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AHA SCIENTIFIC STATEMENT

Evaluation and Management of Chronic Heart Failure in Children and Adolescents With Congenital Heart Disease: A Scientific Statement From the American Heart Association

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ABSTRACT: With continued medical and surgical advancements, most children and adolescents with congenital heart disease are expected to survive to adulthood. Chronic heart failure is increasingly being recognized as a major contributor to ongoing morbidity and mortality in this population as it ages, and treatment strategies to prevent and treat heart failure in the pediatric population are needed. In addition to primary myocardial dysfunction, anatomical and pathophysiological abnormalities specific to various congenital heart disease lesions contribute to the development of heart failure and affect potential strategies commonly used to treat adult patients with heart failure. This scientific statement highlights the significant knowledge gaps in understanding the epidemiology, pathophysiology, staging, and outcomes of chronic heart failure in children and adolescents with congenital heart disease not amenable to catheter-based or surgical interventions. Efforts to harmonize the definitions, staging, follow-up, and approach to heart failure in children with congenital heart disease are critical to enable the conduct of rigorous scientific studies to advance our understanding of the actual burden of heart failure in this population and to allow the development of evidence-based heart failure therapies that can improve outcomes for this high-risk cohort.

Key Words: AHA Scientific Statements ■ adolescent ■ child ■ diagnosis ■ disease management ■ heart disease, congenital ■ heart failure ■ ventricular dysfunction

As a result of remarkable advances in medical and surgical management, most children born with congenital heart disease are expected to survive to adulthood.[1] As the population of children and adolescents with unrepaired, palliated, or repaired congenital heart disease ages, chronic heart failure (HF) is increasingly being recognized as a significant contributor to ongoing morbidity and mortality.[2–6] In some cases, catheter- or surgery-based interventions for residual congenital heart disease can mitigate HF. However, a considerable number of children are at risk of or will develop chronic HF not amenable to interventions. This scientific statement provides an overview of the current epidemiology, pathophysiology, staging, and treatment of chronic HF in children and adolescents with congenital heart disease that is not amenable to catheter-based or surgical interventions. Significant knowledge gaps exist, and the authors hope that this scientific statement will stimulate formation of standardized definitions, surveillance protocols, and treatment algorithms aimed to improve outcomes of chronic HF in this population.

EPIDEMIOLOGY OF CHRONIC HF IN CONGENITAL HEART DISEASES

The incidence and prevalence of chronic HF in children and adolescents with congenital heart disease are

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rising.[2,6] According to a recent report from the Finnish national registry, up to 40% of patients with congenital heart disease are reported to have HF within 20 years after their congenital heart surgery. Up to 20% of patients with congenital heart disease (12% with simple defects, 40% with severe defects) required HF medications during follow-up.[6] HF was a common cause of death among patients with congenital heart disease who died during follow-up.[6] Studies demonstrate that patients with congenital heart disease account for the greatest proportion of pediatric HF admissions, and once hospitalized or admitted to the intensive care unit, they are more likely to die.[2,4,5,7,8] Those with single-ventricle congenital heart disease, advanced HF symptoms, and elevated cardiac biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide] and troponin T) have worse outcomes.[4,9–12] Patients with congenital heart disease with HF and end-organ dysfunction have increased mortality before and after heart transplantation[13,14] (Table 1).

VENTRICULAR FUNCTION AND HF IN CONGENITAL HEART DISEASE

The mechanisms that lead to impaired ventricular function in patients with congenital heart disease include injury as a result of increased myocardial stress from abnormal pressure or volume loading conditions, ischemic damage from coronary insufficiency attributable to cyanosis or impaired coronary blood flow, and, in postsurgical patients, exposure to cardiopulmonary bypass, cold ischemia, or low cardiac output syndrome.[18,19] These stressors can lead to neurohormonal and cytokine activation, inflammation, altered gene expression, and ventricular remodeling, resulting in impaired ventricular function.[20–22] For children with single-ventricle congenital heart disease such as hypoplastic left-heart syndrome, mitochondrial defects contribute to the pathogenesis of the lesion,[23–26] and these can also lead to increased oxidative cellular stress, increasing their risk for subsequent HF.[26] The characterization of adults into those with systolic dysfunction (HF with reduced ejection fraction [EF]) and those with diastolic dysfunction (HF with preserved EF [HFpEF]) has become standard practice in the diagnosis and treatment of adult HF.[22,27] Although such characterization is still not commonplace in discussions of pediatric HF, and even sparingly so in discussions of HF in pediatric patients with congenital heart disease, it may be helpful in attempts to evaluate the relevance of adult HF trials to this population.

DEFINITION OF CHRONIC HF IN PEDIATRIC CONGENITAL HEART DISEASE

Although the structural and functional impairments found in patients with congenital heart disease are far more heterogeneous than those seen in adults with structurally normal hearts,[18] the definition of chronic HF as a "complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood" is as relevant to the pediatric population as to the adult population for which it was developed.[22] At the cellular level, a failing heart has decreased mitochondrial oxidation, increased glycolysis, and perturbed fatty acid oxidation, all leading to decreased myocardial efficiency.[28] The unique anatomical states present in repaired and unrepaired congenital heart disease play important roles in the development of HF in this population (Table 2).

HF With Reduced EF (Systolic Dysfunction)

The presence and degree of left ventricular (LV) systolic dysfunction (based on EF) identify adult patients at risk for worse outcomes and are used to institute and titrate guideline-directed medical therapy.[22] Similarly, the presence of reduced systemic ventricular EF is an important determinant of increased cardiovascular mortality in patients with congenital heart disease.[31] Unlike adults with structurally normal hearts in whom EF-based categorization of ventricular dysfunction is standardized,[32] to date, no such cutoffs have been developed for children and adolescents with congenital heart disease. We propose the following categorization of dysfunction for patients with systemic LV morphology: mild dysfunction, EF of 41% to 51%; moderate dysfunction, EF of 30% to 40%; and severe dysfunction, EF <30%.

It is important to emphasize that EF measurements are operator and load dependent and that in children with congenital heart disease and altered ventricular geometry (from the use of patch material for ventricular septal defect closure or ventriculotomy) or altered intraventricular synchrony (congenital or iatrogenic), these measurements may not be as accurate as in those with structurally normal hearts.[33,34] The categorization of ventricular dysfunction in congenital heart disease lesions with systemic ventricles of right or indeterminate ventricular morphology is challenging.[35,36] The use of echocardiography to estimate EF in such patients is hampered by poor image quality and the lack of geometric models to accurately estimate ventricular volumes.[35–37] Echocardiography-based fractional area change has also been used in patients with congenital heart disease to assess right ventricular (RV) dysfunction and shown to correlate with magnetic resonance imaging–derived RV EF.[38–40] An RV fractional area change <35% is considered abnormal in those with biventricular congenital heart disease (tetralogy of Fallot).[38] Magnetic resonance imaging is often preferred for evaluation of RV size and function in patients with congenital heart disease.[41] However, the risks of intubation or sedation, if needed for magnetic resonance imaging, may be prohibitive for certain patients. For these reasons, it is important to continue to improve our echocardiographic

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Table 1. Contemporary Studies Evaluating HF Epidemiology, Risk Factors, and Outcomes for Patients With Congenital Heart Disease

Authors	Study type	Study dates	Main findings
Assenza et al[13] (2012)	Retrospective, single center	1993–2008	Fontan patients with higher MELD-XI score or those with increasing MELD-XI scores over time have lower freedom from sudden death, death caused by congestive HF, and cardiac transplantation
Amdani et al[2] (2022)	National inpatient, emergency, and death database study	2012 and 2016	Congenital heart disease is one of the most common reasons (along with cardiomyopathy and arrhythmia/conduction disorders) for pediatric HF–related ED visits and hospitalizations
Amdani et al[14] (2022)	Pediatric Heart Transplant Society, multicenter	2005–2018	On multivariable analysis, high MELD-XI scores (HR, 1.007), presence of protein-losing enteropathy (HR, 2.1), and VAD use (HR, 3.4) at transplantation were risk factors for early-phase post–heart transplantation mortality
Auerbach et al[10] (2010)	Post hoc analysis of the Pediatric Carvedilol Trial	2000–2005 Cohort included 60% with cardiomyopathy and 40% with congenital heart disease All had LVEF ≤40% All had symptomatic HF (Ross/NYHA class II–IV)	BNP ≥140 pg/mL and age >2 y identified subjects at higher risk for composite end point of HF hospitalization, death, or transplantation
Raissadati et al[6] (2020)	Finnish population registry	1953–2009	Of 8623 patients, 28% had cardiovascular disease during follow-up. HF was the most common comorbidity. Patients with severe defects were at higher risk for HF than those with simple defects. The need for HF medication was high between 10 and 20 y after the operation. Children with TGA required medications for HF at an average of 6 y, whereas for those with univentricular hearts, the average age was 2.5 y after their first operation.
Burstein et al[4] (2019)	Pediatric Health Information system, multicenter	2004–2015	Children with congenital heart disease and advanced HF have 26% in-hospital mortality Risk was higher in those with single-ventricle congenital heart disease (OR, 1.64), infants (OR, 1.71), those from underrepresented racial and ethnic groups (OR, 1.28), and patients with chronic complex comorbidities (OR, 1.76)
Geerdink et al[9] (2018)	National study (Netherlands)	1980–2014 Diagnosis: Ebstein	On multivariable analysis, presence of Ross class IV HF was associated with increased hazard of death (HR, 12.7 [95% CI, 4.4–36.3]; $P<.001$)
Ghelani et al[11] (2022)	Single-center, cross-sectional study		NT-proBNP >100 pg/mL and high-sensitivity troponin had the strongest correlation with ventricular dilation and dysfunction Ratio of urinary neutrophil gelatinase–associated lipocalin-2 to creatinine correlated with EF and estimated glomerular filtration rate
Schophuus Jensen et al[15] (2022)	Multicenter study, all Nordic patients (Denmark, Finland, Norway, and Sweden)	1967–2003 Diagnosis: TGA s/p Mustard or Senning	Among children with TGA s/p Mustard or Senning, the most common cause of death in the short term (first 10 y after operation) was sudden cardiac death (23.7%, 23/97), followed by HF/heart transplantation (18.6%, 18/97)
Mahle et al[16] (2018)	Multicenter study (Single Ventricle Reconstruction Trial)	2005–2008 Diagnosis: HLHS	Of 461 patients who underwent the Norwood procedure, 66 (14.3%) had HF by 6 y of age. Of these, 15 (23%) died, and 39 were listed for transplantation (59%). Risk factors for HF after Norwood included lower fractional area change, need for extracorporeal membrane oxygenation, non-Hispanic ethnicity, Norwood perfusion strategy, and total support time Shunt type (modified BTT shunt vs RV-PA) did not affect risk for developing HF
Nandi and Rossano[5] (2015)	Kids' Inpatient Database	2000–2009	Pediatric HF–related hospitalizations were highest for children with congenital heart disease (accounting for 58%–62%) Hospitalization costs for congenital heart disease were 2-fold higher ($72 336) than those with other pathogeneses ($34 077)
Rossano et al[17] (2012)	Kids' Inpatient Database	1997–2006	Congenital heart disease was found in the majority of children with HF admissions, increasing from 60.6% in 1997 to 69.3% in 2006
Sadoh et al[8] (2011)	Single-center, prospective study	January 2009–December 2009	Mean percentage of income families spent for children with congenital heart disease and chronic HF was 16.3±26.2% Families with lower SES spent a significantly higher percentage of income on medicines and total care than those with higher SES

(*Continued*)

Table 1. Continued

Authors	Study type	Study dates	Main findings
Wright et al[12] (2022)	Linkage analysis Pediatric Cardiac Care Consortium, US National Death Index and Organ Procurement and Transplant Network databases	1982–2003 Outcome was time from congenital heart surgery discharge to HF-related death, heart transplantation, or VAD placement	All children with congenital heart disease who had undergone surgery had higher rates of HF-related death compared with the general population Compared with children with mild 2-ventricle defect, groups at highest risk were those with moderate and severe 2-ventricle defects (HR, 3.2 and 9.5, respectively) and single-ventricle defects (HR, 31.8) Children with systemic RV were at highest risk 2 y after congenital heart surgery

BNP indicates B-type natriuretic peptide; BTT, Blalock-Thomas-Taussig; ED, emergency department; EF, ejection fraction; HF, heart failure; HLHS, hypoplastic left-heart syndrome; HR, hazard ratio; LVEF, left ventricular ejection fraction; MELD-XI, Model for End-Stage Liver Disease Excluding INR; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PA, pulmonary artery; RV, right ventricle; SES, socioeconomic status; s/p, status post; TGA, transposition of the great arteries; and VAD, ventricular assist device.

capabilities to assess ventricular function in children with biventricular and single-ventricle congenital heart disease. Normative values for EF in systemic right and indeterminate ventricles are lacking, given that these physiologies do not exist in children with normal biventricular circulation. We propose RV dysfunction in those with systemic RV as follows until better correlation of RVEF with HF outcomes is available[42,43]: an RVEF <40% by cardiac magnetic resonance imaging or greater than moderately depressed RV function by echocardiography.

HFpEF (Diastolic Dysfunction)

A proportion of patients with congenital heart disease with relatively preserved EF develop HF symptoms, similar to adult patients with HFpEF. This is often related to chronic exposure to increased preload (atrioventricular or semilunar valve insufficiency) or afterload (aortic stenosis, coarctation of aorta, systemic hypertension) to the systemic ventricle or secondary to the effects of hemodynamic stressors during early life or myocardial fibrosis/scarring from perturbations secondary to the underlying congenital heart disease physiology or surgical operations.[19] Other factors may also play a role in patients with single-ventricle congenital heart disease. Diastolic dysfunction has been noted early in life in those with single-ventricle congenital heart disease.[44–47] One proposed mechanism is that chronic volume deprivation of the single ventricle contributes to diastolic dysfunction in patients with Fontan circulation.[19,48] The presence of diastolic dysfunction is particularly detrimental in patients with Fontan circulation because it leads to further elevations in pulmonary vascular resistance, which plays a key role in the development of Fontan circulatory failure.[49]

Among adults, echocardiography can identify those with elevated LV filling pressures with a high degree of accuracy.[50,51] Among children, however, assessment of diastolic function is challenging and requires incorporation of multiple diastolic parameters.[52,53] Abnormalities in diastolic function have been identified in children with tetralogy of Fallot,[54–57] aortic valve disease,[58] and single-ventricle congenital heart disease.[59,60] However, pediatric studies correlating echocardiography-derived diastolic indices with invasive estimation of ventricular filling pressures are lacking, both in healthy children and in those with congenital heart disease, and should be a key area for subsequent research. For those with congenital heart disease and HFpEF, similar to adult patients with HFpEF, we suggest obtaining an invasive estimation of filling pressures at rest or with provocation (exercise, fluid challenge) to improve the specificity of HFpEF diagnosis.[22]

COMORBIDITIES AND HF IN CONGENITAL HEART DISEASE

Arrhythmias, cyanosis, and pulmonary hypertension are cardiac comorbidities that have the potential to worsen HF in those with congenital heart disease. Fontan-specific comorbidities such as protein-losing enteropathy and plastic bronchitis have been highlighted in a prior American Heart Association scientific statement[61] and are not discussed in this section.

Arrhythmia

The presence of atrial and ventricular arrhythmias or a pacemaker is associated with the development of HF in those with congenital heart disease.[62] Arrhythmias are not uncommon after congenital heart disease surgery and can exacerbate HF, particularly in those with concomitant or underlying systolic or diastolic dysfunction.[63] In patients with Fontan circulation, the occurrence of arrhythmias (atrial/ventricular) and sinus node dysfunction and the need for pacemaker placement have been shown to portend an increased risk for Fontan circulatory failure, need for a heart transplantation, and death during subsequent follow-up.[61]

Cyanosis

Cyanosis is common in patients with Fontan circulation and is often noticed in those with elevated pulmonary arterial (Fontan) pressures in whom veno-venous collaterals form to serve as a "pop-off."[61] Chronic cyanosis

Table 2. Anatomical Classification of Pediatric Congenital Heart Disease[29,30]

	Unrepaired congenital heart disease	Repaired congenital heart disease
Simple lesions	Small shunt lesions (ASD, VSD, PDA) Isolated mild semilunar valve (aortic or pulmonary) stenosis or regurgitation PAPVR (single vein)	ASD, VSD, PDA (any size) without chamber enlargement
Unrepaired or repaired congenital heart disease		
Moderate complexity	Congenitally corrected transposition TGA (with intact ventricular septum, VSD, associated complex lesions [LVOTO, coarctation]) DORV (transposition type, Fallot type, VSD type, doubly committed VSD, intact ventricular septum) Truncus arteriosus Aortopulmonary window PAPVR (multiple veins) TAPVR Congenital atrioventricular valve abnormalities (tricuspid/mitral valve dysplasia, stenosis, or regurgitation) AVSD (partial or complete) TOF Moderate or severe semilunar valve (aortic or pulmonary) stenosis or regurgitation Anomalous origin of the coronary artery Ebstein anomaly Coarctation of aorta	
High complexity	Single-ventricle congenital heart disease (anatomical or functional single ventricle unrepaired or s/p palliation [Fontan]) Cyanotic congenital heart disease Repaired congenital heart disease with residual significant residual hemodynamic lesion (eg, Shone complex with residual supramitral, subaortic obstruction)	

ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; DORV, double-outlet right ventricle; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction; PA, pulmonary artery; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; s/p, status post; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

decreases mitochondrial enzyme activity and increases lactate production in cardiomyocytes, leading to inefficient myocardial mechanics.[64,65] In addition, polycythemia, which is often seen in patients with congenital heart disease with chronic cyanosis, can predispose patients to thrombosis secondary to sludging. This can affect coronary blood flow and contribute to ventricular dysfunction.[66]

Pulmonary Hypertension

Pulmonary hypertension in the presence of congenital heart disease can affect subpulmonary and subaortic (systemic) ventricular-to-ventricular interactions and decrease pulmonary venous return to the systemic ventricle, ultimately leading to ventricular dysfunction and HF.[67,68] The definition of pulmonary hypertension in congenital heart disease in patients with biventricular circulation is a mean pulmonary artery pressure ≥25 mm Hg with a pulmonary capillary wedge pressure <15 mm Hg and pulmonary vascular resistance index >3 Wood units·m^2. In patients with single-ventricle congenital heart disease, it is defined as a mean transpulmonary gradient of >6 mm Hg or a pulmonary vascular resistance index >3 Wood units·m^2.[69] The presence of pulmonary hypertension has the potential to increase morbidity and mortality in children with congenital heart disease and HF.[70]

End-Organ Dysfunction

Patients with congenital heart disease are at increased risk of end-organ dysfunction, particularly renal, hepatic, and pulmonary disease, as a consequence of perioperative acute kidney or liver injury, hemodynamic consequences such as high central venous pressure and low cardiac output as seen in some patients with Fontan circulation, chronic hypoxia, and medications.[18,61] The prevention and prompt treatment of noncardiac comorbidities across the life span have the potential to mitigate progression of HF and improve outcomes. Acute kidney injury is common after congenital heart disease surgery, and although the data are sparse, there is an increasing concern that chronic kidney injury will become more prevalent in the congenital heart disease population as it ages.[71] Chronic kidney injury has the potential to worsen HF and increase the risk of adverse events with pharmacological or advanced HF therapies.[14,72,73] Patients with congenital heart disease lesions associated with elevated central venous pressures such as those with Fontan circulation, Ebstein anomaly, lesions with significant RV dysfunction, or tricuspid insufficiency are at risk for cirrhosis and hepatocellular carcinoma.[74] The presence of liver dysfunction can potentially increase the risk of adverse events associated with pharmacological therapies and morbidity and mortality after ventricular assist device implantation or heart transplantation.[14,72]

GENETIC TESTING FOR CHILDREN WITH CONGENITAL HEART DISEASE TO IDENTIFY THOSE AT INCREASED HF RISK

Genetic testing has the ability to identify children and adolescents with congenital heart disease who may be at increased risk for developing cardiomyopathy, ventricular dysfunction, and HF. Genotype-phenotype correlations for congenital heart disease and LV noncompaction are increasingly being understood. Mutations in α-dystrobrevin have been found in children with LV noncompaction and hypoplastic left-heart syndrome[75]; mutations

in NKX2.5 have been found in children with atrial septal defects and LV noncompaction[76]; and mutations in β-myosin heavy chain have been seen in those with Ebstein anomaly and LV noncompaction.[77] In addition, children with Noonan syndrome are at risk for multiple congenital heart diseases (pulmonary stenosis, septal defects, atrioventricular canal defects, mitral/aortic stenosis, coarctation) but also for hypertrophic cardiomyopathy.[78] These children with Noonan syndrome are at higher risk for presenting in HF than those with other forms of hypertrophic cardiomyopathy.[79]

It is important to have a high index of suspicion and offer genetic testing for children and adolescents with congenital heart disease who have phenotypic features of cardiomyopathy or if they have ventricular dysfunction that cannot be explained by their underlying anatomical or physiological state because it may have important implications for follow-up and counseling.

ASSESSING HF SEVERITY IN CONGENITAL HEART DISEASE

The overall grading of HF severity in children is based on patient or parent reporting of signs and symptoms. The New York Heart Association classification has been validated as a predictor of worse outcome in adults and may be used to assess overall signs and symptoms of HF in older children and adolescents.[22,80] The Ross HF classification was proposed as a means to assess HF severity in infants and younger children and has been used as an outcome measure in pediatric HF trials.[81] A revision of the Ross classification that is age based and incorporates hepatomegaly, echocardiographic measures, and NT-proBNP was recently proposed but has been challenging to adopt in clinical practice.[82] Patient- and parent-reported health-related quality of life can also be valuable in identifying changes in HF severity and the impact of HF on daily living activities. The symptoms and signs of acute decompensated HF in children, similar to adults, can be evaluated by assessment of perfusion (warm or cold) and congestion (dry or wet). However, the prognostic importance of these categories has not been studied in children with congenital heart disease. Figure 1 proposes a framework that can be used to characterize the severity of HF in children with congenital heart disease and chronic HF. The intent is to use a comprehensive approach that incorporates not only functional class (Ross or New York Heart Association) but also growth percentiles, natriuretic peptides, exercise limitations, invasive measurements of cardiac hemodynamics, and number of HF hospitalizations to provide a more sensitive method to grade HF severity. There are currently no HF severity scales for children and adolescents with congenital heart disease. Using this approach will help standardize assessment of HF severity and serve as a meaningful end point for clinical studies. When this HF severity grading is used, it is important to note that children and adolescents with congenital heart disease do not have to meet all the proposed criteria to meet a HF severity grade. The aim is to be sensitive; hence, the presence of any one or a combination of factors should be used to identify the highest grade of HF severity. In addition, it is important to know that HF severity is fluid and can change with therapy (eg, go from moderate to mild HF grade).

Circulating Biomarkers

Biomarkers such as natriuretic peptides (BNP [B-type natriuretic peptide] and NT-proBNP) can help guide response to HF therapies and provide useful prognostic information among adults with HF.[22] It is notable that natriuretic peptide concentrations are influenced by age (higher in infants) and other comorbidities (obesity, renal dysfunction, pulmonary hypertension).[83,84] Although the data are limited, among children with congenital heart disease, natriuretic peptide levels correlate with ventricular volumes, ventricular function, volume and pressure load to the ventricle, and worsening New York Heart Association functional class.[85,86] Other promising biomarkers that need further exploration in children with congenital heart disease and chronic HF are insulin-like growth factor 1,[87] red cell distribution width,[88,89] and C-reactive protein.[90]

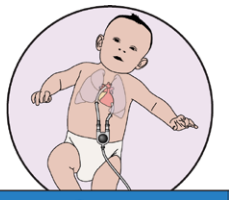
Exercise Testing

Exercise performance measured with cardiopulmonary exercise testing has demonstrated value for monitoring children with congenital heart disease and chronic congestive heart failure.[91–94] Children and adolescents with Fontan physiology are noted to have lower peak oxygen capacity as they age.[95,96] Among patients with Fontan circulation, peak heart rate, heart rate reserve, and exercise oscillatory ventilation are promising markers that have been shown to predict future death or need for heart transplantation.[97] As noted in Figure 1, serial myocardial oxygen consumption (MVO_2) assessment on metabolic stress tests can be used to characterize the severity of HF in children with congenital heart disease. It is important to note that young children (≤8 years of age) may not be able to perform a maximal test; hence, using this test is less helpful in assessing HF severity in that age group.[98] Serial exercise testing can also allow the implementation of cardiac rehabilitation strategies that may reduce the decline in exercise capacity in children with congenital heart disease and chronic HF.[99]

Invasive Assessment

Invasive hemodynamic assessment is routinely used in risk stratification among adults with HF.[100] In children with congenital heart disease, cardiac catheterization



HEART FAILURE SEVERITY	None	Mild	Moderate	Severe
Heart Failure Class NYHA (age ≥5 y) Ross (age <5 y)	1	2	3	4
Growth Percentile (weight-for-length)	z-scores between −2 and 2	z-scores <−2 and −3	z-scores between <−3 and −4	z-scores <−4
Natriuretic Peptides* BNP NT-Pro BNP	Normal	2x higher	>2–4x higher	>4x higher
MVo_2 on Metabolic Exercise Stress Test*	>75% predicted	50–74% predicted	25–49% predicted	<25% predicted
Invasive Measurements CI VEDP	>2.5 L/min/m^2 <15 mm Hg	1.5–2.4 L/min/m^2 15-17 mm Hg	<1.5 L/min/m^2 18-20 mm Hg	<1.5 L/min/m^2 >20 mm Hg
Heart Failure Hospitalizations in the Past Year	None	1	2	≥2

Figure 1. Grading the severity of chronic heart failure in children and adolescents with congenital heart disease.
BNP indicates brain natriuretic peptide; CI, cardiac index; MVo_2, myocardial oxygen consumption; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and VEDP, ventricular end-diastolic pressure.
*Compared with other children with similar congenital heart defects.

is useful in the assessment of systemic ventricular filling pressures and pulmonary vascular resistance and reactivity; evaluation of anatomic contributors to systemic ventricular dysfunction such as pressure or volume overload; and evaluation of the sources of cyanosis.[61,101] Comprehensive hemodynamic evaluation in children with congenital heart disease and intractable HF is critical to the assessment of suitability for advanced therapies (ventricular assist device and heart transplantation) and risk stratification before the use of these therapies.

HF STAGES IN CHILDREN WITH CONGENITAL HEART DISEASE

Although HF is defined as a complex clinical syndrome, identifying patients at risk or in the pre-HF stage has proved useful in the conduct of clinical trials and the development of care guidelines and treatment algorithms for the adult HF population.[22] Similar to adult criteria, ventricular function is an important factor in determining HF stage; however, the presence of complex anatomical and physiological cardiac abnormalities, the frequency of noncardiac anomalies, and the confounding effects of arrhythmias, cyanosis, and pulmonary vascular disease can accelerate the development of HF in the congenital heart disease population.[18]

Figure 2 proposes a framework to help standardize HF stages for the congenital heart disease population. The criteria for staging are based not only on ventricular function but also on the presence of conduction system abnormalities (complete heart block or arrhythmias) and other important comorbidities.

MEDICAL MANAGEMENT

Before pharmacological therapies are considered in patients with congenital heart disease, recognition and management of residual lesions (ie, shunts, atrioventricular valve regurgitation, recoarctation) and sequelae of congenital heart disease (ie, aortopulmonary collaterals, hypoxia) should be optimized.[101] Interventions to improve nutrition, prevent and treat cardiac comorbidities, relieve anemia, and promote exercise and psychological health should be instituted in all patients with congenital

heart disease. Given the paucity of data in the congenital heart disease population, pharmacological management of chronic HF is based on the potential benefit of adult guideline-directed medical therapies. However, the impact of pharmacological therapies on the unique pathophysiology and anatomy of the various congenital heart disease lesions and the potential for adverse events due to the presence and degree of renal/hepatic and other noncardiac comorbidities must also be carefully considered.

Nutrition

Children with congenital heart disease and HF are at risk for illness-related malnutrition attributable to increased metabolic demands, decreased intake, and malabsorption of nutrients. It is well known that poor nutrition can lead to muscle weakness, infection, and poor wound healing.[102] Optimizing nutrition is crucial to improving strength and reducing stress and fatigue related to cardiac insufficiency.[103] Children with evidence of growth failure (declining growth percentiles or changes in *z* scores) should be referred for nutritional assessment by a dietician. In children and adolescents with congenital heart disease who are malnourished, it is important to evaluate for deficiency of micronutrients, iron, vitamin D, and carnitine and, in those with Fontan circulation, assess for protein-losing enteropathy. Hypercaloric formula or expressed breast milk, pediatric formulas, addition of fats to solid food intake, and enteral support through a nasogastric tube may be necessary to help meet the increased metabolic demands posed on children with congenital heart disease and HF. For those with significant malnourishment, parenteral nutrition may also be needed. Obesity is also common in children with congenital heart disease.[104] Obesity is associated with decreased exercise tolerance and the development of hypertension and diabetes, all risk factors for the development of acquired heart diseases that can exacerbate HF.

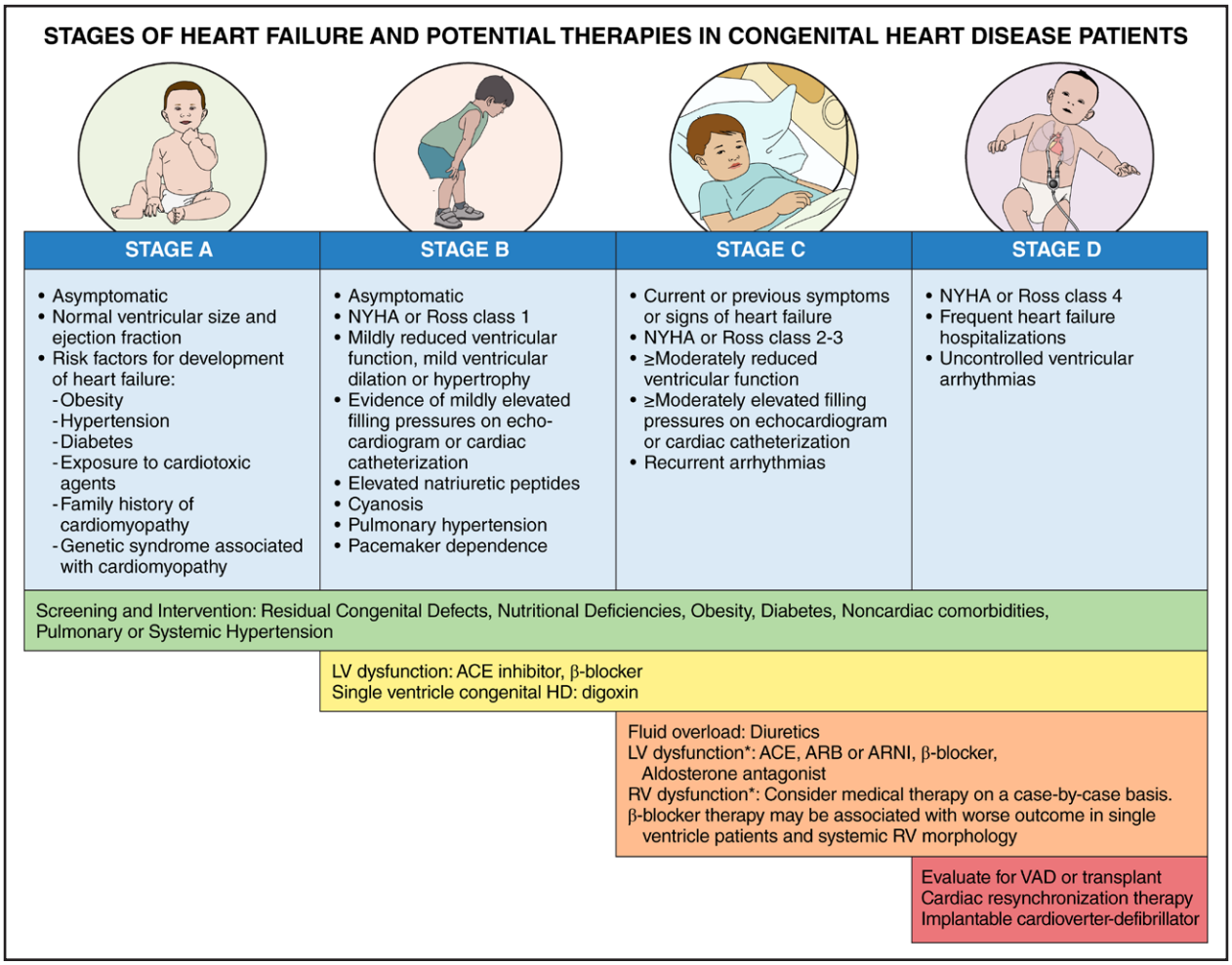


Figure 2. Stages of heart failure and potential therapies in patients with congenital heart disease.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibition; HD, heart disease; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; and VAD, ventricular assist device.
*Caution advised in presence of hepatic or renal dysfunction.

Iron Repletion

Anemia and iron deficiency are associated with worse outcomes in children with HF.[105] Treatment of iron deficiency is important, and consideration for intravenous therapy should be given because of the low efficacy of oral iron therapy in children, including among children with congenital heart disease.[106]

Blood Pressure Control

Blood pressure control is important to avoid exacerbation of HF. This may be a consequence of a previous congenital lesion (eg, coarctation of aorta) or secondary to kidney disease. Regardless of the cause, long-standing hypertension can contribute to cardiac dysfunction, and after residual lesions are ruled out, blood pressure management is critical to avoid worsening HF.[18] In patients with refractory hypertension, consultation with nephrology should be considered.

PHARMACOLOGIC TREATMENT OF CHRONIC HF IN CONGENITAL HEART DISEASE

There is a paucity of evidence to support the use of adult guideline-directed therapies for HF in patients with congenital heart disease. To date, only 2 randomized clinical trials of HF therapies in pediatric patients with congenital heart disease have been performed, 1 trial with enalapril[107] and the other with carvedilol,[108] and both failed to demonstrate benefit in those with subaortic right or single-ventricle anatomy. The Canadian Cardiovascular Society and the International Society for Heart and Lung Transplantation have published recommendations for the evaluation and management of HF in children with cardiomyopathy, but neither of these documents provides recommendations for children with congenital heart disease.[109,110]

In patients with congenital heart disease with reduced ventricular EF, empirical use of adult therapies is often considered, particularly in the setting of biventricular physiology and a systemic LV. The congenital heart disease population has a high incidence of extracardiac comorbidities that need to be considered in the assessment of the potential safety of any long-term HF therapies. This section aims to highlight studies to date that have evaluated the impact of HF therapies in the congenital heart disease population, which has been limited.

Renin-Angiotensin-Aldosterone System Inhibitors

A randomized, placebo-controlled trial of enalapril in infants with single ventricle and normal to mildly reduced EF did not improve somatic growth, ventricular function, or HF severity.[107] A post hoc analysis demonstrated that adverse events were not significantly different between those on enalapril and those on placebo for HF therapy.[111] The US Food and Drug Administration has recently approved sacubitril/valsartan for pediatric patients with symptomatic HF who are >1 year of age.[112] A randomized trial in children with HF is ongoing, but patients with single-ventricle or a systemic RV were excluded from participation in this trial.[113] Renin-angiotensin-aldosterone system inhibitors may be considered in children and adolescents with congenital heart disease and systemic LV dysfunction, especially those with hypertension. For those with systemic RV, these may be considered on a case-by-case basis.

β-Blockers

The efficacy of carvedilol was studied in a randomized, placebo-controlled trial in symptomatic children with HF of various causes.[108] This trial failed to demonstrate a benefit in the study population. A prespecified analysis found that although patients with systemic LV dysfunction trended toward improvement, patients with congenital heart disease and a systemic RV or single ventricle treated with carvedilol trended toward a worse outcome than the placebo group. An ex vivo study of single RV failing hearts demonstrated a unique response of the β-adrenergic signaling pathways compared with failing biventricular hearts.[114] These data suggest that β-blocker therapy could disrupt adaptive contractile responses and, paired with the carvedilol clinical trial results, support caution when β-blocker therapy is considered for those with single-ventricle and systemic RV morphology.

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists have antifibrotic properties and promote reverse remodeling of the dysfunctional ventricle. Mineralocorticoid receptor antagonist use has shown improvements in all-cause mortality, HF hospitalizations, and sudden cardiac death in adult patients with HF with reduced EF.[22,115] Among children with single-ventricle congenital heart disease and underlying RV morphology, it has been noted that fibrosis is not a primary contributor to RV failure; hence, mineralocorticoid receptor antagonists may not be effective in reverse remodeling in this cohort.[19,116]

Digoxin

Digoxin has been used empirically in patients with a single ventricle at risk for HF. An observational cohort study from the National Pediatric Cardiology Quality

Improvement Collaborative found that among patients with single-ventricle congenital heart disease after stage 1 palliation and with no history of arrhythmia, those discharged on digoxin had lower interstage mortality.[117] In a post hoc analysis of the prospective Pediatric Heart Network Single Ventricle Reconstruction Trial, digoxin use in infants with single-ventricle congenital heart disease was associated with significantly reduced interstage mortality.[118] The authors postulated that the indication for placing the patients with a single ventricle on digoxin was ventricular dysfunction or HF because patients who were treated for arrhythmias were excluded from the analysis.

Diuretic Agents

Diuretics play a key role in the management of patients with evidence of fluid overload in the setting of HF. Although there are limited data on their relative efficacy in pediatric HF, adult HF data show that the use of diuretics effectively relieves congestive symptoms, improves quality of life and exercise tolerance, and prevents worsening HF.[22,119] Diuretics can be used to treat symptoms of fluid overload in patients with congenital heart disease with HF. Loop diuretics are the preferred choice, although the addition of thiazide diuretics significantly enhances loop diuretic effect and can be added in patients with limited loop diuretic response and to prevent calcinuria and nephrocalcinosis associated with long-term loop diuretic use.[119,120]

Additional Pharmacological Therapies

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors have now demonstrated benefits in adult patients with HF across the LVEF spectrum.[121,122] Although some experience in adults with congenital heart disease suggests that sodium-glucose cotransporter-2 inhibitors may be safe and efficacious, even in those with systemic RV, its safety and efficacy among children with congenital heart disease and HF need to be determined.[123,124]

Ivabradine

SHIFT [Systolic Heart Failure Treatment With the *I*(f) Inhibitor Ivabradine Trial] demonstrated the efficacy of ivabradine, a sinoatrial node modulator that selectively inhibits the *I*(f) current, in reducing the composite end point of cardiovascular death or HF hospitalization in adult patients with reduced LVEF.[125] An international randomized multicenter study in children with dilated cardiomyopathy demonstrated an improvement in NT-proBNP, LVEF, and New York Heart Association functional class among ivabradine-treated patients.[126] To date, no studies of ivabradine have been performed in patients with congenital heart disease with HF.

Soluble Guanylyl Cyclase Stimulators

In patients with worsening HF despite guideline-directed medical therapy, there may be a role for novel drugs such as oral soluble guanylyl cyclase stimulator (eg, vericiguat). This drug directly binds and stimulates soluble guanylyl cyclase and increases cGMP production with potential beneficial effects of vasodilation, improved endothelial function, decreased fibrosis, and positive remodeling of the heart (the VICTORIA vericiguat trial [A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction (HFrEF) (MK-1242-001)]).[127] A randomized controlled pediatric HF trial is currently recruiting children with reduced LVEF, including those with congenital heart disease and a biventricular circulation.[128]

RHYTHM MANAGEMENT

As with other forms of HF, it is critical to identify arrhythmias that could be contributing to HF in patients with congenital heart disease. Arrhythmias can manifest as bradycardia, complete heart block, or atrial and ventricular tachycardias. Atrial and ventricular tachyarrhythmias are prevalent in patients with congenital heart disease and represent a risk for HF, thromboembolism, and sudden cardiac death.[63,129,130] It is notable that arrhythmia burden increases with age and is influenced by postsurgical anatomy, disruption of cell-cell electrical coupling, myocardial scarring, chronic volume or pressure loading, electromechanical dyssynchrony, and genetic predisposition.[130] Therefore, correction of residual lesions or an electrophysiology study may be considered to minimize arrhythmogenic substrates. Permanent pacing and cardiac resynchronization therapy can be considered to restore the efficiency of myocardial work in patients with a suitable structural substrate. Recently pediatric guidelines for implantation of pacemakers and implantable cardioverter defibrillators for children with congenital heart disease have been developed to aid in decision-making.[130] Specialists with expertise in congenital heart disease electrophysiology are an integral part of the approach to management given the complex nature of arrhythmias, side effects of many of the antiarrhythmic strategies, and challenges with device implantation in patients with congenital heart disease with HF.

THERAPIES FOR CONGENITAL HEART DISEASE WITH ADVANCED HF

The availability and expertise in the use of mechanical circulatory support therapies for patients with congenital heart disease are increasing; these therapies are now commonly used to support children with congenital heart disease and advanced HF (stage D HF,

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Figure 2).[131–134] Common options for support in infants and small children include a pulsatile device (EXCOR; Berlin Heart Inc, Berlin, Germany) or a continuous-flow device (PediMag and CentriMag, Abbott, Chicago, IL; or Rotaflow, Getinge, Gothenburg, Sweden).*[135] Ventricular support in single-ventricle anatomy can pose challenges. A higher cardiac index is required in patients with single-ventricle heart disease to support the parallel systemic and pulmonary circulations. Patients with a single ventricle <0.7 m^2 after a superior cavopulmonary shunt may require conversion to stage 1 physiology before implantation because of the difficulty in ensuring adequate venous return to the device.[132] In larger patients with a superior cavopulmonary anastomosis, completing the Fontan circulation at the time of ventricular assist device implantation has demonstrated superior survival.[132,136] After the Fontan procedure, an intracorporeal ventricular assist device is an option if the body size is >1.0 m^2. In patients with congenital heart disease with an elevated pulmonary vascular resistance, significant restrictive physiology, or the presence of complex intracardiac structural abnormalities, implantation of the total artificial heart (Syncardia, Inc, Tucson, AZ)* or conversion to biventricular support (denoting the anastomosis of the systemic inferior and superior venous return to a right-sided ventricular assist device, in addition to incorporating a second device for the systemic ventricle) may be considered.[132,133]

For patients with stage D HF, the timing for heart transplantation is crucial.[137] Transplantation may be considered not only in patients who are inotrope dependent or receive durable mechanical circulatory support but also in those with worsening exercise intolerance, diminished quality of life, presence of extracardiac organ dysfunction, lymphatic dysfunction (protein-losing enteropathy or plastic bronchitis), or growth/pubertal failure secondary to advanced HF.[137,138] It is important to initiate referral for advanced HF therapies before the onset of progressive end-organ dysfunction. To ensure longitudinal success for the congenital heart disease HF population after heart transplantation, it is important to identify and mitigate the following factors during the wait-list and posttransplantation periods: (1) nutritional and physical deconditioning, (2) end-organ dysfunction (ie, liver and kidney), (3) aortopulmonary collateral flow, (4) allosensitization, and (5) anatomical abnormalities that require surgical reconstruction at the time of heart transplantation.[132,139] Together, these factors highlight the importance of a timely referral and judicious preparation and the need to assemble a multidisciplinary team with great depth of experience in the medical and surgical care of congenital heart disease and in advanced HF therapies to ensure optimal outcomes.

*The devices mentioned in this statement serve only to illustrate examples of these types of devices. This is not intended to be an endorsement of any commercial product, process, service, or enterprise by the American Heart Association.

CONCLUSIONS

HF is a growing concern because survival of patients with even the most complex congenital heart disease lesions has markedly improved. HF has become the leading cause of mortality in the adult congenital heart disease population, and addressing the substrate for HF in the pediatric population has become imperative. The recognition and treatment of factors placing pediatric patients with congenital heart disease at risk for development of HF have the potential to prevent or slow the progression of this deadly disease. In addition to focusing on surveillance specific to the congenital heart disease lesion, evaluation of a child with congenital heart disease should include assessments for HF at every age and stage. An example of a suggested clinical protocol that could be used to monitor patients with congenital heart disease by HF stage is illustrated in Figure 3.

Significant knowledge gaps exist in the understanding of the epidemiology and risk factors for HF in specific congenital heart disease lesions. Harmonizing the definitions, staging, follow-up, and approach to HF in patients with congenital heart disease among health care professionals is critical to allow multi-institutional collaboration and standardized analysis. The knowledge gaps in demonstrating the effectiveness of adult HF therapies in patients with congenital heart disease are substantial. The potentials for harm from medical therapy are higher in patients with congenital heart disease because of the frequency of noncardiac comorbidities. The feasibility of conducting prospective, randomized controlled trials with clinical end points in this population is low because of the heterogeneous diagnoses, small sample size, and low frequency of clinical events in children. Studies assessing the safety and efficacy of HF therapies using novel clinical trial designs, patient-reported outcome measures, bridging biomarkers,[140] real-world big datasets, and detailed analytics leveraging machine learning and artificial intelligence should be explored. Unique mechanisms contributing to the failing single-ventricle heart and the vulnerable RV are beginning to emerge through preclinical and ex vivo work and could contribute to identification of novel therapeutic targets.[141–147] Advancements in this arena will require a partnership among researchers, health care professionals, patients, caregivers, and public and private funding agencies to generate high-quality data and identify optimal therapies for the pediatric congenital heart disease HF population.

SUGGESTED CLINICAL PROTOCOL FOR HEART FAILURE ASSESSMENT

	STAGE A	STAGE B	STAGE C	STAGE D
Frequency of Evaluation	At time of routine visit	Every 6-12 mo	Every 3-6 mo	Every 4-6 wk or as clinically indicated
Clinical Assessment	NYHA or Ross	NYHA or Ross	• NYHA or Ross • Congestion and perfusion assessment	• NYHA or Ross • Congestion and perfusion assessment
Imaging	• Echocardiogram every 2 y • MRI or CT as clinically indicated	• Echocardiogram every 6 mo • MRI or CT every 2 y or as clinically indicated	• Echocardiogram every 3-6 mo • MRI or CT as clinically indicated*	• Echocardiogram, • MRI or CT as clinically indicated*
Rhythm Assessment	• ECG at visit • Rhythm monitoring as clinically indicated	• ECG at visit • Rhythm monitoring every 2 y or as clinically indicated	• ECG at visit • Rhythm monitoring yearly or as clinically indicated†	• ECG and rhythm monitoring as clinically indicated†
Lab Assessment	-	BNP, NT pro-BNP at visit	• BNP, NT pro-BNP at visit • Liver and renal function at visit	• BNP, NT pro-BNP as clinically indicated • Liver and renal function as clinically indicated
Exercise Testing	As clinically indicated	Exercise testing at visit	Exercise testing yearly	As clinically indicated
Cardiac Catheterization	As clinically indicated	As clinically indicated	As clinically indicated	At time of presentation of stage D heart failure

Figure 3. Suggested clinical protocol for monitoring patients with congenital heart disease by heart failure stage.
BNP indicates brain natriuretic peptide; CT, computed tomography; MRI, magnetic resonance imaging; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.
*Care should be taken before administration of anesthesia or contrast. Consultation with cardiac anesthesiologist or nephrologist may be needed.
†Consultation with the electrophysiology team for consideration of either an implantable cardioverter defibrillator or cardiac resynchronization therapy as needed.

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Significant.

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