additionally reviewed by a non-congenital heart disease (non-CHD) cardiologist.

Conflicts of Interest

All members of the writing group were asked to declare any potential conflict of interest. Conflicts of interest were considered broadly to include any relationship, whether financial or otherwise, between any contributing author and any other entity that either would or might be perceived to have influenced the author's contribution to the content of this document. Declared conflicts of interest are noted at the end of the document.

Rationale for a Position Statement

As survival of people with a Fontan circulation increases, so too does recognition of the potential challenges in managing their health [3,4]. Clinicians are often faced with meeting the needs of this population while not yet being able to appreciate a ''whole-of-life'' health trajectory. People with a Fontan circulation and their families expect and need education about their condition, assistance with self-management, professional care, and assessment of their capacity to interact with life in all its joys and challenges. People with a Fontan circulation, their families, and clinicians need to balance optimism with appropriate and timely care, aiming to allow these individuals to live life fully while incorporating the reality that aspects of their future wellbeing remain unknown.

This document aims to allow clinicians, people with a Fontan circulation, and their families to benefit from

consensus agreement about management of the person with a Fontan circulation. Congenital cardiology lacks the large evidence base that is available to many other cardiology subspecialties. Consequently, in producing this document, the input of local experts has been sought, in partnership with patient representatives, to create a consensus care statement that draws together evidence, where available, with experience and wisdom. To date, only a single guideline dedicated to the management of people with a Fontan circulation has been published [5], which is now more than 20 years old. In reviewing the literature, contributors were asked to concentrate on more recent publications, where available. This document aims to be both comprehensive and accessible but also realistic about care within the Australian and New Zealand health care environment.

As this document only considers the care of people with a Fontan circulation, the first part of an individual's and his or her family's journey—the pre-Fontan phase—has not been included. However, the authors recognise that the pre-Fontan period also has significant challenges, that people in this phase will benefit from expert multidisciplinary care, and that it likely creates the foundations for many of the subsequent challenges described herein.

1 Introduction

The Fontan circulation is a broad term for the circulatory state that results after one of several operations where systemic venous return is directed to the lungs without an intervening active pumping chamber. Named after Dr Francis Fontan [6], this type of surgery was first undertaken in New Zealand in 1975 and in Australia in 1980.

1.1 Challenges of Having a Chronic Health Condition

There is a significant body of work on chronic disease, but less attention has been paid to the multidimensional ''whole-of-life'' experience for individuals born with a critical illness, who have never been completely healthy. People with a Fontan circulation or other forms of congenital heart disease (CHD) tend to see themselves as more well and less limited than objective evidence would suggest [7,8]. This is important because subjective perceptions are central to quality of life [9–11]. A meta-analysis exploring chronic childhood diseases and emotional outcomes showed a small increased risk of emotional difficulties that persisted into early adulthood [12]. The broader population of adults with CHD also appears to have an increased risk of anxiety and mood disorders [13]. Although this document focusses largely on the physical disease and its treatment, this should not detract from an understanding that it may be more beneficial to speak with people with a Fontan circulation and their families in terms of achieving and maintaining wellbeing. Additionally, this document assumes that established health maintenance advice for the general population will occur alongside disease-specific treatment.

1.2 The Challenge of Maximising Opportunities While Faced With an Uncertain Future

For health care providers, the challenge is to maintain optimism [14,15] and hope for the future, by encouraging self-determination and planning, alongside a realistic dialogue, while aiming for improved health outcomes [16]. Ideally, this necessitates a close therapeutic relationship that involves non-paternalistic and respectful information exchange, including, at times, respect for the individual's wish to not know more detailed information. Honesty is required about what is unknown, with acknowledgement that uncertainty in illness may itself be a significant source of distress for people with a Fontan circulation and their carers [17]. One's capacity to deal with chronic illness may, at least in part, mirror his or her capacity to interact with life and its challenges [18]. Although perhaps self-evident, recognition of this should underpin heath care providers' interactions with patients and their encouragement of patients' active involvement and participation in life and medical decision making [19,20].

1.3 The Fontan Circulation and a Whole-of-Life Trajectory Overview

One of the greatest impacts for a child with a Fontan circulation is the potential for adverse interaction between medical events and participation in education. Physical limitations may prevent or reduce the child's capacity to interact with peers through play and sporting activities. There are also impacts for parents and siblings, particularly in terms of parental stress and changes in family functioning. The effects of cardiopulmonary bypass and neonatal ill health on neurodevelopment remain active areas of research, and sequelae of this may further complicate school transition and participation.

Adolescence is a challenging life milestone for many people, regardless of their health status [21]. Looking after adolescents requires being comfortable with listening to and encouraging open conversations about sexual maturity and activity, contraception, and the use of alcohol, cigarettes, and illicit drugs. Adolescents with health problems may also seek participation in treatment decision making, which may challenge their parents or carers [22]. It is important to encourage this move to autonomy and independence, recognising this transition as a milestone in personal development, while maintaining a safety net of availability, information, and support [22].

Late adolescence and early adulthood often bring the challenge of transitioning to a new adult health care service [23]. This often occurs when commencing higher education or employment and while navigating the creation of significant personal relationships, parenthood, and other roles and responsibilities [24]. For adults with a Fontan circulation, employment opportunities may be affected by the need for medical appointments and interventions and, for some, will be limited by physical ability. These limitations may also

affect participation in sport and leisure activities and contribute to personal concerns about future parenthood.

Life expectancy is likely to gain increasing focus, particularly for individuals who experience significant complications or deterioration, with recent research highlighting this as a primary concern for people with a Fontan circulation [25]. It is important to recognise that, although we do not know how long people with a Fontan circulation will live, the expectation is that their life expectancy will be lower than for an age- and sex-matched healthy comparison group. As such, access to specialised psychological and palliative care support services should be available, as the need arises.

2 A Consumer Perspective: Comments From People With a Fontan Circulation and Their Parents

For people with a Fontan circulation and their families, access to lifelong quality medical and mental health care is of prime importance. Quality care is recognised as being provided by trained specialists through central and regional services [26].

Quality care is based on a dynamic partnership between the person with a Fontan circulation and his or her family and caregivers. It is a partnership that values the individual by providing clear communication, patience in educating and explaining medical terminology frequently (potentially at every appointment), and active engagement with the patient and his or her family in decision making across the care trajectory. An actively engaged patient and family can better advocate for their needs and wishes and are more likely to remain engaged as the transition to independent adult care occurs [26]. As active agents in their care, people with a Fontan circulation and their families also value their right to participate in and contribute to research opportunities, should they arise, in consultation with their care team.

People with a Fontan circulation aim to live full and active lives outside their clinical appointments, and consideration of their wellbeing, mental health, and broader social and cultural context is important. The greatest concerns focus on uncertainty about life expectancy [25,27] and exposure to hardship and suffering. Referral to appropriate services and linkage with community-based supports are of benefit to patients and families. The value of the ''lived experience'' should be recognised, and mechanisms such as actively seeking the input of representatives within the ANZ Fontan Registry has been found to support optimal health care, research, and development that incorporates perspectives from both people with a Fontan circulation and their families [28].

Care of people with a Fontan circulation is recognised to be complex and best supported by access to multidisciplinary specialists, as required. This may include referral to other medical specialties (e.g. haematology, gastroenterology, neurology, and endocrinology), as well as mental health and allied health services. People born with functionally single ventricles should also receive repeated assessment for neurodevelopmental impairment, with referral to early intervention services that support optimal long-term outcomes [29]. Fractured service provision can be frustrating from a patient's perspective, and communication between the multiple care providers is essential. For logistical and quality care reasons, the preference is typically for a centralised integrated care model, with specialist clinics incorporating the multidisciplinary team (i.e. the ''one-stop shop'' approach).

3 Medical Review

3.1 Overview

Everyone with a Fontan circulation requires lifelong regular medical surveillance and care, which is provided by a paediatric cardiologist in childhood and transitions to an adult CHD cardiologist in the teenage years. American and European guidelines for adult CHD recommend annual medical review, unless more frequent assessment is clinically indicated [30,31]. Although location of medical review is not stipulated, the importance of adult CHD imaging occurring at a service with CHD expertise is recognised [32]. This recommendation therefore often determines the location of care provision, especially for major patient care decision making. Importantly, non-cardiac surgery should ideally be performed in the patient's CHD service hospital, with a cardiac anaesthetist; or, at a minimum, after consultation with the patient's usual CHD cardiologist [30].

The elevated systemic venous pressure and restricted cardiac output that physiologically characterise the Fontan circulation are increasingly recognised as affecting other organ systems, most notably the liver and kidneys [33–37]. Screening for end-organ dysfunction is recommended, but there is no clearly defined age at which to start screening, nor is there sufficient information to define an optimum frequency of testing [31,38]. This relates, at least in part, to a lack of evidence for the sensitivity and specificity of these screening tools in the Fontan population [35,36,39–41]. Emerging biomarkers may be useful, but their predictive value and subsequent application in clinical management have yet to be proven [37,40] (see section 9.3.2).

Clinical practice statements for people with a Fontan circulation are in their infancy and will evolve as population-based research becomes available. Having a benchmark for standards of care is an important starting point. Surveillance suggestions based on an Australasian clinician survey and literature review [42], along with the latest American guidelines for standard of medical care and investigations for ''well'' Fontan patients [30], are shown in Table 1. A timeline to help guide proactive commencement of counselling on different life care aspects for people with a Fontan circulation is presented in Figure 1.

3.2 Electrocardiography

An electrocardiogram (ECG) is a simple clinical surveillance tool for sinus node dysfunction, heart block, and other arrhythmias at follow-up visits. This is particularly relevant for those with

Table 1 Consensus Suggestions for Surveillance of "Well" Patients With a Fontan Circulation*.

Surveillance	Starting Age	Frequency
Clinical review	From Fontan surgery	Paediatric: suggested every 1-2 years [42] Adult: recommended at least yearly [30,42]
Pulse oximetry monitoring	From Fontan surgery	Suggested at the time of clinical review (every 1-2 years) [30,42]
ECG	From Fontan surgery	Suggested at the time of clinical review (every 1-2 years) [30,42]
Transthoracic echocardiogram	From Fontan surgery	Suggested at the time of clinical review (every 1-2 years)
Liver function tests, renal function tests and full blood count	Suggested at 5 and no later than 10 years after Fontan surgery	Suggested every year [30] unless clinically indicated
Cardiac MR	Unless early concerns, suggested around transition (12-16 years of age)	Up to individual clinician decision [30,42] Suggested every 2-3 years [30]
Cardiopulmonary exercise test	Unless early concerns, suggested around transition (12-16 years of age)	Up to individual clinician decision [30,42] Some form of exercise test suggested every 3 years [30]
Holter monitoring	Consider 5 years after Fontan surgery	If a specific arrhythmia concern, American guidelines suggest yearly [30]
Event monitor/ implantable loop recorder	No specific age	If a specific arrhythmia concern [42]
Transoesophageal echocardiogram	No specific age	Specific concerns not answered by other imaging [42]
Cardiac CT/cardiac catheterisation	No specific age	Specific concerns not answered by other imaging [42], including a change from "well" Fontan status necessitating extensive assessment
General advice	Same age as general population	Vaccination Cardiovascular risk factors (primary prevention) Early referral for any other health care concerns (e.g. anxiety and depression)

Abbreviations: CT, computed tomography; ECG, electrocardiogram; MR, magnetic resonance imaging.

*These suggestions are based on two sources: a survey of paediatric and adult congenital heart disease clinicians on care of patients with a Fontan circulation, conducted through the Australian and New Zealand Fontan Registry [42]; and the 2018 American Heart Association guidelines for the management of adults with congenital heart disease [30].

atriopulmonary Fontan connections [43,44] or those in whom the original anatomy suggests an increased risk of development of sinus node or conduction abnormalities. Holter monitoring is useful when clinically indicated in the assessment of chronotropic competency. Its use in regular surveillance has been recommended in the latest American guidelines, but without clear evidence to support routine use [30]. Along with event and implantable loop recorders, the Holter monitor provides an additional option when arrhythmia is suspected.

3.3 Exercise Testing

The impact of lifelong adjustment to a different functional normality may manifest in various ways in people with a Fontan circulation. Under-reporting of symptoms and a discrepancy between subjective and quantitative assessment of functional status are common [45]. Repeated cardiopulmonary exercise testing is therefore a useful tool for regular surveillance. Exercise capacity in people with a Fontan circulation declines over time, and the rate of decline may be a better predictor of future adverse events than exercise performance at any one point in time [46–50]. There is no clear evidence on when to start exercise testing, or its optimal frequency, for the asymptomatic or minimally symptomatic patient.

3.4 Echocardiography

Transthoracic echocardiography is the fundamental imaging tool used in people with a Fontan circulation, given its widespread availability and low invasiveness [32]. Nevertheless, there are significant limitations to its use in this population that arise from poor image quality, especially in older patients, and reliance on geometric indices of ventricular size and function, which are not designed for heterogeneous ventricular morphologies [32]. Newer measures of diastolic and systolic performance may be helpful in people with a Fontan circulation [51–58]. Deformation assessment is the most promising, but small studies to date have not shown consistent results or prognostic correlation [52,56,59–61]. Transoesophageal echocardiography requires a general anaesthetic in young patients

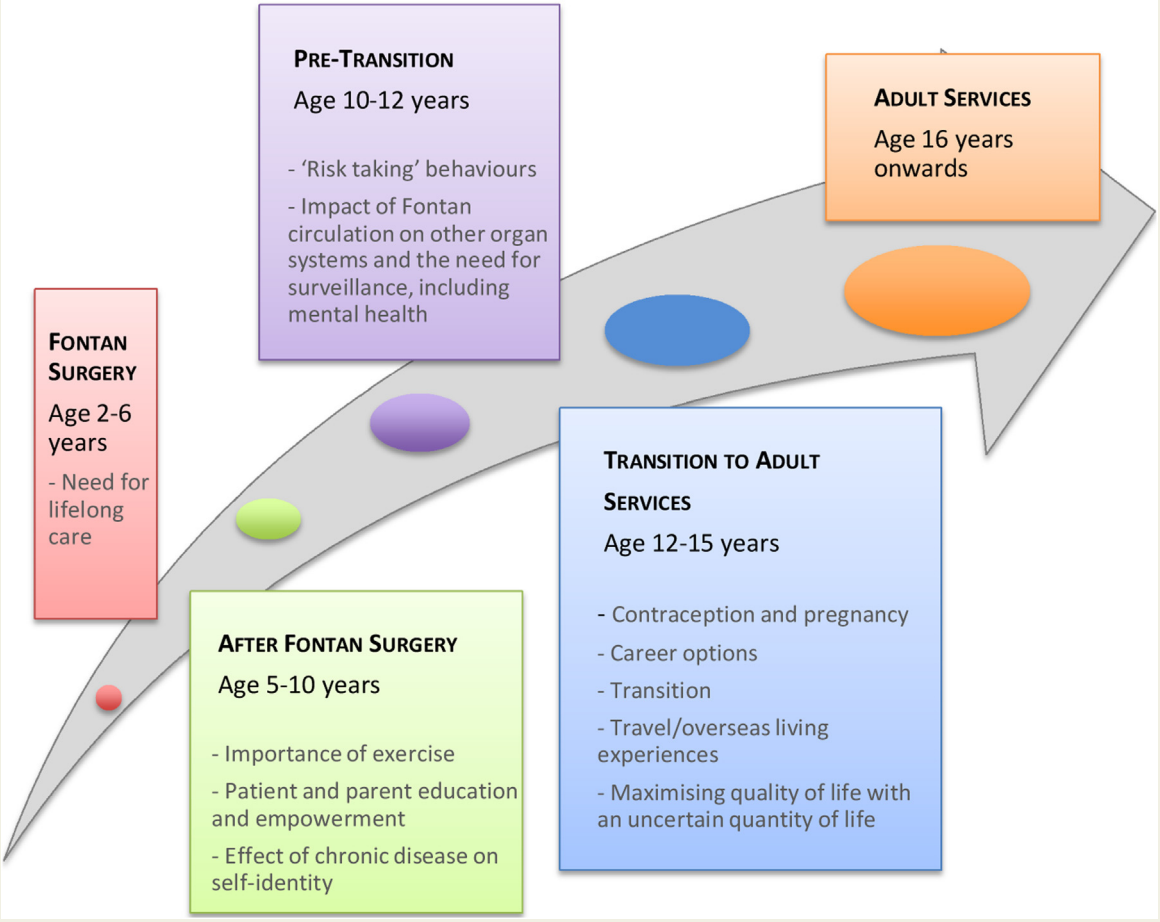

Figure 1 Suggested Commencement Timeline for Counselling Discussions with Patients With a Fontan Circulation. This figure is intended as a general guide to age ranges at which to commence counselling discussions about different aspects of care for the patient with a Fontan circulation. Counselling is recognised to be an ongoing process and needs to be individualised to each situation. It is anticipated that potential issues identified may extend throughout the entire life experience, and the age grouping only identifies the age at which these issues should usually start to be addressed.

or conscious sedation in adults, both with associated risks. Its use should be reserved for situations where it will assist surgical planning, as an imaging adjunct in catheter intervention, or to rule out a thrombus in the heart before electrical cardioversion or after an embolic event [32].

3.5 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) has advantages over echocardiography in assessment of ventricular size and function, particularly for systemic right ventricles, and in its ability to review Fontan flow dynamics. Guidelines had previously left its use in surveillance to individual assessment [31], but there is increasing support for its inclusion, especially for adult patients with a Fontan circulation [30,38,52,62–64]. Use in paediatric settings is limited by the usual requirement for a general anaesthetic until patients reach 10 to 12 years of age, although faster imaging sequences are increasingly allowing younger children to be assessed. The development of both exercise CMR assessment [65–67] and CMR-compatible pacemakers may increase its utility.

3.6 Cardiac Computed Tomography and Cardiac Catheterisation

As cardiac computed tomography (CT) and cardiac catheterisation involve radiation exposure, this needs to be considered, noting prior (and likely future) radiation exposure. CT can provide functional analysis but does not provide comprehensive information on flow haemodynamics [32]. These procedures therefore do not form part of regular surveillance but are useful adjuncts where echocardiography or CMR either cannot provide the information required or are contraindicated (see section 11).

3.7 Antibiotic Prophylaxis

Recommendations for antibiotic prophylaxis are the same as those for the general CHD patient population. Thus, antibiotic prophylaxis is recommended for patients with a history of infective endocarditis; for those with a prosthetic valve (regardless of mode of implant and valve type); for a 6-month period after surgery with prosthetic

material; for patients with residual intracardiac shunts at the site of, or adjacent to, previous repair with prosthetic material or a device; and for those with uncorrected cyanotic heart disease [30].

4 Exercise and Leisure

4.1 Overview

Children and adults with a Fontan circulation often have reduced peak exercise capacity—on average, 60–65% of predicted values [68,69]—and the degree of limitation is associated with the risk of death and need for transplantation [68]. Whether interventions that increase exercise capacity reduce morbidity and mortality is unproven, but current evidence, albeit in small numbers of patients, suggests exercise training may improve exercise capacity and cardiovascular function.

4.2 Fontan Physiology, the Peripheral Muscle Pump and Exercise Limitations

In the absence of a subpulmonary ventricle, systemic venous blood flow to the pulmonary arteries is dependent on gravitational forces, respiration, and the peripheral muscle pump, in addition to cardiac function [66,70,71]. The absence of a subpulmonary pump also restricts preload and reduces exercise-related stroke volume increase—the major factor contributing to exercise limitation [72]. Cardiac filling is further compromised by abnormal pulmonary vascular development and dysfunction, secondary to non-pulsatile pulmonary blood flow [73–76]. Other contributors to exercise impairment are chronotropic incompetence, reduced oxygen saturations, systemic endothelial dysfunction, restrictive lung function, and respiratory muscle dysfunction [75,77–81].

The peripheral muscle pump is of particular importance for venous return in the Fontan circulation [66,70,82], and leg lean mass closely correlates with blood flow increase during exercise [83]. Skeletal muscle contractions may even generate pulsatile pulmonary blood flow in some patients with a Fontan circulation [84].

Concerningly, people with a Fontan circulation often have reduced skeletal muscle mass [82,85], with dysfunctional skeletal muscle aerobic metabolism [82,86] and sympathetic reflex responses [87]. Although it is becoming clear that the pathophysiology of exercise limitation is multifactorial, the relative contribution of each component is not well understood.

4.3 Benefits of Regular Moderate to Vigorous Exercise

About 10% of adults with a Fontan circulation are ''super-Fontan'' individuals, with normal or supranormal exercise capacity. Regular participation (at least three times a week) in moderate to vigorous sporting activities is characteristic of this group [88]. The benefits of moderate to vigorous intensity exercise training in people with CHD have been investigated in multiple studies [80,87,89–106], with most documenting increased exercise capacity and/or physical activity. Of the studies focussed solely on people with a Fontan circulation [87,96,97,101,105,106], two included a Fontan control group and all but one involved aerobic-based interventions with or without a light resistance component. A 20-week high intensity whole-body resistance training program in a group of 11 adults with a Fontan circulation increased skeletal muscle mass by 2 kg and peak exercise capacity by 10%. Stroke volume increased at rest and during exercise in the trained state, likely due to improved venous return [101]. Combined aerobic and light resistance exercise has also been shown to enhance function of skeletal muscle afferent nerves that control blood flow and autonomic responses [87].

Exercise training is associated with superior inspiratory muscle performance in the setting of heart failure (HF) and respiratory disease [107,108], and this may be another benefit of particular relevance to those with Fontan physiology. For children with a Fontan circulation, exercise training may improve ventilatory efficiency [106], in keeping with improvements seen in children after an isolated 6-week inspiratory muscle training program [109]. Additional potential benefits of exercise, such as improvements in

Table 2 Training Intensity Based on Cardiac Abnormalities to Guide Exercise Prescription*.

Ventricular function	Aorta	Outflow tract obstruction	Valvular function	Arrhythmias	Recommended exercise intensity
Normal or only mild dysfunction	No coarctation or dilation	Minimal or none	No or mild regurgitation or stenosis	No history of arrhythmias	Moderate to vigorous intensity AT and RT
Moderate dysfunction	Mild coarctation or dilation	Mild	Moderate stenosis or regurgitation	History of mild arrhythmias	Low to moderate intensity AT and RT
Severe dysfunction	Moderate-severe coarctation or dilation	Moderate-severe	Severe stenosis or regurgitation	History of malignant or significant arrhythmias	Low intensity AT and RT

Abbreviations: AT, aerobic training; RT, resistance training.

*If patients have factors in more than one classification, the higher risk stratification is applied. Modified from Budts et al. [118].

quality of life, body image, mental health, weight, cardiac function, and endothelial function, have been shown in patients with other conditions [110–113]. Maintaining a healthy weight is especially important for those with a Fontan circulation because of the profound respiratory dependence of the circulation.

4.4 Safety

In the past, people with complex CHD were often advised against vigorous exercise because of unproven safety concerns. Experience with maximal exercise testing and exercise training has shown that acute arrhythmic events are rare and, when they do occur, are usually not associated with exertion [114]. No training-related adverse events have been reported in more than 200 patients with a Fontan circulation [89]. In general, screening before an exercise program is recommended, with clinical assessment and exercise testing with oximetry to characterise peak exercise capacity, heart rate response, degree of desaturation, and any arrhythmia. Unless reversible by appropriate intervention, patients with frequent arrhythmias, a right ventricular-dependent coronary circulation, unstable HF, severe aortic dilatation, moderate to severe valve regurgitation or stenosis, outflow obstruction, or ventricular impairment are probably not suitable for moderate to vigorous levels of physical activity and may need close supervision in a hospital setting, even with lighter exercise prescription.

For patients with (non-CHD) biventricular HF, exercise prescription is incorporated into clinical care guidelines [113,115]. In the ANZ Fontan Registry's Super-Fontan study [88], no adverse clinical events were recorded in 4 years of follow-up. This is particularly significant because systemic venous pressure may rise considerably during periods of vigorous activity, in contrast to the normal circulation [116]. It is unclear whether transient increases in venous pressure for short periods predispose to end-organ damage or if exercise-induced flow improves pulmonary vascular physiology and overall reduces resting venous pressure, as suggested by recent data [117].

Choice of sporting activity may need to include consideration of an associated increased risk of bleeding, which will affect people receiving anticoagulation therapy.

4.5 Exercise Prescription

Exercise programs should include both aerobic and resistance exercises (Table 2) and aim for at least 30 minutes a day on most days of the week. For children, exercise through game-based activities should be promoted. At all ages, adherence is improved by enjoyment of the exercise program.

5 Multidisciplinary Transition

5.1 Overview

Evidence shows that between 21% and 76% of patients experience a lapse in regular follow-up cardiology care after transfer from paediatric to adult care [119–125]. The transition of patients with a Fontan circulation from paediatric to adult cardiology care requires a multidisciplinary, holistic, individualised, flexible, and carefully planned approach, with equal emphasis on patients and their parents and carers [126–129].

5.2 Essentials of Transition

Transition should commence during early adolescence and continue into adulthood, until the patient is successfully engaged with adult congenital cardiology care [127,130]. This process should be facilitated by paediatric and adult cardiology teams, including a dedicated transition lead (or leads), who will ideally be a congenital cardiology nurse [26,121,131].

Transition should encompass multiple developmentally appropriate educational, vocational, and psychosocial care sessions, with a focus on self-management, as appropriate, and documented transition plans [120,121,132–134]. Discussions about contraception and pregnancy [131] and other adolescent and young adult concerns are essential [135]. This process requires a strong collaboration between paediatric and adult cardiology services [126,128,136], including a joint transfer process, where feasible, and individualised patient follow-up to ensure a successful transfer.

The patient, his or her parent or carer and the receiving adult congenital cardiology team should each receive a copy of the final diagnostic test results, clinical summaries, operation reports, information relevant to other care needs, and contact details. This referral pack should also include details of the patient's recommended first appointment in adult cardiology care [26,131].

There should be clarity on how and when the transfer to adult cardiology care is completed, including where to seek emergency assistance if needed between the last scheduled paediatric appointment and the first adult appointment. The transition process must also ensure provision of appropriate community supports; for example, from a general practitioner.

Success is most often encountered when this process is supported by an institution-wide policy on transition that is integrated into the cardiology care framework at all sites [130,131,137].

6 Mental Health and Neurodevelopmental Care

6.1 Overview

Children with a Fontan circulation may experience profound emotional, behavioural, neurodevelopmental, and social challenges in the early years of life. This can have lifelong consequences for them and their families, affecting their future health, wellbeing, and quality of life. Recognition and early intervention and support may prevent or minimise these effects [138].

6.2 Neurodevelopment and Neurocognitive Outcomes

Children with a Fontan circulation are at increased risk of neurodevelopmental impairment [29,139,140]. Although a lower mean intelligence quotient (IQ) compared with that of their healthy peers has been reported [141,142], most

people with a Fontan circulation have intellectual function within the normal range [143]. There is, however, a higher prevalence of impairments in executive functioning, visual construction and perception, fine and gross motor skills, language, attention, and academic performance, compared with population norms [29,144–147]. Risk and severity of neurodevelopmental impairment are associated with both individual factors (e.g. presence of a genetic syndrome, hypoplastic left heart syndrome, structural brain abnormalities) and environmental factors (e.g. prolonged deep hypothermic circulatory arrest, perioperative seizures, greater length of hospitalisation, lower socio-economic status, greater parental psychological stress) [145,147–149]. Difficulties may also first emerge in adolescence or adulthood, with HF, atrial fibrillation, cardiac surgery, and stroke increasing vulnerability to late neurocognitive impairment.

6.3 Mental Health

As a group, people with a Fontan circulation have higher rates of lifetime psychiatric diagnosis (65%) than their healthy peers (22%), particularly for anxiety and behavioural disorders, such as attention deficit hyperactivity disorder [150]. Demographic, perinatal, medical, and psychosocial factors tend to be better predictors than intraoperative factors of mental health outcomes [150–152]. Several mechanisms of, or pathways to, psychological morbidity should be considered [153]. Exposure to early adversity and physiological risk [154], perioperative haemodynamic alterations, and systemic inflammation [155] may adversely affect neurobiological development and consequently alter long-term responses to stress, increasing psychological morbidity risk. Parents [151,156] and siblings [157] of people with a Fontan circulation also experience higher levels of psychological distress compared with population norms.

6.4 Clinical Practice Recommendations

Integrated, specialised neurodevelopmental and mental health care should be considered ''core business'' in paediatric and adult CHD services. Regular, long-term screening and assessment for psychological morbidity in people of all ages with a Fontan circulation, and their families, are indicated [150,151]. Neurodevelopmental screening and assessment throughout childhood and adolescence are strongly recommended to facilitate early detection of neurodevelopmental delays and to assist children in accessing appropriate supports and reaching their full potential [29,158,159]. Specialised support of the developing child–parent bond is also strongly recommended to nurture healthy emotional and relational development [160,161]. Involvement of mental health and allied health professionals optimises coordination of transdisciplinary, trauma-informed, patient- and family-centred health care.

At the time of writing, there were no published data on the efficacy of psychological or neurodevelopmental interventions developed specifically for people with a Fontan circulation [162,163]. However, recommendations can be drawn from evidence accumulated for the broader population with CHD [138,163], as well as those with other childhood critical and chronic illnesses, and illness more broadly. Recognition of, and early intervention for, psychological and neurocognitive effects are vital to ensuring the best possible quality of life for people with a Fontan circulation and their families [164,165]. Structured, individualised transition from paediatric to adult health services is also essential (see section 5) and should include medical and psycho-education, as well as information and support regarding mental health and well-being, sexual identity, alcohol and drug use, educational attainment, and vocational pathways [166].

7 Contraception and Pregnancy

7.1 Overview

Although women with a Fontan circulation may safely and successfully carry a pregnancy, the modified World Health Organization pregnancy risk classification describes pregnancy in a woman with a Fontan circulation as class III–IV: significant risk of maternal mortality or severe morbidity and, in some, contraindicated [167,168]. Publications consistently report increased maternal cardiovascular and obstetric morbidity in this population; predominantly atrial arrhythmias (8.4%) and HF (3.9%) [169] and both antepartum (11%) [169] and postpartum bleeding (14%) [169,170]. There are no published reports of maternal deaths during pregnancy, although this may represent both careful patient counselling before conception and publication bias. Fetal risks include high rates of early miscarriage (45%) [169], increased rates of premature rupture of membranes (6.2%) [169,171] and preterm delivery (59%) [169], increased risk of small-for-age babies (20%) [167,172] and neonatal death (5%) [169], and higher rates of medically driven induction or caesarean delivery.

Few data exist on pre-pregnancy risk stratification in women with a Fontan circulation, but general principles are well described in the recent American guidelines on pregnancy in women with complex CHD [168]. Of particular relevance is assessment of exercise capacity. Cyanosis significantly reduces the likelihood of a live birth; oxygen saturation $<85\%$ is associated with a less than 12% likelihood of a live birth [167], and the live birth rate may be even lower with cyanosis of this degree in women with a Fontan circulation [173]. Significant right-to-left shunts may be occluded before conception to reduce cyanosis.

7.2 Contraindications and High-Risk Features

Pregnancy is contraindicated in women with uncontrolled arrhythmia, moderately to severely impaired ventricular function, severe atrioventricular (AV) valve regurgitation, HF, or protein-losing enteropathy (PLE) [167]. Due to the haemodynamic burden and hormonal milieu of pregnancy, atrial arrhythmias are more likely to occur. Previous thromboembolic events likely also increase maternal and fetal risk. Occasionally, pre-conception cardiac catheterisation may be

considered to formally assess significant shunts and haemodynamics.

7.3 Contraception and Fertility

Published data report reduced fertility in women with a Fontan circulation [174,175]. This is presumed to be multifactorial, with contributions from chronic disease, clotting abnormalities, and hypoxia.

Women who are not receiving anticoagulation therapy, or in whom a right-to-left shunt exists, should avoid using the combined oral contraceptive pill (COCP, commonly known as ''the pill'') [176–178] because of its oestrogen-associated thromboembolic risk and the availability of effective alternatives. Progesterone-only formulations are considered safe. Although no adequately powered study has confirmed that concomitant anticoagulation reduces risk, ANZ Fontan Registry patient survey data show significant COCP use in this population (ever used, 49%) [174], with concomitant oral anticoagulation. Post hoc analysis of a non-CHD study (the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism [EINSTEIN DVT and PE] trials) showed no difference in recurrent venous thromboembolism in women receiving anticoagulation therapy, with or without use of hormonal therapy [179]. Concomitant COCP use with anticoagulation would therefore appear a reasonable option, if chosen after discussion with patients that includes consideration of alternative options, risks, and benefits. This is supported by expert opinion in other settings [180]. Of note, compared with the COCP, pregnancy and the postpartum period convey a greater risk of thromboembolism [181].

7.4 Planning and Management of Pregnancy

Education regarding reproduction should commence early, in the teenage years and before transition to adult care. Preconception counselling with multidisciplinary input is a Class 1 recommendation in the recent American Heart Association (AHA) guidelines for adults with CHD [30]. In addition to pre-pregnancy cardiac assessment, specific consideration should be given to medication cessation or substitution [172]. Guidelines support continuation of anticoagulation when there is a pre-pregnancy indication [168], and transition from warfarin to low molecular weight heparin as early as possible after conception, avoiding warfarin at least in the first trimester, given its teratogenic potential. Formal haematological assessment may be warranted in women who are at especially high risk of thromboembolic or bleeding complications.

Management during pregnancy should be overseen by an adult CHD and high-risk obstetric service. Frequent review is required, both for maternal wellbeing and for assessment of fetal growth, including fetal echocardiography at 20 weeks' gestation to assess for CHD [168,172]. Although anticoagulation during pregnancy would logically appear to carry an increased risk of bleeding, the data available to date do not show a clear correlation between anticoagulation and either antepartum or postpartum bleeding [169]. This remains an area of ongoing investigation. For women with a Fontan circulation, cyanosis and increased iron utilisation mean that monitoring of maternal iron status assumes a greater importance than usual in pregnancy [172].

If a pregnancy reaches term, vaginal birth with regional anaesthesia and a reduced or no active second stage of labour may be considered to reduce both haemodynamic stress and the physiological concern that a prolonged Valsalva manoeuvre in a woman with a Fontan circulation will diminish venous return and, consequently, cardiac output. Many women give birth by caesarean section [169] on either cardiac or obstetric grounds. After giving birth, women should be monitored in a high acuity setting, as postpartum fluid shifts may result in HF. Unless already anticoagulated, deep venous thrombosis prophylaxis should be prescribed. No guidance exists on duration of this therapy, but consideration should be given to continuing prophylaxis throughout the puerperium, given that this is generally a high risk time (daily venous thromboembolism risk is increased 15–35 times, with return to non-pregnant levels by the sixth to twelfth week) [182].

8 Genes and Syndromes

8.1 Overview

Under-development of either ventricle is apparent in about 7% of people with CHD diagnosed in childhood, with an incidence of four to eight per 10,000 live births [183].

Most functionally single ventricle hearts are thought to be related to polygenic variation; that is, the cumulative effect of multiple genetic variations, with the additional variable influence of environmental factors, largely involving the intra-uterine environment and placental factors [184]. The developing heart is constantly remodelled by blood flow, which is essential for chamber formation and maturation. Although ''flow'' and its absence in circumstances such as atrioventricular (AV) valve atresia have been seen as central to failure of ventricular development, primary abnormalities of myocyte capability are also recognised [185].

8.2 Gene Defects and Associated Syndromes

There are few single gene defects that are specifically associated with development of a functional single ventricle, although genes associated with hypoplasia of left- or right-sided structures are well known. The most severe phenotypes associated with pathogenic variation in these genes and gene pathways will require a single ventricle surgical repair.

Left-sided abnormalities, including valvular, ventricular chamber and aortic hypoplasia or atresia from the mitral

valve to the descending aorta, are well described and highly heritable. The implicated genes include *NOTCH1*, *NKX2-5*, *MYH6*, *GATA5*, *SMAD6* and *GJA1* [184].

Functionally single ventricles may (though not commonly) be associated with named syndromes. Turner and Kabuki syndromes are associated with left-sided lesions, including hypoplastic left heart syndrome. Down syndrome (trisomy 21) can be present with unbalanced AV septal defects. Functionally single ventricles are often associated with heterotaxy syndromes, where ''sidedness'' is duplicated (left and right atrial isomerism, also associated with positional abnormalities of the heart and apex, as well as intra-abdominal manifestations, including malrotation, polysplenia, and asplenia). Relevant genes in these syndromes include *NKX2-5*, *ZIC3*, *GATA4* and *NODAL* [184].

8.3 When to Perform Genetic Investigations

Thresholds for referral to a clinical genetics service and provision of genetic counselling vary between institutions in Australia and New Zealand. Increasing accessibility of exome and genome sequencing and translational research in the field are influencing the demand for testing, although it remains expensive and the human resources required are scarce.

Most neonates with a functional single ventricle will present sporadically (i.e. with no family history of CHD in first-degree relatives) and will be diagnosed antenatally, as ventricular disproportion is easily recognised. In addition to usual clinical evaluation and establishing a three-generational pedigree, most of these neonates undergo a chromosomal microarray test to detect chromosomal aberrations, such as deletions and duplications.

For a small number of patients with a functional single ventricle, referral to a clinical genetics service is appropriate. This is currently used for families with multiple affected individuals or with extracardiac syndromic manifestations. Sequencing of specific genes or genes relevant to the clinical presentation may be pursued. However, low yield, difficulty in describing the significance of genetic variants identified, and the costs involved all remain a challenge.

8.4 Next Steps in Genetic Testing

In families with multiple affected members and where DNA samples are available from parents and other affected siblings, testing of ''panels'' of relevant cardiac genes, the exome, or even whole genome sequencing may be useful. In some cases, this will provide a specific molecular diagnosis [186,187], which can provide diagnostic certainty and may be of relevance to planning for future offspring and, in adulthood, pre-conception counselling.

Genetic counselling and provision of psychological support within a multidisciplinary clinic are important to help parents and families understand the role of genetic factors and recurrence risks and to assist in managing common parental responses, such as guilt and anxiety relating to siblings and family members [188].

9 Complications

9.1 Arrhythmias

9.1.1 Overview

Most tachyarrhythmias occurring late after Fontan surgical repair are due to intra-atrial re-entry or ''flutter'' mediated by atrial scarring [189]. Focal arrhythmias and classic supraventricular tachycardia, such as AV nodal re-entry or AV re-entry, are far less common. The true incidence of atrial fibrillation is poorly described, as series have often described patients with ''flutter or fibrillation'', and the low amplitude of flutter waves in this population can lead to misdiagnosis of this rhythm as atrial fibrillation.

Atrial arrhythmias often have a long cycle length, potentially facilitating 1:1 conduction, with ventricular response rates over 200 beats/minute. In people with a Fontan circulation, atrial arrhythmias are an important risk factor for sudden death and should not be considered benign [190]. The prevalence of these tachyarrhythmias appears time-dependent and is in excess of 60% for patients with atriopulmonary Fontan circulation at about 20 years after Fontan repair, with one study considering these arrhythmias to be ''inevitable'' [191]. Data are variable as to whether a lateral tunnel repair or extracardiac conduit is associated with a lower risk of late atrial arrhythmias, at least in part due to a shorter duration of follow-up with these more recent surgical innovations [191,192]. Nevertheless, a recent 25-year follow-up of more than 1,000 survivors of Fontan surgical repair showed a significantly lower risk of late atrial arrhythmias in those with either lateral tunnel or extracardiac repairs [3]. Older age at the time of repair has been a consistent predictor of late arrhythmias [191,193].

Direct current cardioversion is a widely used acute management strategy for atrial arrhythmia, but recurrence approaches 50% within 2 years, with the need for repeat cardioversion approaching 80% at 5 years [194].

9.1.2 Medical Therapy

There is a paucity of literature regarding the use of anti-arrhythmic agents in patients who have undergone the Fontan procedure. The available data are difficult to interpret, as studies have grouped patients with different tachycardia mechanisms, including focal atrial arrhythmias, intra-atrial re-entry, orthodromic supraventricular tachycardia utilising an accessory pathway, AV node re-entry, re-entry between twin AV nodes, and atrial fibrillation. Moreover, more than one arrhythmia mechanism may be present, and sinus node dysfunction often coexists with substrates for tachycardia. Ventricular arrhythmias may also be present.

Anti-arrhythmic drugs have been used in patients with a Fontan circulation, with only anecdotal evidence and data from small case series [195], and they are included in guidelines [30,196]. There are limited data to suggest that there is long-term benefit from medical therapy in preventing recurrence of intra-atrial re-entrant tachycardia [196,197].

An important consideration is that some anti-arrhythmic agents, most classically the type IC drugs, may slow atrial

arrhythmia cycle length and potentially allow haemodynamically unstable, life-threatening 1:1 AV conduction [196,197]. Several studies have shown an increased incidence (up to 30%) of amiodarone-induced thyrotoxicosis in adults with CHD, with patients with a Fontan circulation being at highest risk [198,199]. However, other studies have found amiodarone to be safe at lower doses and if patients with low body mass index are excluded [200,201].

Each patient needs to have medical therapy individualised, and careful introduction of anti-arrhythmics, sometimes with inpatient monitoring, along with fastidious monitoring for pro-arrhythmia and side effects, is necessary.

Anticoagulation with warfarin is routine care in patients with atrial arrhythmias [30,196].

9.1.3 Catheter Ablation

For patients with recurrent atrial arrhythmias, catheter ablation or surgical conversion may be considered. A retrospective study suggested that catheter ablation and conversion surgery were approximately equivalent in terms of arrhythmia control [202]. However, conversion surgery carries a perioperative mortality risk of 5–10% [3,203]. Although ''cure'' of arrhythmia is an inappropriate goal, contemporary ablation studies have shown that a high proportion of patients achieve good arrhythmia control, with a low rate of major complications and a very low mortality risk [189,204]. Patients often have more than one arrhythmia circuit, and repeat ablation procedures are frequently necessary [205–208].

It is important to note that the 2016 Pediatric and Congenital Electrophysiology Society and Heart Rhythm Society expert consensus statement on management of arrhythmias in adults with CHD stated that catheter ablation should be performed by ''a cardiac electrophysiologist with the appropriate expertise [in CHD], and in a laboratory with appropriate personnel and equipment'' [197].

Only isolated single reports of catheter ablation of atrial fibrillation in patients with Fontan physiology have been published. These procedures have predominantly targeted the right atrium for triggers and substrate [209,210].

For patients with refractory atrial arrhythmias, AV node ablation via a retrograde approach has been used as bail-out therapy in isolated cases when patients already have a ventricular pacemaker in situ [211].

9.1.4 Pacing

Due to the risk of thrombosis and decreased venous access to the cardiac chambers, pacing after the Fontan operation must be epicardial, requiring thoracic surgery. Postoperative concerns include a known higher failure rate for epicardial leads than endocardial leads, and a lack of CMR conditional systems, which removes an otherwise excellent follow-up modality option from care. Despite these concerns, pacing is required in 25% of patients during long-term follow-up, about half of which is to support the management of atrial tachycardias [212]. Anecdotal evidence exists for the use of transvenous atrial pacing in atriopulmonary Fontan patients with isolated sinus node dysfunction, as an alternative to epicardial lead placement. However, extensive atrial scarring and low voltage amplitude can make it technically challenging to find adequate sensing and thresholds. Similarly, pacing the Fontan ventricle via the coronary sinus tributaries has been reported in single cases and may be an option if coronary sinus access from the systemic venous atrium is available.

Two-thirds of pacing for bradycardia is for sinus node dysfunction [213,214], as junctional rhythm is poorly tolerated and chronotropic incompetence significantly reduces exercise tolerance. The sinus node may have been damaged at the time of the prior superior vena cava–pulmonary artery anastomosis and is more common after the atriopulmonary Fontan procedure [215].

Atrioventricular block is most common with L-transposition of the great arteries, and AV sequential pacing is essential in such cases. Ventricular pacing should be minimised as much as possible because of the risk of causing ventricular dyssynchrony, pacemaker-induced cardiomyopathy, cardiac failure, and AV valve regurgitation. Fontan patients with ventricular pacing have a five-fold risk of transplantation or death compared with matched non-paced controls [216].

The value of cardiac resynchronisation therapy continues to be explored; results are generally disappointing, but recent consensus guidelines suggest it may be useful in some cases [217] (see section 9.3.3).

9.1.5 Ventricular Arrhythmias and Sudden Cardiac Death

The true incidence of ventricular tachycardia (VT) in patients with Fontan surgical repair is unknown, as systematic long-term follow-up data are not available. Symptoms such as palpitations, or even syncope and sudden death, lack specificity in this population. Palpitations are more usually related to atrial tachycardias, and it may be challenging to differentiate between atrial tachycardias with aberrancy and VT on monitoring.

In a cross-sectional multicentre study of more than 500 patients under 18 years of age after a Fontan operation, VT occurred in 3.5% [218]. Older age, syncope, and lower ejection fraction may be risk factors, but this has not been clearly shown. One study found that non-sustained VT was not predictive of sustained ventricular arrhythmias [219].

The relative contributions of VT/ventricular fibrillation, bradyarrhythmias, and rapidly conducted atrial arrhythmias to the risk of sudden death in people with a Fontan circulation remain unknown. Reported predictors of sudden cardiac death in this population have included previous AV valve replacement and post-bypass Fontan pressures >20 mmHg, whereas preservation of sinus rhythm seems to be protective [212].

Sustained VT is a Class Ib indication for an implantable cardioverter defibrillator (ICD) only after haemodynamic and electrophysiological evaluation [196,197]. Catheter ablation or arrhythmia surgery may be considered as an adjunct to ICD therapy, although there is limited experience with either. Beta blockers may have some protective effect against VT (Class IIb recommendation) [196,197].

9.1.6 Defibrillator Implantation

Indications for an ICD in people with a Fontan circulation include cardiac arrest survival and spontaneous sustained VT, after a careful work-up has failed to identify a clearly reversible cause [220]. ICD therapy may be reasonable in adults with a single or systemic right ventricular ejection fraction <35% (Class IIb recommendation), particularly in the presence of risk factors such as complex ventricular arrhythmias, unexplained syncope, New York Heart Association functional Class II or III symptoms, QRS duration ≥140 ms, or severe systemic AV valve regurgitation [196].

However, inappropriate shocks remain a significant problem, with an annual incidence of about 5%, even in more recent studies that have included tailored programming with anti-tachycardia pacing [221]. An ICD may adversely affect the patient's quality of life, with anxiety, depression, and sexual dysfunction having been reported [222].

Individual decision making is crucial in relation to both implant indication and device choice. Classic transvenous implantation is not possible because of the lack of access to the ventricle. In most patients, customised systems consisting of epicardial or subcutaneous coils will be necessary, with both higher implant and late failure risk. Implantation carries significant risks, as it requires a thoracic surgical redo procedure in an often haemodynamically vulnerable patient. The subcutaneous ICD seems an attractive alternative when bradycardia pacing is not necessary [223]. However, the absence of anti-tachycardia pacing, the risk of inappropriate shocks, and the lack of potential to discriminate atrial tachycardia from VT remain significant limitations of this approach [223]. Defibrillation threshold testing is generally avoided, as this process can be lethal in those with severe ventricular failure.

9.2 Thromboembolic Disease

9.2.1 Overview

Thrombosis often presents in people with a Fontan circulation as intracardiac or intravascular thrombosis, ischaemic stroke, or other embolic phenomena [224–230]. Thrombosis forming in the systemic venous system, such as in the Fontan conduit, may cause local obstruction, which can extend or embolise into the pulmonary arteries, potentially leading to Fontan failure [230]. Paradoxical emboli may also occur through fenestrations or right-to-left-shunts. Thrombi occurring on the arterial side may embolise, resulting in tissue infarction or stroke [230].

The Fontan circulation represents an ideal substrate for thrombus formation, with all three factors of Virchow's triad being affected. First, endothelial changes occur, due to the presence of surgically manipulated endothelium or prosthetic material. Second, blood flow is affected, as there is typically low flow due to the absence of a functional subpulmonic ventricle. Third, blood components are affected by intrinsic plasma protein changes, probably related to subtle changes in liver synthetic function and certainly accentuated in patients with PLE.

9.2.2 Incidence and Timing of Thrombosis

Initial cohort studies reported the incidence of venous thrombosis as ranging from 4% to 19% and the incidence of stroke from 3% to 19% in children treated with different thromboprophylaxis regimens [231–238]. In 1,006 survivors of the Fontan operation, the ANZ Fontan Registry reported an overall freedom from thromboembolism of 82% at 25 years after the Fontan procedure (95% CI, 74–87%), with events occurring at a median of 7.6 years. In a subgroup analysis, freedom from thromboembolism in extracardiac Fontan patients was 91% at 12 years. Lateral tunnel Fontan patients had a thromboembolism incidence of 16% [239,240].

The highest risk of thrombosis occurs in the first year after the Fontan operation, with thrombosis risk plateauing at 3.5 years, followed by a second peak more than 10 years after surgery [241–245].

9.2.3 Intracardiac Thrombosis

Intracardiac thrombosis is most often observed in the systemic venous atrium (48%) and pulmonary venous chamber (44%). Numerous studies have shown the superiority of transoesophageal echocardiography over transthoracic echocardiography for detecting intracardiac thrombi in people with a Fontan circulation [246–249]. For example, transoesophageal echocardiography detected intracardiac thrombi in 33% of patients screened, compared with 2% using transthoracic echocardiography [246]. Despite emerging interest in CMR, there are few data on the accuracy of this modality to detect intracardiac thrombi. In people with a two-ventricle circulation, one publication suggests that CMR may be superior to transthoracic echocardiography in patients with a low ejection fraction [250]. Data from patients with a Fontan circulation have shown CMR's capacity to identify intracardiac and branch pulmonary artery thrombi, but these data are largely limited to case reports [251–253]. Equally important is the detection of thrombi in the venous system and distal pulmonary circulation, neither of which is well served by echocardiography.

9.2.4 Randomised Trial Data

The largest randomised controlled trial of anticoagulation in patients after having Fontan surgery reported an overall thrombosis incidence of 22% within the first 2 years. However, the symptomatic thrombosis rate was only 7%, suggesting that silent thrombosis is highly prevalent in this population [224]. Whether silent thrombosis is clinically important is unknown and requires further research. Currently, no evidence links asymptomatic thrombosis with poorer outcomes in people with a Fontan circulation.

9.2.5 Thromboprophylaxis

Given the high risk of thrombosis after the Fontan procedure and the significant morbidity and mortality associated with thromboembolism, the prophylactic use of antithrombotic agents is warranted [254]. A meta-analysis

of trials with an average follow-up of 7.1 years reported that patients without thromboprophylaxis (no aspirin or warfarin) have an incidence of thromboembolism of 18.6%, compared with 8.6% in patients taking aspirin and 9% in patients taking warfarin [255]. Hence, some form of thromboprophylaxis, likely long term, is recommended for all Fontan patients. Antiplatelet and anticoagulant agents are commonly prescribed for thromboprophylaxis in patients with a Fontan circulation; however, there is no consensus on which agent is optimal. Current studies of thrombotic outcomes for people with a Fontan circulation, including consideration of bleeding outcomes, bone density outcomes, and quality of life, may soon enable evidence-based choice between antiplatelet and anticoagulant therapy. Randomised trials of direct oral anticoagulants (DOACs), previously known as novel oral anticoagulants, are underway, and DOAC use should be within the construct of formal trials. Although their use would ideally await evidence, pragmatic clinical care with these agents in adult patients who have been prescribed warfarin, who are non-compliant, or who poorly remain within the therapeutic range, appears reasonable. There are insufficient dosing and safety data for their use in children. Of note, DOACs have failed in trials of artificial valves [256] and circuits [257], so their effectiveness in the setting of graft material (such as that used in extracardiac Fontan surgery) remains to be proven.

9.2.6 Management and Sequelae of Thrombosis

Thrombosis treatment options in patients with a Fontan circulation include embolectomy, thrombolytic treatment, and anticoagulant therapy. The choice of treatment is dependent on the location and size of the thrombi and other underlying potentiating factors.

There are few data pertaining to the management and outcome of thrombosis in the Fontan population. In general, management options include escalation of anticoagulant therapy, either by increasing the target therapeutic range of warfarin or by adding a second agent (e.g. warfarin plus aspirin). Acute therapies, such as thrombectomy or thrombolysis, tend to be used when the Fontan circuit is compromised in terms of reduced cardiac output. However, each patient needs to be treated on individual grounds. Previous reports have ascertained that total resolution of thrombosis occurs in only 48% of patients [258–260]. Moreover, despite treatment, symptomatic thromboembolic events are associated with a mortality rate of 25% in paediatric patients and 38% in adult patients [258–260].

9.3 Heart Failure

9.3.1 Overview

Heart failure is a leading cause of morbidity and mortality in patients after the Fontan operation [260–263]. The incidence of HF increases with age, with up to 40% of adult Fontan patients showing clinical features of HF in one cross-sectional study [264]. Mortality after a diagnosis of Fontan-related HF is high [260] and frequently coincides with worsening arrhythmias and multi-organ dysfunction. Various definitions have been used to identify and classify Fontan-related HF, including Framingham criteria [260], the presence of neurohormonal upregulation and/or reduction in peak oxygen uptake (V_{O_2} peak) on cardiopulmonary exercise testing [265], and ventricular systolic dysfunction. For CHD specialists, the term ''failing Fontan circulation" is preferred because it emphasises the multisystem nature of the disease and the importance of circulatory dysfunction—in particular, chronically elevated systemic venous pressures. Complications of a failing Fontan circulation include recurrent atrial tachyarrhythmia, low cardiac output, clotting abnormalities, venous thrombosis, thromboembolism, liver cirrhosis, hypoalbuminaemia, venous insufficiency, and ascites. Patients with a Fontan circulation may also present with the idiosyncratic complications of PLE and plastic bronchitis [260,266].

9.3.2 Diagnostic Challenges

Diagnosing Fontan-related HF is challenging, particularly in younger patients, who often remain compensated despite significant circulatory impairment. When clinical concern exists, initial assessment should include an ECG, laboratory tests (including a full blood count, electrolyte levels, clotting profile, albumin level, and liver and kidney function tests), a chest x-ray, echocardiography, and cardiac imaging (CMR, computed tomography [CT]), as directed by the history and physical examination.

There is conflicting evidence regarding the prognostic value of cardiopulmonary exercise testing and serum B-type natriuretic peptide (BNP) levels in patients with a Fontan circulation. Among 146 adult Fontan patients (mean age, 21.5 years) in one study, there was a 7.5-fold increase in the hazard ratio for death when V_{O_2} peak fell below 16.6 mL/kg/min [267]. In another study of 321 adult Fontan patients, history of arrhythmia, atriopulmonary Fontan connection, and clinical HF were more predictive of poor survival than V_{O_2} peak, which, when used alone, had no significant prognostic value [268]. Similarly, ventilatory inefficiency during exercise (increased minute ventilation relative to carbon dioxide production [V_E/V_{CO_2}]) is an independent prognostic marker in patients with non-CHD HF and acyanotic CHD, but it is almost universally present in cyanosed patients and lacks prognostic value [269]. Elevated serum BNP level has been associated with late Fontan failure and mortality [270], but no threshold has been defined for accurate diagnosis of HF, and its accuracy for predicting short-term mortality remains untested (see also section 3.1). Despite these uncertainties, cardiopulmonary exercise testing and serum BNP measurement are recommended for objectively tracking each patient's individual trajectory. Significant changes in V_{O_2} peak and serum BNP level that accompany declining functional status indicate progressive failure of the Fontan circulation and should prompt invasive haemodynamic assessment.

In addition to guiding medical therapy (i.e. diuresis, afterload reduction, pulmonary vasodilator therapy), haemodynamic assessment aims to identify residual anatomical or haemodynamic drivers of a failing Fontan circulation. The most common haemodynamic profile is systemic venous hypertension, low cardiac output, and ventricular diastolic dysfunction [271]. However, other cardiac contributors to a failing Fontan circulation, including pulmonary venous obstruction (e.g. secondary to right atrial dilation), ventricular outflow tract obstruction, significant valvular regurgitation, and residual aortic coarctation, should be sought. Volume challenge at catheterisation may be helpful in unmasking diastolic dysfunction [272].

9.3.3 Fontan-Related Heart Failure-Specific Treatments

Treatment of a failing Fontan circulation initially focusses on diuresis to provide symptom relief, to lower filling pressures, and to complement arrhythmia management strategies. Although standard HF treatments, such as angiotensin-converting enzyme (ACE) inhibitors, beta blockers, digoxin, and diuretics, are commonly used in Fontan patients [273], their benefit for patients with a failing Fontan circulation has not been proven. Beta blockers warrant caution in patients with sinus node dysfunction, and ACE inhibitors can cause syncope in the setting of a preload-dependent circulation. Atrial tachyarrhythmias are associated with a substantially higher risk of developing HF [274]. Elevated ventricular filling and systemic venous pressures play a central role, and treatment requires simultaneous correction of volume overload and elimination of arrhythmias to reverse the haemodynamic and clinical manifestations of the failing Fontan circulation.

Less common treatments that are sporadically used to treat a failing Fontan circulation include cardiac resynchronisation therapy, fenestration creation, mechanical circulatory support, and conversion of an atriopulmonary Fontan connection to an extracardiac conduit Fontan in highly selected patients [203,275,276]. Although cardiac resynchronisation therapy has been shown in individual case reports to improve ventricular mechanics, larger series have yielded mixed results [277,278]. Transcatheter fenestration creation has been used in a small number of patients as a bridge to heart transplantation [279], but early spontaneous closure was common, such that the theoretical benefits of shunting to increase ventricular filling and cardiac output did not translate to clinically meaningful improvements in most patients [280]. There are case studies of mechanical circulatory support in adult Fontan patients, but reports of higher mortality in CHD patients with total artificial hearts or biventricular support [281] highlight a pressing need for Fontan-specific mechanical circulatory support options (see section 12).

9.3.4 Timing of Referral for Transplant Assessment

The decision to proceed with listing a patient for heart transplantation is based on an estimated 1-year survival rate of less than 80% [282]. In the absence of clear guidelines, it is reasonable to proceed with transplantation listing for Fontan patients with refractory advanced HF and/or life-threatening arrhythmias in whom there are no further options for transcatheter, electrophysiological, or surgical intervention, if the overall risk of transplantation is deemed acceptable. If alternative surgical interventions are being considered, their likelihood of success must be carefully weighed against their potential to increase the risks associated with subsequent transplantation if they are unsuccessful (e.g. multiple sternotomies, human leukocyte antigen [HLA] sensitisation, and need for postoperative ''rescue'' transplant referral while the patient is in poor clinical condition).

A survival paradox exists among adult patients with CHD who receive heart transplants, in that their high early mortality is balanced by better long-term survival [283]. Compared with adult transplant recipients without CHD, early post-transplantation mortality is highest in the adult Fontan population, with rates of 25–44% [262,284–286]. A lower early mortality rate of about 9% has been reported in children [287,288], indicating significant differences in outcomes for paediatric versus adult Fontan patients undergoing heart transplantation. Regardless of age, early referral is important for patients with a Fontan circulation, due to the complexity of their condition and the longer time they spend on the transplant waiting list [289]. The American Heart Association (AHA) scientific statements on HF and transplantation in patients with CHD provide more detail in this area [290,291].

9.4 Fontan Conversion

9.4.1 Overview

The high rate of complications, most often atrial arrhythmias, that occur after the Fontan operation has been well recognised for many years [43,44,292]. Atrial arrhythmias, due predominantly to macro re-entrant circuits, are understood to result from both postoperative right atrial scarring and progressive right atrial dilatation [293]. In this population, re-entrant atrial tachycardia can be treated with catheter ablation, with moderate success and low risk of complications, but the recurrence rates are significant [189,202,294] (see section 9.1).

9.4.2 Rationale for Conversion Surgery

Conversion of an atriopulmonary Fontan circulation to a lateral tunnel or extracardiac Fontan circulation, initially described by the Chicago group [295,296], has been widely adopted, but selection criteria and optimal timing remain unclear [296,297]. Although some centres may advocate converting all suitable atriopulmonary Fontan patients, the good functional status of a subset of patients and the relatively high surgical mortality (1–2% in some single centre series [296], but over 5% in a large multicentre review [298]) temper this approach. Furthermore, a recent multicentre review reported early mortality, defined as pre-discharge or 30-day mortality, but did not report the subsequent mortality. A report from the ANZ Fontan Registry showed there were as many deaths at a median of 9 months after conversion as there were in hospital [203].

Most groups recommend concomitant conversion surgery in patients requiring cardiac surgery for other indications,

such as valve surgery or relief of outflow tract obstruction. Thresholds for performing conversion surgery for patients with atrial arrhythmias (in the absence of other indications) have varied both internationally and within Australia and New Zealand. Depending on local experience and expertise, individual centres may favour conversion surgery or catheter ablation.

The series from the ANZ Fontan Registry showed that mortality was lower in a centre that pursued a strategy of earlier conversion [203]. This is likely to reflect a combination of risk factors associated with later surgery, including ventricular dysfunction, hepatic complications, less favourable haemodynamics, and longer-term use of drugs such as amiodarone, as well as institutional caseload. It is important to note that the concept of ''earlier'' conversion does not solely refer to patient age or time since Fontan surgery. However, patient age is likely to be a relevant factor, as the average age at conversion in the multicentre review [298] was low (21.6 years; range, 10.2–30.9 years), and will be pertinent to local data, given that the last atriopulmonary Fontan operation in Australia or New Zealand occurred in 1999 [2]. Additionally, it is difficult to establish whether patient selection criteria have been consistent; thus, the possibility exists that the subset of patients undergoing conversion share a favourable risk profile, despite the emergence of atrial arrhythmias.

9.4.3 Assessment, Location of Conversion Surgery, and the Option of Transplantation

Patients being considered for Fontan conversion surgery should have a detailed work-up, including CMR or CT scans, catheter haemodynamics, liver imaging and a hepatologist consultation (with a liver biopsy performed, if indicated), and an electrophysiologist consultation, with or without a diagnostic electrophysiological study. It is likely that the best approach is a multidisciplinary case discussion regarding the options available for an individual patient. There are no randomised controlled trial outcome data on conversion surgery. Local retrospective data do show better outcomes in a centre that performed earlier conversion [203]. That centre reports selection criteria based on patients having an atriopulmonary Fontan connection and recurrent atrial arrhythmias, unless arrhythmias are infrequent (no more than one episode per year) or well controlled with a single anti-arrhythmic agent, other than amiodarone (Tom Gentles, Starship Children's Hospital, Auckland, New Zealand, personal communication, February 2019).

Fontan conversion surgery should be performed in a tertiary CHD centre by an experienced CHD surgeon, with support from experienced adult CHD anaesthesia, cardiology, and intensive care personnel. There are few data to support a minimum number of conversions that need to be performed each year to result in an acceptable mortality profile, but the recent multicentre review found the lowest mortality in the highest volume centre [298].

Assessment may lead to consideration of transplantation rather than Fontan conversion in patients with major complications, including (but not limited to) severe ventricular systolic or diastolic dysfunction, severe AV valve regurgitation, major liver or renal impairment, or PLE (see section 13).

9.4.4 Current Recommendations: Indications and Technique

- All patients with an atriopulmonary Fontan circulation should be closely followed up by an experienced adult CHD cardiologist, to allow timely identification of indications for Fontan conversion.
- Fontan conversion should be considered for all patients with an atriopulmonary Fontan circulation who require cardiac surgery for other indications.
- Fontan conversion or catheter ablation should be considered for patients with an atriopulmonary Fontan circulation and recurrent atrial arrhythmias, unless the arrhythmias are infrequent (no more than one episode per year) or well controlled with a single anti-arrhythmic agent.
- Fontan conversion should be considered for patients with an atriopulmonary Fontan circulation in whom catheter ablation has been unsuccessful.
- Conversion surgery should include a right atrial maze procedure in patients with right atrial macro re-entry circuits only, or a full Cox maze procedure in patients with atrial fibrillation.
- Modification of the right atrial maze procedure to maintain sinus node function and electrical continuity between the sinus node and the AV node should be undertaken whenever possible [299].

9.5 Liver Disease

9.5.1 Overview

People who have undergone a Fontan operation are susceptible to liver disease secondary to several factors, including elevated systemic venous pressure and low cardiac output with tissue hypoxia. The spectrum of liver disease ranges from fibrosis to cirrhosis and hepatocellular carcinoma, although cases of decompensated liver failure are rare. The understanding of time course and risk factors associated with the development of liver disease in this population is limited. For this reason, recommendations for surveillance are based on expert consensus [300]. Additionally, as alcohol is a known liver toxin, it would appear logical to counsel patients against regular or excessive alcohol consumption. Although no specific data exist for this population, the increased risk of liver disease warrants advice to minimise exposure to other causative agents.

9.5.2 Monitoring

Although the literature is limited by short follow-up durations and a preponderance of cross-sectional data, time since Fontan surgery correlates with the presence and eventual progression of liver disease and its complications [301].

It is reasonable to delay the initial hepatology review until 5 years, and no more than 10 years, after the Fontan operation [33,302]. Assessment should include a liver ultrasound, liver

function tests, coagulation tests, platelet count, and measurement of alpha-fetoprotein (AFP) level. A form of non-invasive hepatic fibrosis estimation (FibroScan, acoustic radiation force impulse, magnetic resonance elastography, or shear wave elastography) should be performed [300]. These methods are likely to overestimate fibrosis and cirrhosis in the context of hepatic congestion but may still offer excellent negative predictive value if low readings are achieved.

If cirrhosis is deemed unlikely, a repeat assessment may be undertaken in 5 years, then at 2-yearly intervals, using the same investigations, including non-invasive markers. Biochemistry (liver function testing) is recommended on a yearly basis [30].

9.5.3 Hepatocellular Carcinoma

Although some studies have reported an incidence of hepatocellular carcinoma in people with a Fontan circulation of between 1.5% and 5% [303–305], the follow-up has been limited. Given the progressive nature of liver disease, these rates may be expected to increase as the Fontan population ages. If possible or probable cirrhosis is identified through a combination of imaging, blood tests, and non-invasive methods, routine hepatocellular carcinoma screening should be instituted under the direction of a hepatologist, including 6-monthly liver ultrasound, liver function tests, full blood examination, coagulation studies, and measurement of AFP level. Imaging should be undertaken at a centre with experience with this specific disease entity, given the potentially atypical appearance of the liver in a patient with a Fontan circulation. Hypervascular nodules (focal nodular hyperplasia-like lesions) are common in the livers of people with a Fontan circulation. When small, they should be followed up with ultrasound imaging at frequent intervals. Suspicious nodules—those that are growing or are larger than 1 cm in diameter—should be assessed with quad-phase CT scans or CMR. Routine regular quad-phase CT is not recommended, given the young age of Fontan patients and the potential for significant radiation exposure over an extended period.

9.5.4 Gastroscopy

Episodes of variceal bleeding in people with a Fontan circulation have been rarely reported in the literature [303,306,307] and, on the balance of probabilities, are likely a lower risk consideration. As such, routine gastroscopy is not recommended. However, if patients are identified as having portal hypertension or varices on imaging (e.g. splenomegaly, patent paraumbilical vein, varices), management of varices, including gastroscopy with variceal banding, should be considered. This should be undertaken at a specialist centre with the aid of a cardiac anaesthetist.

9.6 Kidney Dysfunction

9.6.1 Overview

The effects of the Fontan circulation on the renal system remain poorly understood. There is broad consensus that electrolyte, urea, and creatinine levels should be monitored yearly in clinically stable individuals with a Fontan circulation [30]. More frequent monitoring is appropriate for patients with clinical deterioration, intercurrent illness, procedural intervention, or changes to medications (introduction or dose adjustment of medications such as diuretics). Persistent deterioration in renal function or significant decline in estimated glomerular filtration rate (eGFR) may be associated with Fontan failure, and referral to a renal physician should be considered.

9.6.2 Postulated Pathophysiology

There is little evidence to support more intensive screening or monitoring of the renal system in people with a Fontan circulation. However, the process of staged single ventricle palliation imposes multiple renal risks, including congenital, perioperative, and interstage renal insults. After completion of the Fontan operation, elevated venous pressure and low cardiac output may contribute further to chronic renal dysfunction [308]. End-stage Fontan failure is characterised by a cardio–hepato–renal interaction, and it is possible that the contribution of the kidneys to this pathological process has been underestimated [309].

9.6.3 Recent Research and Future Challenges

Due to the unreliability of creatinine-based eGFR measurement, especially in children [310], cystatin C-based eGFR is emerging as a readily available tool that reliably predicts adverse events after completion of Fontan surgery [37]. Routine eGFR is impaired (<90 mL/min/1.73 m^2) in 10% of individuals with a Fontan circulation. In contrast, spot urine testing identifies microalbuminuria in a third of people with a Fontan circulation [35,37,301]. The prognostic utility of spot urine testing, and how this may correlate to future glomerular filtration rate (GFR) deterioration, remains to be confirmed in the Fontan population [37,301]. Emerging urinary biomarkers, such as kidney injury molecule-1 (KIM-1) and N-acetyl-β-D-glucosaminidase (NAG), as well as more cumbersome radionucleotide assays to quantify GFR, are useful research tools, with potential future clinical utility [37,301].

Although the burden of clinical renal disease in this population remains unknown, concerns about a relationship between proteinuria and mortality arise from data in both people with CHD [311] and the wider population [312]. There is currently no proven therapy to treat renal disease in people with a Fontan circulation. Trials of medications shown to be useful in people with diabetic and hypertensive kidney disease are required in people with a Fontan circulation, to prove their efficacy in treating Fontan-related kidney disease.

9.7 Protein-Losing Enteropathy and Plastic Bronchitis

9.7.1 Overview

Protein-losing enteropathy and plastic bronchitis are serious complications of the Fontan circulation that are characterised by the loss of lymphatic fluid through the gastrointestinal tract and lung bronchi, respectively. Their aetiology is not well understood but relates to lymphatic leakage caused by increased lymphatic pressure; there may also be an increase

in lymphatic production and a decrease in reabsorption subsequent to elevated venous pressure [313]. In plastic bronchitis and PLE, there may be an element of inflammation of the bronchus and gastrointestinal tract, respectively [314–316]. Plastic bronchitis typically presents within the first few years after the Fontan procedure, whereas PLE can present later, but usually within the first postoperative decade [317]. Both PLE and plastic bronchitis are forms of Fontan failure, with a 5-year survival rate of 88% reported after the onset of PLE. Mortality is greater in patients with high pressures within the Fontan pathway (mean, >15 mmHg), decreased ventricular function (ejection fraction <55%), and New York Heart Association functional Class III or higher at diagnosis, and those with worse haemodynamics at cardiac catheterisation [266].

9.7.2 Protein-Losing Enteropathy

The onset of PLE is characterised by one or more of diarrhoea, peripheral oedema and ascites, hypoalbuminaemia, immunodeficiency, and growth failure [266,317]. The presentation is often insidious over a period of months.

Screening for PLE in children can be considered, with measurement of serum albumin and protein levels on an annual basis. The presence of an elevated stool alpha-1-antitrypsin level is highly specific for PLE in patients with a Fontan circulation [315,318]. There is no definitive treatment. However, the following management options should be considered.

9.7.2.1 Optimising the Fontan Circulation and Correcting Any Systemic Anomalies, Such as Anaemia. Cardiac catheterisation is indicated to assess central venous pressure, the transpulmonary gradient and ventricular filling pressure, and obstruction to the Fontan circuit. Interventions, including transcatheter angioplasty and coiling aortopulmonary collateral vessels to reduce volume load, should be undertaken if they have the potential to improve these parameters. Creation or enlargement of an atrial level fenestration is often undertaken [266]. Cardiac pacing can be used for treatment of significant bradycardia caused by sinus node dysfunction or conduction system disease.

9.7.2.2 Dietary Manipulation. A high-protein diet may improve nutritional status, depending on the level of protein loss. Substituting long with medium chain fatty acids ensures that a greater proportion of nutrients is directly absorbed into the blood stream, bypassing the lymphatic and thoracic ducts and possibly reducing lymphatic flow and pressure [266].

9.7.2.3 Pharmacological Treatment. Corticosteroid treatment with oral budesonide should be considered [316]. Treatment with a selective pulmonary vasodilator could also be considered, as a reduction in central venous pressure may reduce the lymphatic pressure. Diuretic therapy may relieve symptoms and may also reduce central venous pressure. A positive effect of other agents, including spironolactone [319,320], the somatostatin analogue octreotide [321], and subcutaneous heparin, has been reported in small case series or case reports.

9.7.2.4 Anticoagulation. As protein-losing states increase thromboembolic risk, anticoagulation should be considered.

9.7.2.5 Novel Treatments. Preliminary reports suggest there may be a role for selective embolisation of abnormal gastrointestinal lymphatic vessels [322]. However, this technique remains experimental. Novel surgical techniques, including redirection of the hepatic venous return to the systemic atrium [323], and redirection of the thoracic duct return by implanting the innominate vein to the systemic atrium [324], have also been reported, with promising short-term results.

9.7.3 Plastic Bronchitis

Plastic bronchitis is characterised by the production of thick ''plastic'' casts consisting of inflammatory cells and fibrin. Patients with plastic bronchitis present with breathlessness and coughing fits that, on occasion, produce casts. They may have life-threatening hypoxaemia [314,317]. As with PLE, the initial assessment should include a thorough review, including cardiac catheterisation, to identify factors that might contribute to higher central venous pressure and could be improved with treatment.

Management of plastic bronchitis involves supportive therapy, including provision of oxygen and prompt treatment of associated respiratory infections. Nebulised tissue plasminogen activator reduces symptoms in some patients. An emerging and promising therapy involves assessment with contrast-enhanced magnetic resonance lymphangiography and intranodal lymphangiography, with embolisation of the lymphatic system where lymphatic abnormalities are found [325].

10 Medical Therapy

10.1 Overview

There is limited evidence for the effectiveness of medical therapy for patients with a Fontan circulation. The treatment of reduced ventricular function has largely drawn on data for HF in patients with biventricular circulations. To date, studies of medical therapy in the Fontan population have been small.

10.2 Diuretics and Spironolactone

These drugs are routinely used for management of fluid overload in the acute perioperative setting and in patients with a failing Fontan circulation. There are case reports of the effectiveness of spironolactone in treating patients with PLE (see section 9.7.2).

10.3 Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

These drugs are also routinely used by many clinicians at various stages of management, although positive trial data in this population are lacking. A recent study showed that about a third of patients with a functionally single ventricle circulation was taking an ACE inhibitor [326]. After stage 1

palliation, ACE inhibitors may be useful in balancing relative flow to the lung and systemic circulations. Systemic vasodilatation leads to a relative reduction in pulmonary flow and better systemic perfusion. This effect of increasing relative flow to the systemic circulation is also seen in patients with a bidirectional cavopulmonary connection who are given intravenous enalapril, with no change in cardiac output but a reduction in bidirectional cavopulmonary connection flow and an increase in descending aortic flow observed [327]. A randomised trial found that continued chronic use of enalapril in the first year of life does not affect somatic growth, ventricular function, or HF severity [328]. However, it must be borne in mind that the number of patients with ventricular dysfunction in this study was small.

At subsequent stages of palliation, ACE inhibitors have been used variously for the treatment of ventricular dysfunction or atrioventricular valve regurgitation. In one study, a group of 18 patients with a Fontan circulation, mostly with atriopulmonary connections, were randomly assigned to receive enalapril or placebo in a double-blind fashion. After 10 weeks of therapy, there was no change in cardiac index at rest or exercise duration between the two groups [329]. A small retrospective study of 17 patients undergoing multiple cardiac catheterisations, with ACE inhibitor therapy for an interim period of 9 months (range, 7.3–19.1 months), with or without beta blocker therapy, showed a reduction in ventricular end-diastolic pressure and mean atrial pressure [330].

Results of studies on angiotensin receptor blockers in patients with biventricular hearts with a systemic right ventricle have been negative [331–333].

10.4 Beta Blockers

A large multicentre study of carvedilol in children with cardiomyopathy and CHD did not show any benefit [334]. However, this study had only a small subset of patients with functionally single ventricle circulations. A non-randomised study of carvedilol in patients with functionally single ventricles in Japan showed some potential benefit [335]. In patients aged from 1 month to 35 years and taking carvedilol for a mean of 11 months (range, 1–48 months), there was a reduction in the use of diuretics and a slight but significant decrease in the cardiothoracic ratio on chest x-ray.

10.5 Pulmonary Vasodilators

With the advent of specific oral drugs for the treatment of pulmonary hypertension, there has been excitement about the potential benefit of these compounds for people with a Fontan circulation. The lack of pulsatile flow in the pulmonary vascular bed is thought to lead to changes in endothelial function [73] and the wall structure of these vessels [75,336]. A group at Great Ormond Street Hospital for Children in London showed that patients with a Fontan circulation (median age, 12 years; range, 7–17 years) had elevated pulmonary vascular resistance, which decreased in response to 20 ppm of inhaled nitric oxide [73]. The small studies of response to the new oral therapies have not been conclusive.

10.6 Phosphodiesterase Type 5 Inhibitors

Sildenafil has been the most studied phosphodiesterase type 5 inhibitor in the Fontan population. In a 6-week randomised double-blind placebo-controlled cross-over trial in children and young adults with a Fontan circulation, there was no difference in V_{O_2} max with sildenafil. Acute administration of sildenafil did, however, show some benefit in a study of 10 adult Fontan patients undergoing an exercise test with CMR assessment [337]. In this study, the patients had improved cardiac output at rest and at each stage of graded exercise workload and there was a fall in pulmonary and systemic vascular resistance after sildenafil administration.

10.7 Endothelin Receptor Antagonists

There are varying data regarding the effectiveness of this class of drugs in patients with a Fontan circulation. Two (2) early studies of the use of bosentan showed no difference in exercise capacity with therapy [338,339]. The largest study to date examining the effect of bosentan, in 69 patients (mean $\pm$ SD age, 20 ± 7 years) treated for 14 weeks, showed an improvement in V_{O_2} max, increased exercise endurance, and reduced N-terminal-proBNP levels [340]. In a study of 19 adult patients, eight of whom had reduced systolic function, treated with ambrisentan or placebo for 12 weeks, there was also an improvement in V_{O_2} max with ambrisentan [341]. Another study of children, adolescents, and adults assessed as having elevated pulmonary vascular resistance (>2 WU) and treated with either bosentan or macitentan showed a reduction in pulmonary vascular resistance in 70% of patients [342]. This benefit was seen in all three age groups. A multicentre trial of the effect of macitentan in patients with a Fontan circulation is underway.

11 Catheter-Based Interventions

11.1 Overview

Individuals with a Fontan circulation may require cardiac catheterisation for diagnostic assessment of haemodynamics or to help identify and treat important residua (see section 9.3.2 and Table 1).

The most common catheter-based interventions in people with a Fontan circulation are fenestration closure, pulmonary artery ballooning or stenting, and closure of collaterals (arterial or venous). Less often, arch intervention (ballooning or stenting), fenestration creation, Fontan baffle or conduit stenting, or other more niche interventions are performed. Planning of any interventional strategy should include consultation with the patient's surgeon.

11.2 Common Indications for Catheter Intervention

11.2.1 Fenestration Closure

Indications for fenestration closure are not clearly defined, but it is reasonable to consider this procedure in patients with

significant desaturation either at rest (oxygen saturation below 90%) or with exercise (e.g. oxygen saturation below 85%). Fenestration closure may improve somatic growth and exercise performance in children, although data on the latter are conflicting [343–346]. The available literature suggests that oxygen saturation usually rises to percentages in the mid 90 s with fenestration closure. This is accompanied by an increase in pressure within the Fontan circuit, usually by 1–2 mmHg [347,348].

Before proceeding to fenestration closure, both resting haemodynamics and haemodynamics with test occlusion (in particular, Fontan pressure and mixed venous oxygen saturation as a surrogate for cardiac output) should be assessed to ensure that the increase in Fontan baffle pressures is not more substantial. This is significant because of the potential adverse effects of elevated Fontan venous pressures on hepatic congestion and the contribution of elevated splanchnic pressures to the risk of PLE [347,349]. Closure of a fenestration may also be considered to mitigate the risk of thromboembolic events in particular settings, such as a known procoagulant state, prior transient ischaemic attack or stroke, orthopaedic (including spinal) surgery, or before pregnancy.

11.2.2 Pulmonary Artery and Fontan Baffle or Conduit Ballooning or Stenting

Small gradients within the cavopulmonary circuit circulation are disadvantageous to Fontan haemodynamics, and relief of any anatomical narrowing within the Fontan baffle or branch pulmonary arteries should be achieved wherever possible, particularly in the presence of any demonstrable pressure gradient [350,351]. Few data exist on the long-term outcome of stenting, but overall it appears that the complication rate in experienced centres is low and neointima formation modest [350,352]. A stent that can achieve an appropriate diameter in the target vessel should be chosen, bearing in mind the potential for somatic growth.

11.2.3 Closure of Collateral Vessels

Venovenous collaterals typically form between the systemic veins and pulmonary veins, usually in response to pressure elevation in the Fontan circuit. They manifest as cyanosis/desaturation or a thromboembolism, being a potential conduit for paradoxical emboli. Closure of venovenous collaterals may be effective in initially increasing arterial oxygen levels [353,354], but the benefit is often not sustained. Additionally, there may be long-term harm associated with worsening haemodynamics, as closure may reduce cardiac output through a reduction in ventricular preload. Embolisation of venovenous collaterals was a predictor of increased mortality at 5 years in one study, particularly in the presence of elevated Fontan pressures [355]. In the absence of an alternative explanation for documented thromboembolism or significant cyanosis that limits exertional capacity, venovenous collateral closure may nonetheless be considered, as long as the Fontan circuit pressure is not significantly elevated and the collaterals arise proximal to significant Fontan pathway obstruction that is amenable to intervention. Closure should be avoided if Fontan pressures are >18 mmHg at baseline, if there is an increase in Fontan pressure with test occlusion, or if there is co-existent PLE, hepatic dysfunction, or ascites.

Pulmonary arteriovenous malformations are often seen in the setting of a classic Glenn or heterotaxy syndrome with inferior vena cava interruption. Their formation may relate to absence of ''hepatic factor'' and will manifest in a similar fashion to venovenous collaterals. Device or coil closure is recommended for treating symptomatic cyanosis or documented thromboembolism and is usually effective in increasing oxygen saturations and reducing ventricular preload. However, subsequent interventions (e.g. Fontan revision surgery, hepatic vein inclusion, brachial AV fistula creation, or catheter-based rerouting) should be considered to provide hepatic blood flow to the affected lung. Lobectomy or pneumonectomy may be required.

Accessory sources of pulmonary blood flow, such as aortopulmonary collaterals or ventriculo-pulmonary connections, may provide a volume load to the functionally single ventricle, contribute to power loss in the Fontan circulation (competitive perfusion), or cause haemoptysis. Transcatheter closure is reasonable for large, discrete aortopulmonary collaterals, but there is significant variability in practice and no clear evidence of benefit [356,357].

11.3 Uncommon Indications for Catheter Intervention

In the setting of poor Fontan haemodynamics with elevated filling pressures, Fontan fenestration creation may be considered. Various methods of achieving this have been described, including conduit puncture and balloon dilation (in lateral tunnel Fontan circulations). More recently, techniques have been described for transcatheter creation of a fenestration in patients with extracardiac conduits, by placing a covered stent between the pulmonary artery and the atrium, for example [358–360]. A detailed understanding of the anatomy in this setting is vital, and cross-sectional imaging is useful in planning the best approach.

Aortic arch hypoplasia or stenosis can be seen in patients with functionally single ventricles and may be dealt with in infants or small children by ballooning or at the time of surgical intervention. In follow-up, arch anatomy should be assessed and any residual arch gradient actively sought and considered because of the potential impact on single ventricle function. Depending on the location, it may be possible to treat the area of concern by balloon dilation or stent placement.

Lymphatic interventions are emerging as a potential therapeutic tool for PLE. In a small single-centre review of patients with PLE at the Children's Hospital of Philadelphia, occlusion of abnormal hepatoduodenal lymphatic connections using n-butyl cyanoacrylate glue resulted in a sustained improvement in albumin level in some patients [322].

12 Device Therapy and Support

12.1 Overview

Heart transplantation is not likely to scale to meet the needs of the growing population of people with a Fontan circulation [3], and it might be envisioned that mechanical circulatory support will be necessary, not only for bridging to transplantation but also as destination therapy [361,362]. Implantable cardioverter defibrillator implantation, often used in patients with terminal acquired heart disease, is of limited utility in patients with a Fontan circulation, as fewer than 10% of deaths that occur late after Fontan completion are sudden and potentially related to lethal arrhythmias [212,363] (see section 9.1.6).

Historically, mechanical support of the failing Fontan circulation has been associated with poor survival [364]. However, recent reports suggest that it is necessary to understand the mode of Fontan failure to allow selection of the appropriate mode of support. The precedent for using mechanical support has been largely set in patients with reduced systolic function [365–367]. The challenge is that half of the patients with a Fontan circulation who die or require heart transplantation have normal systolic function [261], and fail with primary or concomitant features of elevated systemic venous pressure, such as prolonged pleural effusion, ascites, liver or renal failure, PLE, or plastic bronchitis.

12.2 Systemic Ventricular Assist Device

Systemic ventricular support (systemic ventricle to aorta) with pulsatile devices in patients with isolated systemic ventricular dysfunction, who survive the initial 2 weeks after insertion, is associated with a 60% to 70% rate of successful bridging to transplantation [368]. These relatively disappointing results likely reflect that this type of support provides no mechanical assistance to the systemic venous return and, consequently, the central venous pressure remains elevated. Based on modelling studies [369] and limited case reports [370], continuous flow devices may be more effective in reducing central venous pressure in Fontan patients and are currently the favoured mode of support of the Fontan circulation.

12.3 Right Ventricular Assist Device

Development of a subpulmonary ventricular assist device, or cavopulmonary assist device, is an attractive concept for supporting a failing Fontan circulation associated with raised central venous pressure, in the absence of systemic ventricular systolic dysfunction. In a single case report, this approach was used to successfully bridge an adult patient to transplantation after 13 months of support [371].

12.4 Biventricular Assist Device or Total Artificial Heart

There are anecdotal reports of biventricular assist device support for the failing Fontan circulation [372], although most are restricted to earlier stages of single ventricle palliation. There have also been reports of total artificial heart use in this setting, but the currently available device is not well suited to smaller patients [373].

12.5 Conclusion

Mechanical circulatory support has a role as a bridge to transplantation in selected patients with systolic dysfunction. This is relevant for patients with a Fontan circulation because they experience long waiting times, as they are frequently sensitised and often require optimal donor organ selection, with a short ischaemic time, given the complexity of the surgery and its impact on the risk of primary graft and end-organ dysfunction after transplantation. The indications and best modalities for temporary support are yet to be determined. However, it is anticipated that further technological refinements and better understanding of candidate selection will result in destination therapy ventricular assist devices finding a place in the management of people with failing Fontan circulations.

13 Transplantation

13.1 Overview

Heart transplantation remains the ultimate therapy for patients with all forms of Fontan circulation failure, including those with systolic dysfunction and those with preserved systolic function and so-called restrictive physiology (plastic bronchitis and PLE). The latter group comprise about half of all patients with Fontan failure. Information relating to transplantation for CHD is derived almost exclusively from registry and single-centre outcome data. No randomised trial or meta-analysis data exist for transplantation in patients with CHD [291].

In several AHA statements dealing with heart transplantation in children and in patients of all ages with CHD, generally accepted (Class I) indications for transplantation include HF with a requirement for ventilatory or circulatory support; and past or present symptoms of HF with severe limitation of exercise and activity, growth failure, untreatable life-threatening arrhythmias, or the presence of reactive pulmonary hypertension [290,374]. Commonly accepted (Class IIa) indications include anatomical and physiological conditions that are considered untreatable and likely to worsen the natural history of treated CHD, such as coronary stenoses, valvular dysfunction, ventricular dysfunction, and pulmonary hypertension [290,374]. A peak maximum V_{O_2} of <50% predicted for age and sex (<15 mL/kg in adults) would be expected in patients with severely reduced exercise capacity who are able to undergo metabolic exercise testing [374].

13.2 Barriers to Transplantation

Compared with patients without CHD, adults with CHD are less likely to receive ICD therapy or a ventricular assist device as a bridge to transplantation, are more likely to be listed as lower urgency status, and are less likely to achieve

transplantation at any given time after listing [289]. They also spend a longer time on the waiting list than patients without CHD [375]. In Australia, transplantation rates for patients with a Fontan circulation are low relative to the numbers who die, and there is considerable regional variability in transplantation rates [288]. Possible explanations include the difficulty in assessing single ventricular function, uncertainty about outcomes of HF therapy, the presence of end-organ dysfunction arising from longstanding venous hypertension, and the risks of transplantation itself [291].

13.3 Challenges in Transplantation for Patients With Congenital Heart Disease

Patients with end-stage CHD have unique pathophysiology and comorbidities that require specialised care from physicians experienced in both CHD and heart transplantation [176,290]. Risk factors for transplantation are common in patients with CHD and include HLA sensitisation (panel-reactive antibodies >10%) from the use of homografts and multiple blood products; elevation of pulmonary vascular resistance (which is difficult to assess in a functionally single ventricle circulation); and prior surgical procedures in those with complex anatomy leading to adhesions, increased bleeding, longer surgical times, and a requirement for additional surgical reconstruction [290,376]. Although the impact of hepatic cirrhosis on post-transplantation outcomes is unclear, the presence and severity of hepatic fibrosis or cirrhosis should be documented, along with hepatic vein wedge pressures and liver synthetic function. Although it is uncommon for any individual risk factor to preclude transplantation, this may be the case with the additive risk of multiple relative contraindications.

Historical registry data indicate that heart transplantation carries a higher risk in patients with a Fontan circulation. One-year (1-year) survival rates are about 75–80% and are somewhat lower than those for patients with other CHDs and significantly lower than those for patients without CHD [377]. Most of the differences in survival are accounted for in the early postoperative period [377]. Specifically, adult patients with CHD have a four-fold increase in early in-hospital mortality [378]. Many single-centre studies report better results, and it is likely that peri-transplantation mortality in adult patients with CHD is falling.

13.4 Perioperative Issues and Post-Transplantation Complications

Poor nutrition and considerable deconditioning are important comorbidities in patients with advanced HF that need to be resolved before transplantation. Significant aortopulmonary collaterals should be identified and embolised. Peripheral cannulation for cardiopulmonary bypass may be required if problems with adhesions are likely. A complete vascular ultrasound should be performed to ascertain patency of femoral and jugular vessels, in particular.

After transplantation, adult patients with CHD require renal replacement therapy and chest re-exploration more often than patients without CHD. Other post-transplantation problems associated with early mortality in CHD patients include primary graft dysfunction, right ventricular failure from an elevated pulmonary vascular resistance, renal and liver dysfunction, and high-output HF from aortopulmonary collateral vessels [379,380]. Appropriate donor selection is important because of the additive effect on post-transplantation mortality of recipient age, donor age, and ischaemic time, particularly for donors aged >19 years [290,381].

Sensitised patients face a higher risk of both cellular and antibody-mediated rejection. Selection of an immune compatible (T and B cell matched) donor may not be possible in those who are most sensitised and who have a higher wait-list mortality. Potential strategies to lower elevated pre-transplantation panel-reactive antibody titres include prior desensitisation and augmented post-transplantation immune suppression, in association with heightened surveillance for all forms of rejection.

13.5 Long-Term Outcomes

Adult patients with CHD who survive the first year after transplantation have long-term outcomes that are generally comparable to those of patients without CHD. If present, PLE and plastic bronchitis usually resolve, although PLE can recur late in the setting of cardiac dysfunction and sepsis. Higher rates of retransplantation and a higher 5-year mortality rate have been documented in adult patients with CHD after transplantation [375,382].

14 End-of-Life Care

14.1 Overview

The World Health Organization defines palliative care as an approach that improves the quality of life of patients and their carers who are facing the problems associated with life-threatening illness, through the prevention and relief of suffering, in physical, psychosocial, and spiritual domains [3,383].

Palliative care services focus on quality of life for those living with chronic illness, as well as provision of best care for those nearing, or at, the end of life [384]. A landmark study published in 2010 found that early involvement with palliative care services not only improved quality-of-life measures and reduced depression and anxiety but also improved survival for patients with incurable lung cancer [385]. These findings have been replicated across North America, Europe, and Australasia in patients with cancer and non-cancer conditions [386–390]. Importantly, no studies have shown harmful outcomes from the involvement of palliative care services in terms of psychosocial, physical, or prognostic outcomes [385–390], despite concerns from clinicians about patients not being ready for palliative care or fearing the loss of hope [391].

People with a Fontan circulation often have an unknown prognosis. Emerging evidence suggests there is some negative life experience and a variable impact on quality of life for those living with a Fontan circulation [392,393], but a positive outlook and focus on remaining healthy are common [392]. Although there is evidence from randomised trials that shows improved

quality of life, less depression, and greater spiritual wellbeing with palliative care for those with advanced non-congenital HF [394], there are few data to directly guide palliative care for those with a Fontan circulation [395]. Although not an ideal predictor of death, a suggested pragmatic approach to involving palliative care is to ask clinicians to reflect on the question, ''Would I be surprised if this patient died in the next 12 months?''. If the answer is ''no'', a referral to palliative care should be considered [396].

14.2 Practical Approach

Any involvement of palliative care services should be adapted to each patient's life stage, development, and needs [395]. Children with terminal illnesses may experience inadequately recognised symptoms, fear, and sadness [395,397]. Parents and siblings of patients can also experience short-term and longer-term effects, including complicated grief and bereavement. Involvement of palliative care services has shown improvements in adjustment, education, and employment outcomes [398]. For adolescents and young adults, the normal transitions in this phase of life add a further dimension to palliative care service provision [399].

Clinicians should also be aware that their own subjective assessment of their patient's quality of life in the setting of CHD may be limited and discordant with the view expressed by the patient [393]. Discussions about advance care plans, and specifically about end-of-life issues, can be beneficial for patients with CHD [400–403], but only a minority report having such discussions and completing advance care plans [400–402]. An overwhelming majority of adults with CHD report that they would prefer to have these discussions with their clinicians [400], even when prognostication is difficult or unclear [404]. It is possible to start these conversations gently by exploring the patient's values, fears, and general life goals before discussing specific interventions.

Recognition of patient needs and demonstration of improved outcomes have led to the pivotal development of position statements that include recommendations that palliative care and discussions about end-of-life issues and advance care planning should be available to everyone with life-limiting conditions, including those with CHD [30,405,406]. The challenge remains to develop integrated models of palliative care and cardiology services, creating an evidence base from which to understand and then seek to meet the specific needs of these patients, to achieve meaningful benefits and outcomes.

15 Concluding Remarks

The past 50 years have been a time of remarkable progress in both survival and wellbeing for those born with a functionally single ventricle. Although much remains unknown, it is clear that engagement with cardiologists and cardiothoracic surgeons with CHD expertise improves survival. Furthermore, a collaborative approach, taken by the person with a Fontan circulation, his or her family, and the health care community, is key to identifying previously unrecognised issues and creating management strategies that aim to maintain wellbeing. The importance of planned transition and the involvement of multidisciplinary allied care support continue to gain traction. It is hoped that the shared common vision of long-term wellbeing will continue to drive improvements in quality of life in this patient population and eventually translate into improved survival.

Conflicts of Interest

Dominica Zentner's institution received funding from Actelion for her role as site principal investigator in the RUBATO trial (Clinical Study Assessing the Efficacy and Safety of Macitentan in Fontan-palliated Subjects). David S Celermajer was a contributing author to the AHA Fontan guidelines and a co-investigator in the RUBATO trial, sponsored by Actelion. Yves d'Udekem has received payment as a consultant to Merck, Sharp and Dohme and Actelion. Rachael Cordina, Clare O'Donnell, and Julian Ayer are co-investigators in the RUBATO trial, sponsored by Actelion. Leeanne Grigg's institution received funding from Actelion for her role as an associate investigator in the RUBATO trial. Juliet Ward is a site coordinator in the RUBATO trial, sponsored by Actelion. None of the above authors contributed to the Medical Therapy section of this document. Kathryn Rice is a principal investigator in the RUBATO trial, sponsored by Actelion; she contributed to the Medical Therapy section of this document but not the subsection on pulmonary vasodilators. All other authors have no conflicts of interest to declare.

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Glossary

This is not intended to be an exhaustive list of technical terms used in this document but aims to support the comprehension of people with a Fontan circulation and their families. It was compiled at the request, and with the assistance, of members of the Fontan community

Adjunct: An additional treatment, procedure etc. used to supplement the main treatment, procedure etc.

Anticoagulation: Treatment with an anticoagulant medicine (e.g. warfarin) to thin the blood and reduce the risk of blood clots

Arrhythmia: An abnormal heart rhythm, where the heart beats too fast (tachycardia), too slow (bradycardia) or irregularly (flutter or fibrillation)

Ascites: Abdominal swelling caused by build-up of fluid that can be caused by problems in different organs, including the liver and the heart

Atresia: A condition in which a passage or an opening in the body is closed or absent

Atriopulmonary connection: An older type of Fontan procedure where the atrium receiving blood returning from the body (the systemic venous atrium) is joined directly to the pulmonary artery

Atrioventricular valve: The valve between an atrium and a ventricle

Biomarker: A naturally occurring molecule or characteristic in the body that can be used as a measure of a disease process

Cardiac catheterisation: A procedure for diagnosing or treating cardiovascular conditions, in which a long thin tube (catheter) is inserted in an artery or vein in the groin, neck or arm and threaded through the blood vessels to the heart

Cardiac output: The volume of blood pumped by the heart per minute

Cardioversion: A procedure that returns an arrhythmia to normal rhythm using electrical current or medication

Chronotropic incompetence: Inability of the heart to increase the heart rate to match increased activity or demand

Cirrhosis: Liver damage characterised by irreversible scarring (fibrosis), with many different causes, including heart disease and viral hepatitis

Coarctation: Narrowing of a short section of the aorta (the large blood vessel from the heart that supplies blood to the body) that is present at birth

Congenital heart disease: An abnormality in the heart's structure that is present at birth

Contraindicated: Indicates that a certain treatment should not be used because it could cause harm to that patient

Cyanosis: A bluish discolouration of the skin or mucous membranes caused by low oxygen saturation

Cystatin C-based eGFR: A way of estimating kidney function (glomerular filtration rate)

Dilatation: The process of enlargement or expansion (e.g. of a blood vessel)

Ejection fraction: The amount (volumetric fraction) of fluid ejected from a chamber (e.g. left ventricle) with each heartbeat; used to measure pumping efficiency of the heart

Endothelial: Relating to the endothelium (a thin membrane that lines the inside of the heart and blood vessels)

Epicardial: Relating to the epicardium (the outer surface of the heart)

Exome: All the exons, or coding regions, within the genome; the exome makes up about 1% of the genome, and changes in the exome can affect development and health

Extracardiac: Outside the heart

Flow haemodynamics: The physical factors that control blood flow, such as pressure and resistance

Focal: Arising from a single site, rather than multiple sites or circuits

Functionally single ventricle: Condition where the heart functions with a single pumping chamber; sometimes this includes a smaller chamber that is connected with the main pumping chamber by a large hole (a ventricular septal defect)

Genome: A person's complete set of genetic material, thought of as an instruction manual for how the person's body functions and their physical characteristics

Hepatic: Relating to the liver

Hepatocellular carcinoma: The most common form of primary liver cancer

Hypoplasia: A condition that is present from birth in which a tissue or organ is incompletely developed

Ischaemic stroke: A stroke caused by a blood clot in an artery that interrupts blood supply to the brain

Maze procedure: A surgical treatment for atrial fibrillation that involves creating scars in the atria by several possible means, such as direct incision with a scalpel or use of heat (radiofrequency ablation) or cold (cryoablation)

Meta-analysis: A statistical analysis that combines the results of multiple scientific studies

Modality: A particular way of collecting information, often referring to a type of medical imaging (e.g. CT, CMR)

Morbidity: Disease or ill health

Neurohormonal upregulation: Release of neurotransmitters and hormones that accompany heart failure; serves an initial role as a compensatory mechanism, but the chronic state contributes to further dysfunction

Palliative care: Care that is not curative but provided with the aim of improving quality of life for a patient with a chronic illness; includes but is not limited to end-of-life care

Post hoc analysis: Statistical analysis conducted after a study has been completed, to address a question that was not the original one posed; it is presumed that these analyses have less statistical validity

Preload: Filling pressure of the heart; used in this document to describe the volume that returns to the ventricle

Pre-pregnancy risk stratification: An assessment of maternal risk before conception

Proteinuria: The presence of protein in urine

Psychosocial factors: Psychological and social factors that may be associated with ill health, such as work-related stress, unemployment or relationship issues

Pulmonary arteries: Vessels that carry deoxygenated blood from the right ventricle to the lungs; in the Fontan circulation,

these vessels will receive the deoxygenated blood directly from the Fontan chamber or conduit

Pulmonary venous system: Vessels that take oxygenated blood from the pulmonary circulation back to the left atrium

Radionucleotide assays: Imaging tests that use radioactive material

Re-entry: Used to describe arrhythmias where the electrical signal propagates in a loop

Regurgitation: Leaking heart valve, which can cause the heart to work harder

Sequelae: Conditions resulting from a previous disease, injury or event

Sequencing: The process of determining the DNA sequence (usually applied to particular genes of interest)

Shunt: An abnormal communication between the right and left sides of the heart or between the systemic and pulmonary vessels, allowing blood to flow directly from one circulatory system to the other

Sinus node dysfunction: Abnormal initiation of the electrical signal in the heart causing slower heart rates or pauses

Splanchnic: Relating to the internal organs, especially those in the abdomen

Stenosis: Abnormal narrowing of a passage (e.g. a heart valve) in the body

Stool alpha-1-antitrypsin level: Measurement of the protein alpha-1-antitrypsin (a biomarker of PLE) in the faeces

Stroke volume: The volume of blood pumped from the left ventricle per beat

Syncope: Fainting (i.e. a temporary loss of consciousness)

Systemic venous pressure: Pressure in the venous pathways that return deoxygenated blood to the heart; this is much lower than the pressure in the arterial side of the circulation that takes oxygenated blood to the body

Systemic venous system: Vessels that bring deoxygenated blood from tissues and organs back to the heart

Systolic function: The pumping action of the heart

Thromboembolism: Formation of a clot (e.g. a deep venous thrombosis) which may then embolise (travel) to a circulation further downstream (e.g. the lungs)

Transdisciplinary: Crossing different areas of specialty

Ventricular systolic dysfunction: Reduced pumping action of the main pumping chamber (ventricle) in the heart