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## Clinical Research Priorities in Adult Congenital Heart Disease

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### Abstract

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**Background**—Adult congenital heart disease (ACHD) clinicians are hampered by the paucity of data to inform clinical decision-making. The objective of this study was to identify priorities for clinical research in ACHD.

**Methods**—A list of 45 research questions was developed by the Alliance for Adult Research in Congenital Cardiology (AARCC), compiled into a survey, and administered to ACHD providers. Patient input was sought via the Adult Congenital Heart Association at community meetings and online forums. The 25 top questions were sent to ACHD providers worldwide via an online survey. Each question was ranked based on perceived priority and weighted based on time spent in ACHD care. The top 10 topics identified are presented and discussed.

**Results**—The final online survey yielded 139 responses. Top priority questions related to tetralogy of Fallot (timing of pulmonary valve replacement and criteria for primary prevention ICDs), patients with systemic right ventricles (determining the optimal echocardiographic techniques for measuring right ventricular function, and indications for tricuspid valve replacement and primary prevention ICDs), and single ventricle/Fontan patients (role of pulmonary vasodilators, optimal anticoagulation, medical therapy for preservation of ventricular function, treatment for protein losing enteropathy). In addition, establishing criteria to refer ACHD patients for cardiac transplantation was deemed a priority.

**Conclusions**—The ACHD field is in need of prospective research to address fundamental clinical questions. It is hoped that this methodical consultation process will inform researchers and funding organizations about clinical research topics deemed to be of high priority.

## Keywords

Congenital Heart Disease; Tetralogy of Fallot; Transposition of the Great Arteries; Fontan Procedure; Survey

## Introduction

Adult congenital heart disease (ACHD) clinicians are hampered by the paucity of robust data to inform clinical decision-making. The American College of Cardiology/American Heart Association 2008 Guidelines for the Management of Adults with Congenital Heart Disease have been an important effort in standardizing ACHD care, although limited by a lack of strong evidence to support many of the recommendations. The document consists of 513 individual recommendations, of which 5 (0.97%) are based on level A evidence (multiple randomized trials or meta-analyses), 161 (31.4%) based on level B evidence (a single randomized trial or nonrandomized studies), and 347 (67.6%) based on level C evidence (expert opinion, case studies, or standards of care). (1)

To date, the vast majority of multi-center research studies in ACHD have been descriptive or observational. However, newer efforts including notable examples from pediatric cardiology and congenital cardiac surgery have demonstrated the feasibility of prospective, randomized trials. (2) (3) The development of large, nationwide registries, such as the Dutch CONCOR registry and others have contributed importantly to our understanding of prevalence and natural history of CHD. (4) The Alliance for Adult Research in Congenital Cardiology (AARCC) has also pooled resources to complete multicenter studies. (5) As prospective, randomized trials are expensive and time-intensive, careful prioritization of potential study topics is prudent.

Given scarce resources for executing studies, it is worthwhile to focus on topics with the greatest potential to positively impact clinical management. Therefore, the aim of this study

was to methodically pool opinions of key stakeholders, including both patients and providers, in identifying top priorities in clinical ACHD research.

## Methods

Initially, a list of potential clinical research questions was generated through “brainstorming” sessions by AARCC investigators based on a list of congenital heart defects and general topics to ensure comprehensive consideration of all lesions. Distinct and specific research questions were generated for each, rather than general issues. Questions were circulated and revised over several iterations during a 12-month period. Overlapping questions were consolidated. From this initial list, general approximations of potential impact (considering both frequency of the population to be studied and the impact on clinical management) and feasibility were determined by consensus. From a total of 86 research questions initially posed and ranked on the basis of impact and feasibility, the top 45 questions were retained for further consideration. This number was selected based on natural break points in the order list, and included all questions considered to have either very high feasibility or very high impact.

A survey was then generated using these 45 questions and administered to attendees at the 2012 International Symposium on Congenital Heart Disease in the Adult held in Toronto, Canada. A hard copy version was distributed to all attendees, including faculty, and collected at the end of the conference. Respondents were asked to rate the feasibility and impact of each topic using a 5-point Likert scale (5=highest impact/priority). Space was provided for notes and additional feedback. Each respondent was also asked to provide the percentage of clinical time they spent treating ACHD patients (<25%, 25–50%, 50–75%, or >75%) and their academic position (RN, NP/PA, MD/DO, or other).

Responses were entered into a database, including write-in questions/comments. Each response was weighted by the respondent’s time spent in ACHD (1–4 scale based on the indicated percentage). Weighted feasibility and impact scores were averaged for each question and then added to generate an overall score. Write-in questions and comments were reviewed and incorporated whenever possible. Corrections or rewordings were made as necessary.

In parallel, patient input was sought via the Adult Congenital Heart Association (ACHA). Research priorities were discussed at several in-person community meetings attended by a large cross-section of ACHA membership in different geographic locations, as well as through online forums. Through these collective efforts, patients were provided with a list of general research topics and asked to rank them by perceived importance (1–5 scale). The average score for each topic was calculated (Table 1), and categories ranked accordingly. These results were then factored into weighing the Toronto survey. Each research question from the provider survey was reviewed for its relevance to general categories selected by the ACHA. The sum of the final physician and patient ranks was used to determine a final priority score.

The 25 top ranking questions were then sent to large list of self-identified ACHD providers worldwide in the form of an online survey ([surveymonkey.com](http://surveymonkey.com)). Each question was re-ranked on a scale of 1 to 5 based on perceived priority (low, intermediate, high, very high, and top priority). Respondents were specifically encouraged to use the entire spectrum of scores. Options for write-in comments or additional questions were provided, and respondents were again asked to estimate their amount of time spent in ACHD care. A reminder to complete the survey was issued 4 weeks later such that the survey was open for a three-month period of time, until no additional responses were received.

## Data Analyses

Data are presented as frequencies and percentages. All responses were weighted according to the relative proportion of time spent in ACHD care using an ordinal scale (i.e., 0.25, 0.5, 0.75, and 1.0). Research questions were then ranked by score to generate a final priority list. Comments and write-in questions were reviewed and qualitatively incorporated in results.

## Results

A total of 57 surveys were received from the Toronto conference. Respondents included 43 MD/DO, 8 RN, 5 NP/PA, and 1 other. Of these, the time spent in ACHD care was >75% for 44% of respondents, 50–75% for 19% of respondents, 25–50% for 12% of respondents, and <25% for 23% of respondents. The top 25 ranked questions that were further considered are listed (Table 2).

The online survey yielded 139 responses. Of these 50 (36%) reported >75% of time spent in ACHD care, with 15%, 27%, and 22% of responders indicating 50–75%, 25–50%, or <25% of time in ACHD care, respectively. No questions were left blank by any respondent. The top 10 ranked questions were retained for discussion in this manuscript. Two relate to tetralogy of Fallot, 3 to patients with a systemic right ventricle (RV), 4 to Fontan palliation, and 1 with general application.

Of the write-in questions, some lent themselves to inclusion within existing questions, or helped to correct/clarify existing topics. Comments that were not included were: 1) too broad or general to lend themselves to specific research topics, 2) previously included in the original brainstorm list, 3) felt not to be feasible, or 4) previously addressed or the subject of ongoing studies. One respondent wrote “All the topics listed above are important with very little variations in their priority,” which is an important reminder that topics not included in the final selection should not necessarily be viewed as unimportant. Many respondents spontaneously expressed interest in participating in multicenter research trials.

## Discussion

While no list can incorporate all potential important research questions of interest, our objective was to highlight research topics deemed to be of high priority by a methodical consultation process of relevant stakeholders. Each of the top 10 research questions is discussed in greater detail, in random order, below.

### What is the optimal timing of surgical pulmonary valve replacement in tetralogy of Fallot?

Despite intense interest and numerous publications during the past 15 years on pulmonary valve replacement (PVR) in adults with repaired tetralogy of Fallot (TOF), optimal timing remains uncertain. (6–8) There is growing evidence that severe pulmonary regurgitation (PR) in TOF leads to RV dilation and dysfunction, worsening tricuspid regurgitation, LV dysfunction, arrhythmias, exercise limitations, worsening heart failure symptoms and death. (9–14) Pulmonary valve replacement is effective at addressing PR, (15, 16) however, studies examining the benefits of PVR have relied on surrogate outcomes, such as RV size and function or freedom from ventricular arrhythmias. (17) Historically, the decision to refer a patient with TOF and significant PR for PVR was based on symptoms such as exercise intolerance, arrhythmias or worsening heart failure. (18, 19) Relying on symptoms may not be an effective strategy, as adults with CHD often do not recognize gradual changes in their exercise capacity. (20, 21) Subsequently, referral for PVR may be delayed until the RV is severely dilated and/or dysfunctional. There is some discrepancy regarding threshold preoperative RV ventricular volumes (RV end-diastolic volumes <150–170 ml/m<sup>2</sup>, RV end-

systolic volume  $<90 \text{ ml/m}^2$ ) that are associated with postoperative normalization of RV size. (6, 15, 22, 23) Additionally, normalization of RV size is of uncertain value as an outcome, with no evidence that PVR improves survival late after TOF repair. (17, 24) Furthermore, published guidelines differ in the indications and timing for PVR in TOF patients. (1, 25, 26)

Therefore, the timing of PVR in patients with TOF must balance the benefits of elimination of PR, restoration of RV size and preservation of RV function before irreversible changes occur. (27) Although surgical mortality for PVR is low (5 year mortality 2.2%), there is a risk of valve failure, with some evidence that this is more likely to occur in younger patients at the time of PVR. (28, 29) Traditionally, PVR has been a surgical procedure; however, with the increasing experience of transcatheter pulmonary valves, the decision regarding timing of PVR may change. (30) In summary, there is currently significant variability in the timing of referral for PVR in the adult with repaired TOF, and there remains a paucity of outcome data for this intervention.

### **What criteria should be used to determine the need for ICD placement for primary prevention in TOF?**

Sudden cardiac death of presumed arrhythmic etiology is the leading mode of death in adults with TOF. (13, 31) The incidence of sudden death, as derived from several large series, has been estimated to be  $<0.3\%$  per year. (13, 31–33) These devastating events appear to be predominantly due to ventricular tachyarrhythmias and have been the focus of clinical investigations for decades. The ultimate challenge of risk stratification lies in identifying a subpopulation of patients at sufficiently high risk for sudden death to warrant implantation of a primary prevention ICD, within a much larger lower risk population. (34)

Despite numerous studies that identified factors associated with malignant ventricular arrhythmias and sudden death, risk stratification remains imperfect. The earliest investigations focused on surgical trauma to the atrioventricular conduction system, with attention later turning to determinants of ventricular tachyarrhythmias. (35) Cohort studies revealed that few patients die suddenly in the first 10 to 15 years after corrective surgery, with a small but steady decline in freedom from sudden death thereafter. (13, 31, 36, 37) Reported associated factors include frequent ventricular ectopic beats and non-sustained ventricular tachycardia, (38) elevated right ventricular systolic pressures, (36, 39, 40) complete heart block, (36, 41) JT dispersion, (42, 43) and decreased left ventricular systolic and longitudinal function. (12, 13, 31, 36, 37, 44) In a cohort of 793 patients with surgically repaired TOF, the four identified independent predictors of sudden death were: older age at repair, QRS interval  $\geq 180 \text{ ms}$ , transannular patch, and annual increase in the QRS interval. (13) Subsequently, a study that included 252 patients from 8 centers addressed the potential role of electrophysiological testing. (45) Inducible ventricular tachycardia was found to be a powerful albeit imperfect predictor of clinical ventricular tachycardia or sudden death, independent of non-invasive markers. More recently, a risk score was generated in a multicenter cohort of patients with TOF and primary prevention ICDs to predict the likelihood of receiving appropriate ICD shocks. (46) Factors identified by regression analyses consisted of a prior palliative shunt, inducible ventricular tachycardia, QRS  $\geq 180 \text{ ms}$ , ventriculotomy incision, non-sustained ventricular tachycardia, and a left ventricular end-diastolic pressure  $\geq 12 \text{ mmHg}$ . Later reports have since confirmed the association between left ventricular diastolic dysfunction and ventricular tachyarrhythmias. (47, 48)

Despite these advances, no reliable risk stratification scheme has yet emerged. (1) Complexities include the fact that risk exists on a continuum, changes over time, and is modified by factors such as evolving surgical approaches. (34, 49) To date, risk factors

identified in TOF have been derived from non-randomized largely retrospective research subject to potential residual confounding and imperfect surrogate outcomes.

### **What are the best echocardiographic techniques to determine systolic systemic right ventricular function?**

While echocardiography is a ubiquitous, harmless, and cost-effective tool for the assessment of ventricular function, the systemic RV is challenging to image in patients with congenitally corrected transposition (CCTGA) and d-transposition of the great arteries (d-TGA) following an atrial switch procedure. The systemic RV's location in the chest, limited acoustic windows, and geometric variation render standardized measurements difficult. "Normal" values for right ventricular dimension and function are lacking across the entire age spectrum of CHD making echocardiographic data difficult to use for risk stratification and management decisions.

Despite several studies evaluating systemic right ventricular function, the optimal echocardiographic technique remains to be clarified. Methods in current use, including fractional area change (50–52) or the myocardial performance index (50, 53, 54), have advantages and disadvantages, including weak reproducibility. Emerging use of RV free wall strain is attractive and clinically predictive. (55) Importantly, "normal" reproducible values for some of these metrics are emerging. (55–60) Volumetric 3D analysis of the RV overcomes geometric assumptions and is often reliable. (61–63) Knowledge-based reconstruction of systemic RV from specific data based algorithms is a promising new technique but is user dependent and reliant upon adequate acoustic windows and sector size. (64) Studies have been small given the relatively low frequency of systemic RV patients in any single ACHD center. Many have used cardiac magnetic resonance imaging (CMR) as the gold standard. Yet, there are ongoing debates about the best way to use CMR to quantify RV volumes (e.g., methods to contour a systemic RV) and the financial and technical constraints of CMR make are obstacles to widespread applicability as a routine screening tool. (65)

It remains important to study echocardiographic techniques in the evaluation of the systemic RV given the ubiquitous nature of echocardiography. Both geometric and non-geometric echocardiographic methods deserve research attention with coordination of multiple ACHD centers to determine expected or "normal" values and values that offer risk stratification for adverse outcome.

### **What criteria should be used to determine need and timing of systemic atrioventricular (ie tricuspid) valve replacement in a systemic RV?**

Many patients with a systemic RV will develop tricuspid regurgitation (TR) over time. These patients are also prone to developing systemic right ventricular dysfunction. (66–70) While TR and RV dysfunction seem to be related, it is often unclear whether TR causes or contributes to the RV dysfunction or is a result of it. (71) While patients with systemic right ventricles as a result of CCTGA and d-TGA following atrial switch procedures are often considered together, the natural history of right ventricular and tricuspid valve function likely differs between the two populations. Patients with the atrial switch operation have generally good 20–30 year postoperative survival, however, RV function appears to be an important predictor of morbidity and late mortality. (71, 72) Patients with CCTGA, particularly those without associated anomalies such as ventricular septal defects or abnormal tricuspid valve, tend to have reasonable survival and may not be diagnosed until adulthood. (69) Unlike adult onset mitral regurgitation where there is evidence to support guideline recommendations for timing of repair and intervention on the mitral valve (73), there is only scant literature, typically small case series, on long term outcomes in patients

with systemic RVs and TR with or without valve intervention. (66–71, 74–81) Better understanding of appropriate timing and anatomy for tricuspid valve intervention may help to improve outcomes and patient counseling.

The few prior studies have reported disparate results regarding tricuspid valve repair or replacement in this patient population, often with residual TR and RV enlargement and dysfunction. Two small recent studies evaluated patients after having tricuspid valve surgery. A Dutch study included 16 patients and showed no change in RV function but improved tricuspid valve function and functional status. (81) Mortality was low in those with no more than moderate RV dysfunction at the time of surgery. Valve replacement was thought to be the preferred option in this patient group since those with valve repair had more residual or recurrent TR. A study from the Mayo clinic included 46 patients with CCTGA and examined preoperative RV ejection fraction as a predictor of long-term mortality. They concluded that surgery should be performed before the RV ejection fraction decreases to <40% or the subpulmonary ventricular systolic pressure increases to >50 mmHg. (74)

Therefore, if surgery is considered, the current literature would support tricuspid valve replacement before a significant decrease in ventricular function or elevation of pulmonary pressures. However, further evidence and study are required to better understand timing and technique of this operation in order to preserve function and quality of life and ultimately avoid or delay transplantation.

### **What criteria should be used to determine need for ICD placement for primary prevention in a patient with a systemic RV?**

The incidence of sudden death in patients with CCTGA is poorly characterized. In contrast, d-TGA with atrial switch surgery is among the congenital heart defects associated with the highest incidence of sudden death. Indeed, sudden death of presumed arrhythmic etiology appears to be the most common cause of late mortality in this population. (32, 82–87), with an estimated incidence of 4.9 per 1000 patient-years, second only to left-sided obstructive lesions and more than threefold greater than TOF. (32) Unlike some forms of CHD where risk begins to increase years after surgery, (13) propensity for sudden cardiac death in patients with Mustard and Senning baffles appears early and seems relatively constant over time. (32)

Identification of risk factors for sudden death in patients with a systemic RV has been somewhat elusive. Few studies have addressed this issue in CCTGA. In a series published in abstract form of 131 patients with CCTGA followed for an average of 7 years, the 56 (43%) patients with a systemic RV ejection fraction <35% had a higher prevalence of ventricular tachycardia/fibrillation or cardiac arrest (23% versus 3%) and sudden death (16% versus 1%). (88) While studies have not specifically addressed primary prevention ICDs in this population, patients with CCTGA have been included in cohorts of ICD recipients with CHD at large. (89–92) In contrast, several investigations have attempted to identify factors associated with ventricular tachyarrhythmias and sudden death in d-TGA. While bradyarrhythmias were once thought to be primary triggers for sudden death, this notion was later refuted in light of evidence suggesting that pacemakers had little impact on outcomes. Reported factors associated with ventricular tachyarrhythmias and sudden death have largely been confined to systemic ventricular dysfunction, severe tricuspid regurgitation, prolonged QRS duration, and atrial tachyarrhythmias. (84, 93, 94) In 359 patients with Mustard or Senning baffles, 15 (4.2%) died suddenly. (82) Associated factors were severe tricuspid regurgitation and/or RV dysfunction and supraventricular tachyarrhythmias. In a case control study that included 47 patients with a Mustard or Senning baffle and sudden death or a near-miss event, the strongest predictors were symptoms of arrhythmia or heart failure and

documented supraventricular tachyarrhythmias. (93) One multicenter study specifically addressed the role of ICDs in high-risk patients with d-TGA. (95) Supraventricular arrhythmias were found to be important triggers for ventricular tachyarrhythmias, beta-blockers were associated with a lower incidence of appropriate shocks, and ventricular stimulation studies appeared to be of little value in predicting risk. Importantly, the rate of appropriate ICD shocks in patients with primary prevention indications was exceedingly low, highlighting current limitations in reliably identifying suitable candidates and the need for further research into risk stratification.

### **Is pulmonary vasodilator therapy beneficial in Fontan patients?**

A normal or low pulmonary arterial resistance is integral to the adequate function of the cavo-pulmonary circulation. With age, the pulmonary arterial resistance is known to gradually increase in Fontan patients and elevated pulmonary resistance is associated with worse clinical outcomes (96, 97). It stands to reason that therapies that decrease pulmonary arterial resistance may improve pulmonary blood flow and functional capacity in patients with Fontan physiology. With the understanding that the pulmonary vascular bed is reactive to nitric oxide (98), safety and at least limited efficacy of sildenafil in non-failing Fontan patients has been demonstrated, including ~30% improvement in resting and exercise pulmonary blood flow (99), myocardial performance indices and estimates of cardiac output (100), respiratory rate and minute ventilation at peak exercise, and decreased ventilatory equivalents of carbon dioxide at the anaerobic threshold, though not peak oxygen consumption. (101) Interestingly, this improvement in ventilator equivalents was limited to patients with a serum BNP > 100 pg/ml. Furthermore, elevated endothelin-1 levels in Fontan patients suggest that endothelin blockade may be an effective approach. In a small prospective study of bosentan in patients with failing Fontan physiology there were non-significant improvements in resting and ambulatory oxygen saturation but no improvement in maximum oxygen consumption, 6 minute walk distance, or quality of life measures. (102). Another prospective randomized control trial also failed to demonstrate improvements in exercise, quality of life, or pro-BNP. (103) Given the mixed results of these early studies, the use of endothelin blockade in Fontan patients is of questionable efficacy, though larger studies are required.

In summary, immediate and short-term improvement in functional capacity has been reported in Fontan patients receiving pulmonary vasodilator therapies. The existing data suggests greater benefit of the phosphodiesterase-5 inhibition over endothelin blockade. There are no long-term studies as of yet that have assessed the impact of pulmonary vasomodulation on survival, arrhythmias, Fontan failure, hepatic dysfunction, or arrhythmias. Hence, there is a need for further studies that are sufficiently powered and of sufficient duration to evaluate the long-term benefits and side-effects of pulmonary vasodilators in the Fontan population.

### **Are warfarin and/or aspirin beneficial in preventing primary thromboembolic events in adult Fontan patients?**

While there are widely varying estimates of the prevalence of venous pathway thrombosis in patients with a Fontan circulation due to different assessment methods and definitions, estimates approximate ~20%. (104–108) Mortality related to thromboembolism (including pathway obstruction, pulmonary embolism, cerebrovascular accident and other systemic embolism) is high. (109, 110) Among adults, death is attributed directly to thromboembolic events in about a quarter of cases, and thrombus within the Fontan circuit is a univariate predictor of death in this population. (110) Preventing thrombosis and its sequelae, including Fontan pathway obstruction and thromboembolic events, are therefore critical goals of care for these patients. Unfortunately, there are few data to guide the clinician.



In a multicenter randomized trial comparing aspirin to warfarin in children (mean age ~5 years) after the Fontan procedure there was no difference in incidence of thrombosis between the groups over 2 years. (111) Of note, the incidence of thrombosis in this closely monitored cohort was very high (19% over the 2 year follow-up despite treatment with either aspirin or warfarin) yet the majority of events were clinically silent. There are no similar data in adults with a Fontan circulation. In addition to chronic anticoagulation, understanding optimal approaches to anticoagulation in situations of increased thromboembolic risk such as pregnancy, certain types of contraception, hospitalization for medical illness and non-cardiac surgery is also a major priority. (112–115)

With the development of newer anticoagulants and antiplatelet agents, warfarin and aspirin are not the only potential approaches to thromboprophylaxis. Beyond identifying a specific effective medical regimen, major considerations in study design to address the optimal approach to thromboprophylaxis include identifying clinically important outcomes (e.g., thromboembolic events versus incidentally identified thrombosis), (107) interplay with common comorbidities and their management (e.g., the drug metabolism effects of cirrhosis or the incidental benefit of subcutaneous heparin for protein losing enteropathy), (116–118), cost, (119) and common medication interactions. (120)

### **What is the optimal medical therapy for preservation of ventricular systolic and diastolic function in Fontan patients?**

As patients with Fontan palliation enter into their fourth decade of life, several long-term sequelae associated with Fontan palliation are increasingly appreciated. The three most common modes of death include thromboembolism, sudden cardiac death and heart failure from ventricular dysfunction. (110, 121) Ventricular dysfunction, both systolic and diastolic has been increasingly recognized in such patients. (122–124)

The etiology of ventricular dysfunction is multi-factorial. Prior cyanosis, abnormal ventricular architecture, pressure/volume loading leading to ventricular hypertrophy and dilation (125, 126), abnormal ventricular relaxation and decreased ventricular compliance (122, 125), and ventricular morphology (126) all play a role.

To date, optimal medical management of the failing Fontan has generally been anecdotal. Effective or optimal medical therapy for patients with Fontan physiology with ventricular systolic or diastolic dysfunction includes strategies extrapolated from the treatment of congestive heart failure in adult cardiovascular disease. (127, 128) There is evidence for increased sympathetic activity due to chronic heart failure that can worsen ventricular function through prolonged adrenergic activation that leads to myocardial hypertrophy and cell death, which can be altered by beta blocker and ACE inhibitor therapy. (129) Yet existing studies are limited and of small caliber, with mixed results. Carvedilol has been demonstrated to improve ejection fraction as well as signs, symptoms and NYHA class in patients with a Fontan. (130) In a 25-year retrospective series, long term survival improved over the last decade (121), in part due to better medical therapy. Several studies have demonstrated elevated levels of hormones that modulate fluid homeostasis such as antidiuretic hormone, aldosterone, renin, and angiotensin, in patients with Fontan circulation. (131, 132) Theoretically, ACE inhibition may be effective for patients with failing Fontan physiology, but only a few such studies have been conducted, with no clear benefit in this patient population. (125, 133)

Owing to a universal lack of established guidelines and consensus management, medical therapy for ventricular dysfunction in patients with single ventricular physiology after the Fontan operation continues to vary widely among centers (134), and is therefore a high priority topic for prospective research.

### **What is the optimal medical treatment algorithm for Fontan patients with protein-losing enteropathy (PLE)?**

Protein losing enteropathy (PLE) has been observed in 5–15% of patients. (135, 136) PLE is characterized by the enteric loss of proteins, such as albumin, immunoglobulins, and clotting factors. Prior studies have reported 50% mortality at 5 years post diagnosis although more recent center specific studies show improved survival rates of 75% at 5 years post diagnosis. (137)

PLE therapies fall into three categories: 1) treatment of cardiac causes of low systemic output or high venous pressure, 2) treatment of hypoproteinemia, or 3) treatment of the intestinal mucosa. Arrhythmia control to establish atrial-ventricular synchrony is important, and anti-arrhythmic medication, catheter ablation, pacemaker therapy, and Fontan revision with maze procedure have all been utilized. (138, 139) Relief of obstruction along the Fontan pathway by either catheter technique or surgical revision in addition to Fontan fenestration creation have also been shown to improve PLE in some cases. Medical therapies such as ACE inhibitors, aldosterone antagonists, diuretics, and sildenafil have also shown some success, but only in a subset of patients with PLE. (140, 141) Cardiac transplantation can be curative, but affected patients have very high rates of surgical morbidity and mortality (142). Treatment of hypoproteinemia consists of instituting a high protein, medium chain triglyceride diet and albumin repletion. Treating the intestinal mucosa has received more attention in the last few years with the use of oral controlled-released (CR) budesonide, a steroid with low systemic absorption and high enteric activity (143), which theoretically results in fewer systemic side effects due to its low systemic absorption. However, a subset of patients develops liver disease following the Fontan operation, resulting in more systemic side effects with CR-budesonide. (144) Heparin has also been proposed as a treatment for PLE and is thought to promote intestinal membrane stabilization. (145) Octreotide, a somatostatin analog, was recently reported as a potential therapeutic option. (146) Reports are limited, but the mechanism of action relies primarily on reducing vasoactive hormones and lymphatic extrusion.

Complicating aspects of PLE treatment include the varied proposed therapies and high failure rate. Currently, treatment is highly individualized. Prospective research may be of value in identifying an optimal treatment algorithm for PLE following the Fontan operation.

### **What are the ideal criteria for transplantation referral in ACHD?**

Aside from the general recommendation by the ACC/AHA that adult CHD patients undergo transplantation in centers with expertise in CHD, there are no specific guidelines for transplant referral that exist for adult with complex CHD. (1) Typically, the decision to evaluate the non-congenital adult for transplant candidacy is based on an estimated life expectancy of less than one year. In the absence of appropriate pre-transplant criteria and identification of risk factors unique to the adult with complex CHD patient, survival cannot be accurately assessed.

Extrapolating prognostic scores from the acquired heart failure population has not proven useful in the adult CHD patient, making decisions concerning the timing of transplantation exceedingly difficult. (147, 148) However, as we consider criteria for the adult with CHD, we must avoid generalizing from the non-CHD end-stage heart failure community and rather focus on the unique aspects of the adult with CHD. In the absence of large, multi-center trials pre-transplant assessment of pulmonary vascular resistance is important to exclude pulmonary hypertension, yet difficult to measure accurately in some congenital populations. (149) Currently, there is no consensus regarding what level of elevation of pulmonary vascular resistance would preclude successful transplant in the adult with CHD. The small

amount of literature on this subject differs with respect to the influence of elevated pulmonary vascular resistance on post-transplant outcomes in ACHD patients. (150, 151) Furthermore, current criteria for listing status based in part on pharmacologic or mechanical support seem to favor those without CHD. (152)

Ultimately, risk stratification of the adult CHD patient requires an understanding of clinical risk factors associated within a wide spectrum of anatomic subtypes referred for transplantation. Unfortunately, little is known about transplant frequencies or outcomes in adults with CHD as the United Network for Organ Sharing database does not capture the underlying diagnosis for this growing population. Consequently, current adult CHD transplant data is reported from either single-centers or case reports. In a retrospective, single-center study to assess mortality after cardiac transplantation, the most common pre-transplant diagnosis was single ventricle (50%) followed by d-TGA (16%). (153) Compared to the non-CHD recipient, risk of adult CHD mortality is two-fold greater at the time of transplant. (151, 154) In the high-risk adult Fontan patient, early mortality is as high as 28.5%; with common causes of death including hemorrhage and sepsis. (155) As a consequence, greater insight into transplant mortality is now required. At this time, transplantation of adults with complex CHD should be undertaken with the recognition of potential for high early mortality. Pre-transplant criteria are warranted, but can only be achieved through multi-institutional studies that code adult CHD patients according to subtype to further identify risk factors for poor outcomes in this growing patient population.

### Limitations

Elaboration of the high priority list was exclusively limited to clinical research. Surveys did not and could not reach every ACHD provider, nor every patient, and it is difficult to estimate to what extent responses were representative of the target population. However, given the methods utilized, including repeated surveys to different audiences, a wide representation of providers and patients was captured. While our final survey sought an international response, the geographic location of responders was not tracked. Importantly, given the vast heterogeneity of the ACHD population and the numerous sequelae and post-operative complications encountered, the results should not be construed as suggesting that research questions not included in the priority list generated are unimportant or unworthy of prospective research. The distinction in importance between one research question and another is ultimately a matter of opinion. Our objective was to capture and synthesize opinions across a wide and diverse group of stakeholders.

### Conclusions

The ACHD field is in need of dedicated prospective research to address fundamental questions in clinical management. We sought to consolidate and provide some focus on the myriad of research topics that could be pursued, while fostering patient-physician partnerships. It is hoped that this list will spark interest and inspire researchers and funding organizations to pursue required studies in the field and address important care-limiting issues.

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**Table 1**

Classification of Research Priority Categories from Patient Surveys

<b>General Topic</b>	<b>Mean Score</b>	<b>Rank</b>
Heart Rhythm Problems	4.6	1
Surgery	4.6	2
Insurance	4.3	3
Devices	4.3	4
Quality of Life/ Social/ Psychological Concerns	4.2	5
Physical Symptoms	4.1	6
Medications	4.0	7
Pregnancy	3.9	8
Exercise	3.9	9
Kidney and Liver Function	3.6	10
Sexual Function	3.2	11

**Table 2**

Complete list of research questions.

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**Top 25 questions ranked from the Toronto Survey**

1. What is the optimal medical management of a dilated aorta in the setting of a bicuspid aortic valve?
2. What is the optimal timing of surgical pulmonary valve replacement in TOF?
3. Are warfarin and/or aspirin beneficial in preventing primary thromboembolic events in adult Fontan patients?
4. Is pulmonary vasodilator therapy beneficial in Fontan patients?
5. What is the long-term outcome of valve sparing root replacement in bicuspid aortic valve?
6. What is the optimal medical management for a dilated aorta in Marfan syndrome?
7. What criteria should be used to determine need for ICD placement for primary prevention in TOF?
8. What liver screening tests are justifiable in Fontan patients, and at what intervals?
9. What is the optimal medical therapy for hypertension in coarctation patients?
10. What criteria should be used to determine need for ICD placement for primary prevention in transposition of the great arteries?
11. Does exercise capacity predict prognosis in Fontan patients?
12. What is the ideal standard approach to contraception in ACHD?
13. What criteria should be used to determine need and timing of systemic atrioventricular (ie tricuspid) valve regurgitation in a systemic RV?
14. What is the optimal medical therapy for preservation of ventricular systolic and diastolic function in Fontan patients?
15. What are the ideal criteria for transplantation referral in ACHD?
16. When is Fontan conversion favorable to ongoing medical therapy in patients with a classic aortopulmonary Fontan palliation?
17. What are the best echo techniques to determine systolic function of a systemic RV?
18. What should be used as standard techniques and references for quantification of systemic RV size and function by MRI?
19. What criteria (from imaging or clinical exam) should be used to determine need for intervention in recoarctation after initial repair?
20. What is the prevalence of ostial coronary obstruction in the arterial switch population? How should it be detected?
21. What is the optimal medical treatment algorithm for Fontan patients with PLE?
22. Should all coarctation patients be screened for cerebral aneurysms using MRI or CT?
23. Are phosphodiesterase inhibitors (such as sildenafil) beneficial in patients with a systemic right ventricle?
24. Should ACHD patients listed for transplantation have separate criteria for organ allocation status?
25. Are beta blockers in patients with transposition of the great arteries (d-TGA) without pacemaker safe?

**Additional questions evaluated with the Toronto Meeting Survey (in order of decreasing priority)**

26. What is the incidence of sleep disordered breathing in Fontan patients?
27. Are destination ventricular assist devices feasible in failing Fontan patient?
28. Should re-intervention for coarctation be done via catheter or surgery?
29. What is the cause for "Fontan failure"?
30. What criteria should be used for a preoperative risk score for reoperation of ACHD patients?
31. What limits exercise capacity in Fontan patients?
32. What is the prevalence of coronary artery disease in coarctation patients?
33. Is CPAP therapy beneficial or harmful in Fontan patients with sleep disordered breathing?
34. What are the optimal criteria for determining need for intervention for an anomalous coronary artery?
35. What is the ideal metric for determining need for surgery on a dilated aorta in Turner syndrome?
36. Are pulmonary vasodilators beneficial in patients with Ebstein's anomaly or other causes of severe TR?
37. Is an extracardiac conduit favorable to a lateral tunnel for total-cavopulmonary circulation?
38. Should additional imaging be performed to inspect the pulmonary veins in every patient referred for ASD closure?

39. What is the relationship between radiation exposure in early life and cancer over the long-term?
40. What is the ideal surgical approach for an anomalous coronary artery?
41. Should coarctation of the aorta be considered a CAD equivalent (similar to DM)?
42. What is the long-term outcome of surgical intervention for an anomalous coronary artery?
43. What is the natural history of an unoperated L-TGA patient with VSD/PS?
44. With what frequency should Fontan patients have routine hemodynamic assessment by catheterization?
45. What is the incidence of endocarditis in small unrepaired VSDs in the current era?

**Previously Considered Questions (in order of relative decreasing priority)**

46. Why do some people develop pulmonary vascular disease with an ASD and how can we predict this?
47. What are the outcomes and risks of surgical as compared with trans-catheter closure of ventricular septal defect?
48. What is the optimal timing for repair or replacement of the left atrioventricular valve in patients with repaired atrioventricular septal defect?
49. What is the rationale for closing a tiny patent ductus arteriosus in an asymptomatic adult?
50. What is the utility of screening first degree relatives of patients with bicuspid aortic valve?
51. How often should patients with bicuspid aortic valve be monitored for progression of aortic stenosis, insufficiency, and aortic dilatation?
52. How to approach mixed aortic valve disease (moderate aortic stenosis and regurgitation) in the setting of a bicuspid valve?
53. What is the optimal timing of intervention to prevent aortic valve disease in a patient with subaortic stenosis?
54. Should aortic dimensions be indexed to body size metrics?
55. What are the optimal means of predicting rupture or dissection with aortopathy?
56. Should aortic diameter or area be used to follow aortic dimensions in patients with an aortopathy?
57. Can wall thickness be used to define wall tension in aortopathy?
58. What are the differences in outcomes between patients undergoing transcatheter pulmonary valve replacement as compared with surgical pulmonary valve replacements?
59. Are criteria for pulmonary valve replacement in a patient with congenital PS the same as for TOF?
60. What is the optimal timing of tricuspid valve repair or replacement in unoperated individuals with Ebstein anomaly?
61. Is tricuspid valve repair or replacement the best option for patients with Ebstein anomaly?
62. How do congenital coronary anomalies cause death?
63. Is there a benefit of anticoagulation use for primary prevention of events in Eisenmenger syndrome?
64. Do pulmonary vasodilators prolong life in patients with Eisenmenger syndrome?
65. What is the role of oxygen therapy in patients with Eisenmenger syndrome?
66. How should anemia be evaluated with Eisenmenger physiology, and what is its impact on prognosis?
67. At what aortic dimension should patients with TOF undergo aortic root replacement?
68. What is the cause of LV dysfunction in TOF?
69. What are the best echo techniques for evaluating systemic RV function?
70. What are the differences in neurodevelopmental outcome between patients who have undergone the arterial switch operation as compared with atrial switch procedures?
71. Is systemic atrioventricular valve replacement superior to medical therapy in adults with d-TGA after atrial switch procedures?
72. What is the efficacy of biventricular pacing in CCTGA?
73. Is tricuspid valve replacement superior to medical therapy in adults with CCTGA and tricuspid regurgitation?
74. What are the alternatives to Fontan and/or Fontan take down?
75. What is the rate of bioprosthetic valve deterioration during pregnancy?
76. What are the social and ethical implications of child bearing in patients with severely limited life expectancies and best approach to counseling?
77. Does chronic hepatitis C cause cirrhosis in some ACHD patients faster than others (i.e. single vs. 2 ventricle repair of pulmonary atresia-intact ventricular septum)?

78. Should we tell all patients with Fontan circulation (or subpulmonary ventricular dysfunction or tricuspid valve disease) to avoid all alcohol consumption?
  79. Do multiple thoracotomy/sternotomy patients have measurably different pulmonary function?
  80. What are the causes of renal dysfunction in CHD? What are the respective roles of cyanosis, antegrade perfusion, and altered perfusion pressures?
  81. What are the effects of ACE inhibition in patients with CHD and renal dysfunction; friend or foe?
  82. What are workable models for ACHD centers to work with general cardiologists at a distance?
  83. ACHD at adult or pediatric hospitals: which model, or a hybrid, is best?
  84. What is the efficacy of colchicine in preventing postop pericarditis in ACHD?
  85. How does genetic testing change real clinical practice?
  86. Can we identify biomarkers to predict specific events in specific lesions?
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TOF: tetralogy of Fallot. ICD: Implantable Cardioverter-Defibrillator. ACHD: adult congenital heart disease. RV: right ventricle. PLE: protein losing enteropathy. d-TGA: d-transposition of the great arteries. ASD: atrial septal defect. VSD: ventricular septal defect. PS: pulmonary stenosis. LV: left ventricle.