Circulation

AHA SCIENTIFIC STATEMENT

Treatment Strategies for Cardiomyopathy in Children: A Scientific Statement From the American Heart Association

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ABSTRACT: This scientific statement from the American Heart Association focuses on treatment strategies and modalities for cardiomyopathy (heart muscle disease) in children and serves as a companion scientific statement for the recent statement on the classification and diagnosis of cardiomyopathy in children. We propose that the foundation of treatment of pediatric cardiomyopathies is based on these principles applied as personalized therapy for children with cardiomyopathy: (1) identification of the specific cardiac pathophysiology; (2) determination of the root cause of the cardiomyopathy so that, if applicable, cause-specific treatment can occur (precision medicine); and (3) application of therapies based on the associated clinical milieu of the patient. These clinical milieus include patients at risk for developing cardiomyopathy (cardiomyopathy phenotype negative), asymptomatic patients with cardiomyopathy (phenotype positive), patients with symptomatic cardiomyopathy, and patients with end-stage cardiomyopathy. This scientific statement focuses primarily on the most frequent phenotypes, dilated and hypertrophic, that occur in children. Other less frequent cardiomyopathies, including left ventricular noncompaction, restrictive cardiomyopathy, and arrhythmogenic cardiomyopathy, are discussed in less detail. Suggestions are based on previous clinical and investigational experience, extrapolating therapies for cardiomyopathies in adults to children and noting the problems and challenges that have arisen in this experience. These likely underscore the increasingly apparent differences in pathogenesis and even pathophysiology in childhood cardiomyopathies compared with adult disease. These differences will likely affect the utility of some adult therapy strategies. Therefore, special emphasis has been placed on cause-specific therapies in children for prevention and attenuation of their cardiomyopathy in addition to symptomatic treatments. Current investigational strategies and treatments not in wide clinical practice, including future direction for investigational management strategies, trial designs, and collaborative networks, are also discussed because they have the potential to further refine and improve the health and outcomes of children with cardiomyopathy in the future.

Key Words: AHA Scientific Statements ■ cardiomyopathies ■ child ■ heart diseases ■ precision medicine

Pediatric cardiomyopathy is an uncommon but life-threatening disease affecting 1 in 100 000 children. There are many pathogeneses, but in aggregate, cardiomyopathy remains a leading cause of heart transplantation in childhood. Lipshultz et al[1] previously published an American Heart Association (AHA) scientific statement focused on the classification and diagnosis of cardiomyopathy in children. This follow-up scientific statement discusses treatment strategies for pediatric cardiomyopathies with an emphasis on dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) and 2 areas of focus: the unique variation of causes of pediatric cardiomyopathy that guide management and pediatric cardiomyopathy as a problem for which therapeutic considerations exist for patients who are at risk for developing cardiomyopathy, patients with asymptomatic cardiomyopathy, patients with symptomatic cardiomyopathy, and those with end-stage disease. Treatment strategies specifically for left ventricular (LV) noncompaction, restrictive cardiomyopathy (RCM), and

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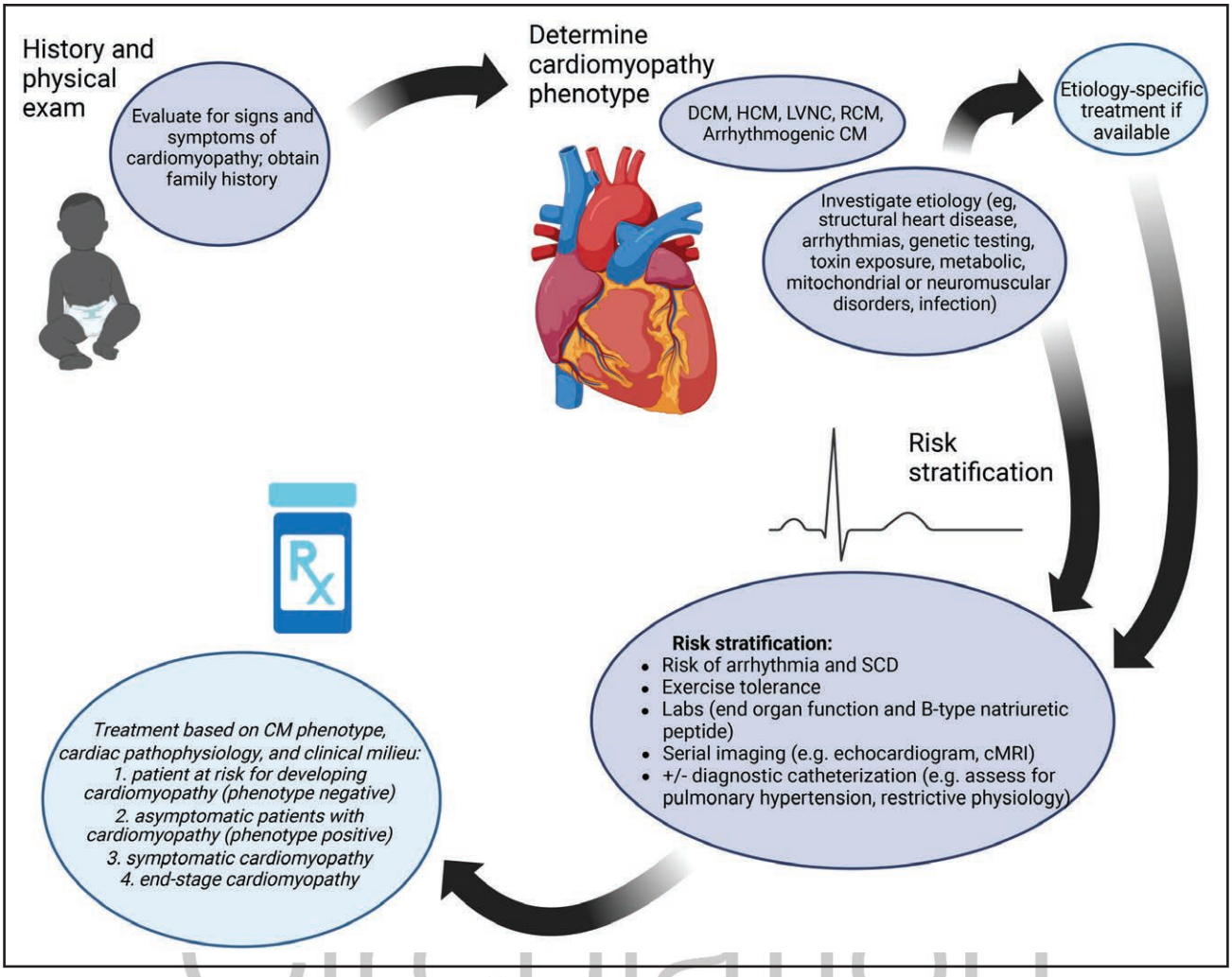

Figure 1. Central illustration of the article.
CM indicates cardiomyopathy; cMRI, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; and SCD, sudden cardiac death.

arrhythmogenic cardiomyopathy are discussed but in less detail. Figure 1 shows the central illustration of this article.

STAGES OF CARDIOMYOPATHY IN CHILDREN

Dilated Cardiomyopathy

Strategies for Treating Pediatric DCM

Recent AHA guidelines have proposed a 4-stage system for therapeutic interventions in adult heart failure (HF).[2] In stage A (at-risk patients), the patient is at risk for HF but has no structural heart disease or symptoms of HF. Stage B (asymptomatic patients) is characterized by structural heart disease but without signs or symptoms of HF. Stage C (symptomatic patients) is marked by cardiomyopathic heart disease with current or past symptoms of HF. Patients with stage D disease (refractory patients) have refractory HF requiring specialized interventions. This staging system can be harmonized with the various clinical milieus one can observe in pediatric DCM as a framework with which to consider specific therapeutic interventions.

Over the past 3 decades, a series of large, randomized, placebo-controlled clinical trials in adults with HF associated with reduced LV ejection fraction found that certain drugs reduced the incidence of hospitalization and mortality. These drugs are angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, angiotensin receptor/neprilysin inhibitors, ivabradine, and most recently sodium-glucose cotransporter 2 inhibitors. Although there are evidence-based, goal-directed medical therapy treatment algorithms that are often updated by the AHA,[3] the American College of Cardiology,[4] and the European Society of Cardiology[5] (Figure 2),[4] a similar evidence basis does not yet exist for children.

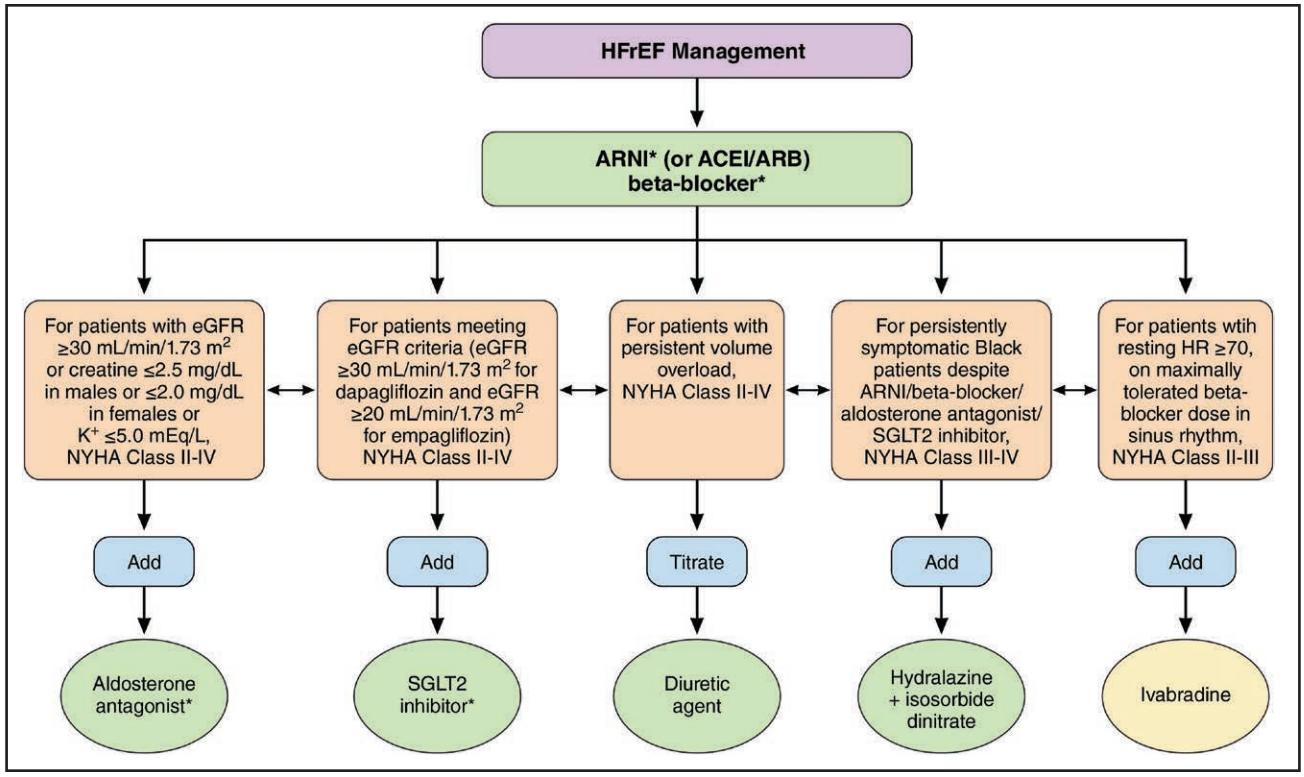

Figure 2. The most recent revision of American College of Cardiology/AHA treatment algorithms for treating adults with HF and reduced left ventricular ejection fraction.

Green ovals show Class I therapy; and yellow oval, Class II therapy. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; NYHA, New York Heart Association; and SGLT2, sodium-glucose contransporter-2. *The 4 Class 1 therapies that are simultaneously initiated in adults with HFrEF. Reprinted from Maddox et al[3] with permission. Copyright © 2021 American College of Cardiology Foundation.

A review of the literature identifies only limited data on managing children with HF. The most recent treatment guidelines, by the International Society for Heart and Lung Transplantation in 2014, include 35 recommendations for pharmacological therapy but only 8 Class I (strong) recommendations supported at best with Level of Evidence B (moderate).[6] Current pediatric guidelines are therefore based primarily on expert consensus and generally mirror the recommended goal-directed medical therapies for adults but with less certainty and overall lower quality of evidence from primarily single-center trials and few large, multicenter trials in children.[6,7]

Another issue in applying goal-directed medical therapy HF guidelines developed for adults to children is that the use of ACE inhibitors and β-blockers for HF with DCM in children has not been shown to improve transplantation-free survival.[8,9] Furthermore, symptoms and outcomes did not improve in a randomized trial of 161 children with HF who received carvedilol in addition to ACE inhibitors.[10] Relative to adult HF populations, there are additional barriers to executing clinical trials in children with heart conditions, including inadequate statistical power associated with small sample sizes, phenotypic heterogeneity, limited observational periods, and age-specific variation in pharmacokinetics and pharmacodynamics. In addition, there is accumulating evidence that HF in children differs in important ways from that in adults, and children lack many of the comorbid conditions present in adults, contributing to the accumulating evidence that HF in children differs in important ways from that in adults.[11,12]

Therefore, although extrapolating the results of studies in adults may be reasonable in certain diseases or age groups, it is not uniformly appropriate across all diseases, underscoring the importance of developing standards for the care of and for conducting studies in children with cardiomyopathy and HF. Current studies of pediatric cardiomyopathies and HF differ widely in the medications used, dosing, frequency of follow-up, and expertise of medical teams. All of these differences, given the lack of multi-institutional data in children, hamper assessment of the responses to therapy.

Unique Characteristics of HF in Children

The pathophysiology of HF in children is similar to that in adults, although increasing evidence indicates

some inherent differences in myocardial adaptations secondary to DCM. The natural history of pediatric DCM also differs from that of adult DCM in that death or transplantation usually occurs within 2 years after presentation with DCM, suggesting that many children and adolescents have advanced disease at presentation.[13,14] These differences may contribute to the differential responses reported in clinical trials in children with HF treated with therapies developed for adults, as discussed previously. For example, total myocardial β-adrenergic receptor expression is decreased in both children and adults with idiopathic DCM, but children downregulate both the β-1 and the β-2 adrenergic receptors, whereas adults downregulate only the β-1 adrenergic receptors.[15] This differential receptor expression could influence the response of children to nonselective β-blocker drugs such as carvedilol because the effects of medical blockade of the already downregulated β-2 adrenergic receptors are unknown.

With respect to the phosphodiesterase system, both children and adults with idiopathic DCM have decreased myocardial cAMP concentrations, but these concentrations improve only in children treated with phosphodiesterase-3 inhibitors (eg, milrinone) and remain low in adults.[16] Although long-term treatment of adults with HF with phosphodiesterase-3 inhibitors is associated with increased morbidity and mortality, several clinical series have reported that long-term use of milrinone in children is safe and efficacious as a bridge to oral HF therapies or transplantation.[17–19] However, there are no large controlled studies on the long-term use of phosphodiesterase-3 inhibitors in children with HF.

Echocardiograms of children with DCM show LV dilation and decreased systolic function, but the extent of adverse cardiac alterations, defined by cardiac fibrosis, cardiomyocyte hypertrophy, inflammation, and capillary loss, is less than in adults with HF.[20–22] Compared with age-matched nonfailing control subjects, coronary microvascular density as assessed by CD34 staining is higher in children with DCM compared with adults. [20] It is important to note that these findings seem unrelated to the time since diagnosis of DCM or the presence of cardiovascular comorbidities (eg, hypertension, chronic kidney disease, diabetes).

Other studies have shown differences in stem cells and their signaling in children with failing hearts compared with those with nonfailing hearts. In a global transcriptome study of (n=37) explanted pediatric DCM hearts, genes associated with pluripotent stem cell signaling (eg, enrichment of WNT, fibroblast growth factor, Notch), cell growth, and differentiation were dysregulated compared with those in age-matched nonfailing donor controls.[21] These results complement the finding that children with end-stage HF have more cardiac stem cells than age-matched children with congenital heart disease but normal cardiac function.[23] In another study of explanted DCM hearts, genes associated with sarcomeric remodeling, inflammation, and fatty acid metabolism were upregulated in adults, whereas genes associated with cell adhesion and ion and transmembrane transport were upregulated in children.[20]

An important point is that differences in DCM between adults and children are not limited to heart tissue. Among 1310 plasma proteins, a DNA aptamer array found 20 peptides and proteins that were significantly increased in pediatric patients with DCM compared with age-matched healthy control subjects and that circulating protein biomarkers differed greatly between children and adults with DCM.[24] Many studies have evaluated microRNAs as biomarkers of HF in adults, and although studies of children are fewer, the circulating microRNA profiles in children are unique compared with the profile seen in adults with DCM. An unbiased array revealed that 4 microRNAs (microRNA-155, -636, -646, and -639) were differentially regulated between children with DCM who required a heart transplantation and those who recovered ventricular function.[25,26] None of these 4 microRNAs are biomarkers of DCM in adults. Although the studies are limited by their cross-sectional nature, they provide a framework for understanding the novel molecular and biomarker signatures associated with pediatric DCM, emphasizing the importance of better understanding the mechanisms of this disease and identifying age-appropriate therapies.

Therapy in Pediatric Patients at Risk for Developing DCM (Phenotype Negative)

The American College of Cardiology and AHA Task Force on Practice Guidelines devised a classification of HF that emphasized the expected progression of heart disease.[2] This classification underscores the important possibility that, for patients in stage A, progression of further HF could be delayed or prevented.

In pediatrics, one of the most recognizable conditions for which this type of categorization is relevant is the dystrophinopathies. The dystrophinopathies, including Duchenne muscular dystrophy (DMD) and the milder Becker muscular dystrophy, are a group of neuromuscular disorders caused by abnormal dystrophin. Treating this condition in Stage A is now being practiced. Although the primary manifestation of dystrophinopathies is skeletal muscle weakness, the incidence of DCM increases with age. Among male individuals with DMD, >50% will have cardiac involvement by 10 years of age, and 90% will have cardiac dysfunction after 18 years of age.[27]

Current treatment guidelines for dystrophinopathies recommend beginning ACE inhibition therapy before adolescence when patients are in stage A (at risk).[28,29]

Initial studies[30,31] suggested that ACE inhibition delayed the development of DCM and ultimately improved survival. A Cochrane review[32] suggested that early use of ACE inhibitors or angiotensin receptor blocker inhibitors may be beneficial, although the quality of the evidence was low. However, a recent retrospective analysis of the French multicenter DMD registry[33] found that ACE inhibition in patients in stage A markedly improved survival and reduced hospitalizations for HF. Early mineralocorticoid receptor inhibition may also stabilize and slow progressive LV systolic dysfunction.[34] These small studies are promising, but larger controlled trials are needed to establish the efficacy of this treatment.

It is estimated that ≈70% of patients with deletions associated with DMD can be treated by single exon skipping.[35] Four US Food and Drug Administration–approved antisense oligonucleotides (AONs) administered as weekly intravenous infusions circumvent this problem by skipping over the mutated exons. AONs consist of 20 to 30 nucleotides that act on the pre-mRNA to splice out the mutated exons, thereby converting an out-of-frame mutation to a less severe in-frame mutation. However, this therapy is limited to certain mutations and by issues of tissue penetration and efficiency because it provides <5% of normal dystrophin content.[36] The cardiac efficacy of AON treatments is unknown.

Adeno-associated virus gene therapy to produce microdystrophin is currently being investigated. Case findings in mild Becker muscular dystrophy have helped identify the essential regions of the gene.[37] Theoretically, adeno-associated virus gene therapy can be used to treat all forms of DMD, regardless of mutation, and requires only a single administration. Furthermore, the amount of dystrophin produced is greater than that of AON therapies, and cardiac expression is expected, given the use of specific cardiac and skeletal muscle promotors.[38] If successful, microdystrophins would be the first gene therapy for a form of childhood-onset cardiomyopathy.

Last, precision gene-editing techniques hold great potential for the development of gene therapies. In particular, delivery of CRISPR/Cas9 nucleases capable of genome editing with delivery through adeno-associated virus vectors has been shown to be feasible in preclinical studies. These studies aim to restore the gene reading frame to produce a truncated but partially active protein, an approach similar to AON treatment. As in gene therapy, gene editing may require only a single administration. Again, given the affinity of certain adeno-associated virus serotypes for the heart, cardiac correction is expected.

Treatment in Pediatric Cardio-Oncology

Advances in cancer therapy and standardization of care over the past decades have substantially improved the number of childhood cancer survivors. Currently, 5-year survival among children with cancer is ≈85%, with an estimated 500 000 survivors as of 2020.[39]

All children who have received cardiotoxic cancer therapies are at risk for HF (stage A disease). Cardiovascular complications such as cardiomyopathy (with progression from a dilated to restrictive physiology)[40] and valvular and vascular dysfunction that can lead to HF are more prevalent in cancer survivors than in the general population. These complications can compromise otherwise successful cancer treatment in childhood and early adulthood[41] unless these complications are addressed.[42]

Risk factors for cardiotoxicity in cancer survivors include higher anthracycline doses, radiation therapy that includes the heart in the treatment field, younger age at diagnosis, female sex, and underlying cardiovascular disease, in addition to the common risk factors for cardiovascular disease.[40] Furthermore, new cancer therapies may be cardiotoxic. Chimeric antigen receptor T-cell therapy manufactures genetically engineered T cells that target cancer cells. During this process, patients are at risk for cytokine-release syndrome, which can cause major cardiac events, including HF. Treatment begun during stage A could prevent cardiovascular events related to this syndrome. For example, anti–interleukin-6 receptor antagonist such as tocilizumab can reduce morbidity and mortality during this stage.[43–46] Small-molecule inhibitors such as tyrosine kinase inhibitors have become first-line treatments for some pediatric cancers and may be useful in treating relapses. Monitoring acute and early-onset cardiac toxicities, including HF, pericardial effusions, and hypertension, is necessary to identify the range of cardiovascular side effects of both new and conventional chemotherapy agents.[44–51]

Immune checkpoint inhibitors, which are increasingly used to treat cancer in adults, are now being studied in children. The cardiotoxic effects of these inhibitors include immune-mediated myocarditis (which can be fulminant) and are reported in ≈1% of adult patients with cancer. These cardiotoxic effects allow risk stratification that can guide the development of preventive measures to reduce further injury to the myocardium.[40,41]

The importance of beginning treatment in stage A for children exposed to cardiotoxic cancer therapies is now beginning to be recognized among practitioners. Furthermore, several genetic variants that may increase the risk of anthracycline-mediated cardiotoxicity can now identify patients most likely to benefit from preventive therapies such as concurrently giving the iron chelator dexrazoxane at the time of anthracycline administration.[52]

Current evidence does not support using standard oral HF therapies to prevent treatment-related cardiotoxicity in asymptomatic children. Instead, consensus statements have emphasized primary prevention strategies such as managing modifiable cardiovascular risk factors (hypertension, hyperlipidemia, obesity, diabetes) and the use of cardioprotective medications.[53,54] Dexrazoxane can prevent or reduce anthracycline-related cardiotoxicity in

adults and children without reducing the effectiveness of cancer therapies or increasing the incidence of secondary malignancies.[55–57] Dexrazoxane is the only drug approved by the US Food and Drug Administration for the primary prevention of cardiac toxicity in adults and has been granted pediatric orphan drug status.[58] Furthermore, in 2017, the European Medicines Agency issued a decision that treatment with dexrazoxane is no longer contraindicated in children expected to receive a cumulative dose of >300 mg/m^2 doxorubicin or the equivalent cumulative dose of another anthracycline.[59–61] The European Medicines Agency found no data indicating that dexrazoxane was associated with an increase in second primary malignancies, interfered with chemotherapy, or increased the risk for early death in children. This recent decision allows virtually all children to receive dexrazoxane starting with the first dose of anthracycline at the discretion of the treating health care professional.

Treating phenotype-negative pediatric patients at risk for developing DCM as described earlier for young children with dystrophinopathies and childhood cancer survivors has the potential to increase survival and to improve the quality of life for these high-risk patients. Identifying genetic, mechanistic-based, or lifestyle modification approaches to treating children with stage A disease and other cardiomyopathies could improve disease prevention and outcomes. Centers with dedicated HF teams have begun to form multidisciplinary teams that have begun to see patients with muscular dystrophy or cancer and survivors. Multidisciplinary programs are a platform to screen, treat, follow, and conduct quality improvement (QI) and research in a systemic approach that will ideally improve outcomes.

Therapy in Pediatric Patients With DCM (Phenotype Positive) Who Are Asymptomatic

Identifying patients in this stage depends primarily on screening those with a family history of cardiomyopathy for an associated genetic variant or those such as dystrophinopathy or childhood cancer survivors who were at risk for developing DCM and undergo periodic surveillance for development of DCM. When cardiomyopathy is identified in a child without a known preexisting risk, panel genetic testing or whole-exome sequencing is recommended. A pathogenic or likely pathogenic variant in the proband should prompt cascade genetic testing of first-degree relatives who are at risk for cardiomyopathy. Cardiac surveillance is no longer necessary for family members with informative negative genetic test results. In 83 consecutive unrelated patients referred for genetic evaluation of cardiomyopathy between 2006 and 2009, 63 had a familial, syndromic, or metabolic basis for their disease.[62] Findings were similar in the study by Ware et al.[63] Therefore, both clinical surveillance and cascade genetic testing for first-degree relatives of probands with cardiomyopathy are important. Indeed, screening guidelines recommend a 3-generation pedigree, cardiac screening, and cascade genetic testing for at-risk family members.[1] The Heart Failure Society of America recommends screening for children with a first-degree relative with DCM: annually for children 0 to 5 years of age, every 1 to 2 years for children 6 to 12 years of age, every 1 to 3 years for children 13 to 19 years of age, every 2 to 3 years for adults 20 to 50 years of age, and every 5 years for adults >50 years of age.[64] Treatment strategies at this stage focus on treating risk factors, intervening in structural heart disease when applicable, and initiating medical therapy with ACE inhibitors. ACE inhibitors are proposed as first-line therapy and β-blockers are also considered for patients with ejection fraction <40% in the recently proposed adult HF guidelines.[4]

Therapy in Symptomatic Pediatric Patients With DCM

The current guidelines for adults with stage C HF (Figure 2) recommend combination therapy with angiotensin receptor/neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors and the addition of ivabradine if the heart rate cannot be reduced enough with β-blockade. A combination of hydralazine and isosorbide dinitrate is recommended for persistently symptomatic Black patients.[4,65]

No large randomized controlled trials have identified effective therapies for stage C HF in children, although most clinical studies in pediatric cardiomyopathy have focused on these patients. A randomized, placebo-controlled trial of carvedilol for treating children with symptomatic HF found no difference between groups in the primary composite outcome.[10] However, several factors made interpretation of this trial challenging. First, symptom improvement in the placebo-treated study subjects was greater than expected and may have been related to the requirement for all subjects to be on ACE inhibitor therapy at the time of enrollment, with many being on additional HF treatments such as digoxin, diuretics, and spironolactone. Second, the trial enrolled subjects with HF from a wide range of diagnoses, including single ventricle and other forms of congenital heart disease. Although the study was not powered to evaluate the primary outcome in DCM specifically, subjects with a systemic LV treated with carvedilol did have an improvement in fractional shortening. In addition, a post hoc analysis[10,66] found that children with a systemic LV treated with carvedilol had echocardiographic evidence of reduced LV size and natriuretic peptide concentrations.

In a recent phase 2/3 randomized trial comparing ivabradine with placebo,[67] most of the 116 children were on ACE inhibitors or angiotensin-receptor blockers (98%), mineralocorticoid receptor antagonists (79%), and β-blockade (76%) after 1 year. Children in the ivabradine group had significantly improved LV ejection fraction and reduced natriuretic peptide concentrations with a trend

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toward improved functional status. In children of all ages, 70% of those receiving ivabradine achieved the targeted 20% reduction in resting heart rate, whereas only 12% of control subjects did. This study made ivabradine the first US Food and Drug Administration–approved medication for treating children >6 months of age with symptomatic HF. Furthermore, the study population expanded to other cardiomyopathies and LV dysfunction beyond DCM.

Most recently the PANORAMA-HF trial (Prospective Trial to Assess the Angiotensin Receptor Blocker Neprilysin Inhibitor LCZ696 Versus Angiotensin-Converting Enzyme Inhibitor for the Medical Treatment of Pediatric HF)[68] compared the effects of sacubitril/valsartan (Entresto) with enalapril in pediatric HF. On the basis of a preliminary data analysis showing improvement in natriuretic peptide levels in subjects 1 to 18 years of age who received sacubitril/valsartan compared with those receiving enalapril, the US Food and Drug Administration approved the use of the drug in children >1 year of age. However, when the primary results of the study were analyzed, no differences in HF outcome measures were seen between the groups 12 months after randomization, including natriuretic peptide levels.[69] The impact of this study on the future use of this combination drug remains to be determined.

The most recent PCMR (Pediatric Cardiomyopathy Registry) report of outcomes of children with DCM[9] found that mortality (but not the rate of heart transplantation) was significantly lower between 2000 and 2010 than between 1990 and 2000. The authors concluded that nontransplantation therapies improved survival, with survival curves diverging both in the first months after diagnosis and during follow-up (Figure 3). Figure 3 shows estimated time to death for children with idiopathic DCM. Children in the early cohort were more likely to die without heart transplantation ($P<0.001$). The reasons for this improvement were likely multifactorial and potentially the result of overall improvements in therapies for children with acute and chronic HF. Although only an associative finding, it is consistent with findings from other studies done during the same periods.[70,71] It is also consistent with the observation that pediatric cardiologists increasingly treated these children with ACE inhibitors and β-blockade, as well as with mineralocorticoid receptor antagonists, between 2010 and 2020.[72] Newer therapies are being investigated in patients with stage C disease. In particular, this targeted approach may benefit children, who are more likely to have monogenetic forms of cardiomyopathy.

Newer therapies targeting the mechanisms producing cardiomyopathy in patients with stage C (symptomatic) disease are promising according to adult studies. The myosin activator omecamtiv mecarbil acts directly on the sarcomere to improve contractility in adults with HF with reduced ejection fraction.[73] Sodium-glucose cotransporter 2 inhibitors may also improve sarcomere function by improving passive stiffness of cardiomyocytes.[74]

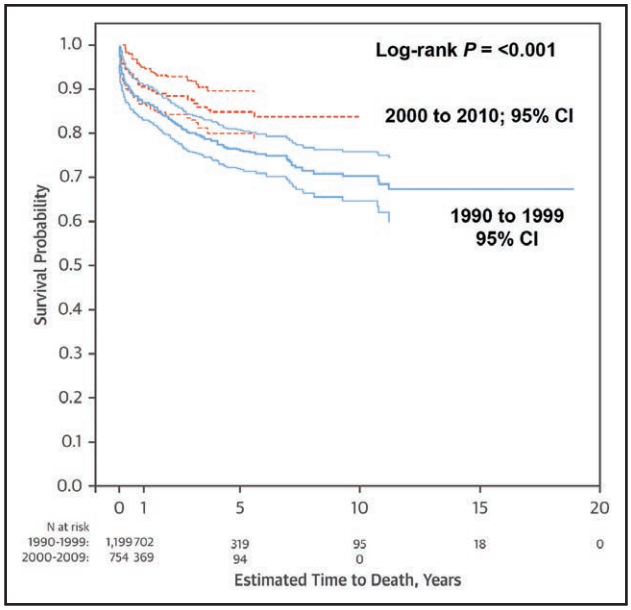

Figure 3. Era effect on survival after a diagnosis of pediatric cardiomyopathy between 1990 and 1999 vs 2000 and 2009.[9] Red dashed lines are for 2000 to 2010; blue solid lines are for 1990 to 1999. In each group, the estimate is the middle line, and the outer lines are 95% CIs for the estimate.

Mendelian diseases provide specific genetic targets for research into the mechanism of disease. For example, a high incidence of sudden cardiac death (SCD) and major ventricular arrhythmias stimulated studies of diagnostic and prognostic biomarkers and new therapeutic genetic targets in *LMNA* cardiomyopathy.[75] The REALM-DCM study (A Study of ARRY-371797 (PF-07265803) in Patients With Symptomatic Dilated Cardiomyopathy Due to a Lamin A/C Gene Mutation) is an ongoing phase 3 trial evaluating the efficacy of ARRY-371797, an oral p38 mitogen-activated protein kinase inhibitor, in adults with symptomatic DCM caused by Lamin A/C mutations.[76] Despite the initial focus on adults, this research can enhance our understanding of the associated genetic variants in children, improve personalized risk stratification, and provide the basis for developing targeted therapies.[77]

Therapy in End-Stage Pediatric DCM

AHA stage D HF identifies patients with refractory HF who remain symptomatic despite maximal medical therapy. These patients may benefit from specialized interventional strategies such as mechanical circulatory support, continuous intravenous inotropic infusions, cardiac transplantation, and palliative or hospice care.[65] Acute decompensated HF in DCM is generally apparent; however, the gradual deterioration of chronic HF from stage C to D may be less noticeable. Identifying stage D HF is vital given the limited treatment options and substantial morbidity and mortality. The current treatment guidelines for children with advanced HF from DCM recommend

evaluation for cardiac transplantation in carefully selected patients with stage D disease who remain symptomatic despite maximal medical therapy.[78] According to current adult HF guidelines, for carefully selected patients with stage D disease with acute hemodynamic compromise, nondurable mechanical circulatory support options, including a percutaneous ventricular assist device (VAD) are reasonable as a bridge to recovery or a bridge to a decision.[65] In a multicenter study on implantations in children and adolescents, cardiogenic shock (28 of 39, 73%) was the most common indication for implantation. Explantation was due to ventricular recovery in 16 patients, transition to another device in 12, death in 5, and cardiac transplantation in 1.[79] Mechanical support such as extracorporeal membrane oxygenation has been a standard of care in pediatric end-stage HF as a bridge to heart transplantation; however, it is associated with high wait-list mortality and poor survival to hospital discharge.[80] The use of paracorporeal and continuous-flow VADs in children has experienced exponential growth in use in the past decade, mainly because of improved technology, reduced adverse effects, enhanced survival statistics, and changes to listing status policy that prioritize patients with cardiomyopathy on mechanical support. According to the International Society for Heart and Lung Transplantation guidelines for the management of pediatric HF, durable mechanical circulatory support is beneficial in carefully selected patients with advanced HF as a bridge to cardiac transplantation, candidacy, or destination therapy.[6] In pediatric DCM, the wait-list mortality in advanced HF has dramatically improved with mechanical assist device use.[78,81] According to the current Pediatric Interagency Registry for Mechanical Circulatory Support report, the indications for pediatric VADs implantation were a bridge to cardiac transplantation (listed) in 48%, bridge to candidacy in 38%, bridge to recovery in 9%, and destination therapy in 1%.[81] Continuous home inotrope infusions may be used as palliative therapy to improve end-of-life quality in select patients with DCM with advanced HF who are refractory to medical management and are not eligible for heart transplantation or mechanical circulatory support.[65,82] According to an adult study, long-term intravenous inotrope use was associated with high mortality with a median survival of 3.4 months but reduced hospital readmissions and improved quality of life.[83] In addition, adult trials have shown that destination mechanical circulatory support is superior to long-term inotropic treatment in select patients with advanced stage D HF.[65] Palliative care should be considered early in the course of stage D HF to help ensure that the parent's and child's goals of care are clearly identified. Refractory HF care across the disease spectrum may gradually transition from aggressive intervention to palliation, comfort, and quality of life. A multidisciplinary team approach involving advanced HF specialists, cardiothoracic surgeons, and palliative care is essential in making these decisions.[82]

Myocardial Recovery

Despite our best efforts to determine the most appropriate timing and treatment of children with HF, complete recovery is uncommon. Among children with DCM in the PCMR, only 22% recovered normal heart function within 2 years of diagnosis. Full recovery was more likely in children <10 years of age with less severe ventricular dilation.[14] Of children recovering normal ventricular size and function, 9% eventually underwent heart transplantation or died within 2 years, indicating a risk of HF relapse.[14] The effectiveness of medications in both recovery and relapse was not clear in the PCMR population. The recovery rate in adults is 15% to 20%, which is similar to that in children.[84] However, the withdrawal of pharmacological treatment for HF in patients with recovered DCM (TRED-HF study [Therapy Withdrawal in Recovered Dilated Cardiomyopathy–Heart Failure]) indicated that one-third to one-half of adults who "recovered" from DCM relapsed from HF within 6 months of discontinuing their HF medications.[85]

Mechanical unloading with a VAD combined with pharmacological therapy can reverse the progression of HF. However, despite beneficial changes in myocardial shape and function secondary to mechanical unloading, recovery leading to VAD explantation is uncommon.[81,86–88] The fifth Pediatric Interagency Registry for Mechanical Circulatory Support report[81] notes that ≈10% of children with VADs recover enough to allow explantation. Recovery rates are higher in children with myocarditis or congenital heart disease than in children with DCM. In addition, recovery rates were higher for children managed with paracorporeal continuous-flow devices, although it is not possible to determine whether device choice was influenced by the perceived potential for recovery.[81,86]

Assessment and Management of Pediatric HCM

The diagnosis of HCM is defined in the AHA 2020 guidelines as the presence of LV hypertrophy (LVH) without evidence of a cardiac, systemic, or metabolic disorder that can explain the magnitude of hypertrophy.[89] In contrast, the 2014 European Society of Cardiology guidelines on HCM[90] and the AHA scientific statement on cardiomyopathy in children[1] define HCM on the basis of cardiac morphology rather than pathogenesis as the presence of increased LV wall thickness that is not explained solely by abnormal loading conditions, regardless of the presence of extracardiac disease, thereby including both sarcomeric and nonsarcomeric causes. The threshold level of wall thickness considered diagnostic for HCM in adults is 15 mm, with 13 to 14 mm constituting probable HCM. In contrast to the recommended diagnostic criteria in adults, the wall thickness value considered diagnostic of HCM in children must account for body size. This is typically calculated as the wall thickness *z* score relative to body surface area (the number of SDs from the normal mean

value relative to body surface area). In an adult of 1.8 m^2, 15 mm is equivalent to a *z* score of 5, and 13 to 14 mm is equivalent to a *z* score of 3 to 4.

As detailed in the 2019 AHA scientific statement,[1] the causes of HCM in children are heterogeneous, and causes other than maternal diabetes are almost exclusively genetic. Clinical findings, outcomes, and response to therapy differ substantially among the various causes, indicating that the first step in management is determination of origin. For example, sarcomeric HCM (SHCM) is associated with a higher risk of SCD compared with HCM associated with systemic disorders such as the RASopathies (genetic conditions caused by mutations in genes of the RAS/mitogen-activated protein kinase pathway) and mitochondrial and storage diseases.[91] In contrast, morbidity and mortality due to HCM secondary to RASopathy presenting before 1 year of age is high during the first 2 years of life (24%) secondary to congestive HF, whereas sudden death in this group of disorders is uncommon (9%), highlighting the utility in defining the origin.[75,91]

Furthermore, SHaRe (Sarcomeric Human Cardiomyopathy Registry) has determined that specific sarcomeric mutations can be an important risk predictor. For example, in SHCM due to *MHY7*, the onset is earlier and the incidence of adverse events (eg, death, HF, malignant arrhythmias, and atrial fibrillation) is higher than with other mutations. In general, pathogenic or likely pathogenic sarcomeric mutations confer the highest risk of death, transplantation, LV assist device implantation, and stroke.[90] In addition, even variants of unknown importance in sarcomeric genes may be clinically relevant.[90]

Although cause-specific therapies are few, the importance of cause-specific diagnosis has become greater with the increasing availability of disease-specific therapies. For example, α-glucosidase (enzyme) replacement therapy or α-glucosidase in vivo gene transfer using adeno-associated virus vectors is now in phase 1 trials[92] for Pompe disease. In mice with Noonan syndrome secondary to mutations in the *PTPN11* gene, low-dose dasatinib improved cardiomyocyte contractility and function.[93] Trametinib, a highly selective reversible allosteric inhibitor of MEK1/2, approved for treating RAS/mitogen-activated protein–mitogen-activated protein kinase–mutated cancers, reversed cardiac failure and valvar obstruction in 2 newborns with *RIT1* mutations, Noonan syndrome, HCM, and severe hypertrophy.[94] In 2 other patients, trametinib was associated with a reduction in LVH and valvar obstruction over 17 months and returned NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations to normal.[95] Last, mavacamten is a promising, new, non–mutation-specific, negative modulator of cardiac myosin that directly diminishes sarcomeric force generation, markedly reduces NT-proBNP and cardiac troponin I concentrations, and is associated with improved health status in adults with obstructive HCM.[96,97]

Strategies for Treating Pediatric HCM

Pediatric patients may present for treatment of HCM when they are phenotypically negative but at risk for developing HCM, have the phenotype of HCM but are currently asymptomatic, have symptomatic HCM, or have end-stage disease. Although the primary symptom in pediatric DCM is HF that is generally progressive and fits in with a concept of progressive stages of HF, this progressive pattern is not replicated in HCM because symptoms are frequently not related to HF or may require therapeutic considerations in multiple clinical milieus. This issue is most relevant in therapeutic considerations for sudden death in pediatric HCM that are relevant to pediatric patients with HCM who are asymptomatic, symptomatic, or have end-stage disease.

Management of Therapy in Pediatric Patients at Risk for Developing HCM (Phenotype Negative)

Current guidelines recommend that genotype-positive, phenotype-negative patients and all children who are first-degree relatives of affected individuals be screened with echocardiography every 1 to 2 years through adolescence and every 3 to 5 years as adults.[89] At present, it is not known whether the presence of preclinical findings such as reduced diastolic tissue velocities and nonspecific electrocardiographic changes (as reported in the VANISH study [Valsartan for Attenuating Disease Evolution in Early SHCM][98,99]) justifies longitudinal monitoring in individuals without identifiable pathogenic variants. Currently, genotype-positive, phenotype-negative individuals have no exercise or activity restrictions, although there is considerable interest in identifying and starting disease-attenuating interventions for these at-risk genotype-positive individuals in this group.

One study of patients with early phenotypic manifestations of disease but no LVH has shown that the calcium channel blocker diltiazem may improve early LV remodeling in patients.[100]

The VANISH study found that high-dose valsartan titrated to a target dose based on age and weight with a maintenance dose for 2 years improved cardiac structure and function more than placebo in patients with LVH.[98,99,101]

Management of Risk of Sudden Death in HCM

For asymptomatic children who meet diagnostic criteria for HCM, routine diagnostic testing for the risk of sudden death is recommended regardless of symptom status. The goal of longitudinal testing is to identify potential opportunities to reduce the risk of sudden death, to provide early intervention for new-onset symptoms, and to detect the unusual development of pulmonary hypertension in children with HCM. Periodic electrocardiography, echocardiography, exercise testing, and ambulatory monitoring for rhythm disturbances are the primary modalities for longitudinal monitoring in children with HCM and are recommended every 1 to 2 years in preadolescents and

annually during adolescence. The options for longer-term rhythm monitoring have increased over the past 5 years, including the availability of monitors with longer recording times and implantable options. The utility of exercise stress tests for evaluating arrhythmias and stress echocardiography to detect exercise-induced or exacerbated outflow tract obstruction is well documented.[102] Periodic cardiac magnetic resonance imaging evaluation of late gadolinium enhancement as evidence of myocardial fibrosis is recommended, although the frequency of testing and the threshold level of fibrosis that represents a risk factor for sudden death remain uncertain in pediatrics given the limited outcome data. Monitoring for the development of restrictive physiology is based on assessment of left atrial size and Doppler assessment of pulmonary and tricuspid regurgitant velocities, with right-sided heart catheterization for patients with findings suggestive of pulmonary or right ventricular hypertension. Similarly, various blood and imaging biomarkers are being studied in the hope of categorizing the degree of myocyte disarray and fibrosis for risk stratification in children.[103]

Predictive models of outcomes in pediatric HCM have generally relied at least in part on data extrapolated from adults because data on pediatric-specific risk factors are limited. Only recently have SHCM risk prediction models specific to children become available. Norrish et al[104] performed a retrospective evaluation of the European Society of Cardiology guidelines, evaluating 411 children for the contribution of several potential risk factors, including severe LVH, unexplained syncope, nonsustained ventricular tachycardia, and a family history of SCD. The primary end point was a composite of SCD or an equivalent event, which included aborted cardiac arrest, appropriate implantable cardioverter defibrillator (ICD) discharge, or sustained ventricular tachycardia. The area under the receiver operating characteristic curve (C statistic) was 0.62 at 5 years.

Norrish et al[105] also reported a multicenter study that included 1024 children followed up for a median of 5.3 years with a sudden death or equivalent event rate of 8.7%. The risk model, which they labeled HCM Risk-Kids, included functional class, unexplained syncope, nonsustained ventricular tachycardia, maximal wall thickness *z* score, left atrial diameter *z* score, and maximal LV outflow gradient. It achieved a 5-year risk of sudden death prediction model with a C statistic of 0.69. Miron et al[106] performed a similar analysis based on 572 children with HCM, assessing the predictive value of age at diagnosis, documented nonsustained ventricular tachycardia, unexplained syncope, septal and LV posterior wall thickness *z* scores, left atrial diameter *z* score, peak LV outflow tract (LVOT) gradient, and the presence of a pathogenic gene variant. The 5-year composite outcome was SCD, resuscitated sudden cardiac arrest, or an appropriate shock from an ICD used in primary prevention. The C statistic for this study was 0.75 in the base model and 0.76 when gene variants were included.

Ostman-Smith et al[107] reported an analysis of 151 children <19 years of age with either SHCM (n=110) or RASopathy HCM (n=41) and calculated a risk score for SCD or cardiac arrest using a previously published risk algorithm derived from electrocardiographic findings alone.[108] They reported a 5-year C statistic of 0.69 and a 7-year C statistic of 0.76.

Norrish et al[109] have reported the HCM Risk-Kids risk prediction model, which is based on unexplained syncope, degree of hypertrophy, left atrial diameter, and nonsustained supraventricular tachycardia in a cohort of 421 patients 1 to 16 years of age. If all 4 risk factors were present, the 5-year risk of experiencing the composite end point was ≈10%. The composite outcome was SCD, aborted cardiac arrest, appropriate cardioverter defibrillator therapy, or sustained ventricular tachycardia associated with hemodynamic compromise. The strongest association with the study outcome was nonsustained supraventricular tachycardia.

A primary limitation of 3 of the above models[104,106] is the inclusion of appropriate ICD discharge as an outcome, which is known to overestimate the incidence of sudden death. The predictive capacity of other models that include additional potential risk factors such as blood and imaging biomarkers (eg, magnetic resonance imaging T1 mapping) is being studied.[103] Given that the risk of major cardiac events associated with SHCM relates primarily to arrhythmias, placing an ICD as a primary preventive measure remains an important consideration in managing children with HCM, but at present, this decision relies in large part on data gathered in adults.

Management of the risk of exercise-associated sudden death in children with HCM has been a controversial topic, in large part because of its rarity, the limited relevant data, and the challenge encountered in determining the risk-benefit ratio in this population, resulting in reliance on consensus rather than data-driven recommendations. Mild- to moderate-intensity exercise is associated with improved cardiorespiratory fitness, physical functioning, and quality of life, and no restriction on these activities is recommended. Although exclusion from participation in high-intensity sports as a means of preventing exercise-associated SCD has been advised by prior AHA recommendations,[110] a causal relationship with exercise has not been definitively established, as demonstrated in a recent population study of SCD in individuals 10 to 45 years of age in Ontario in which 44 cases of definite HCM-related sudden death were identified with an annual incidence of 0.31 per 1000 HCM person-years. Of these, 64.8% of deaths occurred during rest and 18.5% during light activity.[111] The benefit of exclusion from high-intensity sports participation is difficult to assess, but this exclusion clearly impinges on the usual freedom of self-determination, and the net risk-to-benefit ratio for sports participation remains elusive. It should be noted that the current outcomes and long-term

follow-up studies related to exercise risk and outcomes have been affected by the long-standing recommendation to avoid competitive exercise. It is unclear whether liberalizing exercise decisions will change the risk of SCD moving forward. The most recent AHA guidelines[89] have taken a more nuanced approach to this conflict by recommending a comprehensive evaluation to inform a shared discussion about the potential for increased risk of sudden death and ICD discharges. Regardless, eligibility for participation may still be subject to oversight by third-party representatives from schools or teams.

Consideration of ICD Implantation

Current published guidelines by others for ICD implantation for primary prevention in adults with SHCM include documented cardiac arrest, sustained ventricular tachycardia, or a composite score of 2 or more of the following risk factors: SCD in a first-degree relative, massive LVH (≥30 mm), ≥2 recent episodes of syncope suspected by clinical history to be arrhythmic, LV apical aneurysm, and reduced ejection fraction.[89] These recommendations are the same as those for adolescents 16 to 18 years of age, with the additional recommendation that adolescents engage in shared decision-making. Evaluating late gadolinium enhancement with cardiac magnetic resonance imaging is a 2B recommendation and is generally not done in preteens given the potential need for general anesthesia. Recommendations to implant an ICD have to be age stratified when applied to children given the risk of unintentional shocks and the other risks associated with placement of an ICD in small children. Current AHA guidelines for ICD implantation in children are the same as those for adults with the caveat that "ICD placement is reasonable after considering the relatively high complication rates of long-term ICD placement in younger patients."[89]

Therapy in Symptomatic Pediatric Patients With HCM

As discussed, management of the risk of sudden death in HCM encompasses multiple clinical milieus from asymptomatic patients to those with end-stage disease. The approach to management of symptoms in patients with HCM is highly variable and is based on clinical experience and observational studies with limited data to support specific mechanisms. Some experts reserve medications for patients with symptoms, whereas others initiate therapy, usually with β-blockers, in any patient who has moderate or greater LVOT obstruction regardless of symptoms. Patients who have LVOT obstruction are known to be at greater risk for the development of symptoms and progression to death from HF,[112] although progression to HF is rare in pediatrics. Medical or surgical therapy aimed at reducing LVOT obstruction is the primary strategy for reducing symptoms of chest pain, dyspnea, and fatigue. β-Blockers and calcium channel blockers are typically chosen as first-line therapies. Disopyramide has been used alone or in combination with one of the above-mentioned medications, although the pediatric experience with this medication is substantially less than in adults.[113]

1. β-Blockers are the most commonly used medication in HCM for relief of chest pain and dyspnea. They are also used for rate control in patients with arrhythmias. Their proposed primary mechanism of action for chest pain and dyspnea is speculated to be secondary to prolonging diastole and increasing ventricular filling by heart rate reduction and a possible decrease in outflow tract obstruction by reducing inotropy, but they have not been shown to improve exercise tolerance. Nonvasodilating β-blockers are favored in patients with HCM with obstruction to avoid exacerbating the outflow gradient.[114] Side effects, including depression, disordered sleep, and impaired school performance, can be an issue. Use of cardioselective agents such as atenolol or metoprolol may help to ameliorate some of these unwanted effects.
2. Nondihydropyridine calcium channel blockers such as verapamil are thought to improve dyspnea and exercise tolerance by increasing diastolic relaxation, leading to reduced diastolic LV pressure and mean atrial pressure.[115] They also improve microvascular function and increase myocardial perfusion,[116] thought to be the mechanism by which they reduce chest pain. Early in the experience with verapamil, there were isolated case reports of cardiovascular collapse with intravenous administration of verapamil in patients with supraventricular tachycardia and hypotension. However, oral verapamil is well tolerated in children, even in neonates.[117] Side effects are rarely encountered in young patients with HCM despite the association of calcium channel blockers with HF in older adults.
3. Disopyramide is an antiarrhythmic agent with negative inotropic properties and is used as second-line therapy in combination with either β-blockers or calcium channel blockers. Disopyramide inhibits multiple ion channels, leading to lower calcium transients and force generation, ultimately resulting in decreased LVOT obstruction.[118,119] Although it has not been studied extensively in pediatric patients with HCM, it has demonstrated a reasonable side-effect profile in pediatric patients with neurocardiogenic syncope,[120] and associated vagolytic side effects are generally managed with cholinesterase inhibitors.[119,121,122] However, disopyramide can prolong QTc and accelerate atrioventricular nodal conduction and is therefore not generally used as first-line therapy.[119]
4. Septal infarction after transcatheter infusion of absolute alcohol or coil septal coronary perforators can reduce septal thickness and reduce LVOT

obstruction, with improved symptoms and increased exercise tolerance in adults. Procedural complications are higher than for surgical myectomy, related primarily to a significant incidence of permanent complete heart block.[89] Success is highest when obstruction is related to basilar septal hypertrophy, whereas patients with intrinsic mitral valve abnormalities or obstruction that is more apical are poor candidates. There is almost no reported experience with these techniques in children, related in part to the smaller coronary vessels in younger children and concerns about the lifetime consequences of a large septal infarction. Accordingly, the American College of Cardiology Foundation/AHA guidelines currently advise against routine use of alcohol septal ablation in childhood and young adulthood.[123]

5. Surgical myotomy-myectomy in symptomatic subaortic stenosis results in symptomatic improvement in nearly all patients, and most contemporary studies have documented a high success rate, near-zero mortality, and few complications with the procedure in adults when performed by high-volume, experienced HCM surgeons.[124] Results in children have been similar to those reported in adults, with survival rates as high as 98.6% at 5 years.[125,126] Mitral regurgitation often improves in response to myectomy as a result of improved intraventricular flow patterns, and surgery permits concomitant mitral valve repair in patients with underlying mitral valve abnormalities. Although recurrence of obstruction is rare in older patients (2%),[127] it is more common in neonates and infants, likely because of continued myocardial growth and associated disease states, when present, in these age groups.

Both supraventricular and ventricular arrhythmias are encountered in HCM. Atrial fibrillation is the most common supraventricular dysrhythmia, although it is infrequent in patients <30 years of age. Patients with left atrial enlargement, mitral regurgitation, severe LVH, extensive myocardial fibrosis, and symptoms of HF are at highest risk for developing atrial fibrillation. The risk of thromboembolism is high, and prophylactic anticoagulation is necessary. In general, therapy is aimed at rate reduction (β-blockers/calcium channel blockers, alone or in combination) and may include cardioversion in those who are markedly symptomatic or hemodynamically unstable. Ventricular arrhythmias are common and range from isolated ventricular premature beats to nonsustained (>3 beats) to sustained (>30 seconds) ventricular tachycardia and ventricular fibrillation. As assessed by ambulatory electrocardiographic monitoring, ventricular premature beats are highly prevalent, seen in 88%, with nonsustained ventricular tachycardia present in 31% in a study of 178 adult patients.[128] For patients who experience repeat ICD shocks secondary to frequent ventricular arrhythmias, agents such as a class III antiarrhythmic drug (eg, sotalol) may be effective. Amiodarone may also be considered in such cases, although long-term oral amiodarone is associated with photosensitivity, thyroid dysfunction, and pulmonary and hepatic toxicity, and this side-effect profile limits its use in pediatric patients.

Therapy in End-Stage Pediatric HCM

Patients with end-stage HCM have unmanageable HF, arrhythmias, or pulmonary hypertension requiring specialized interventions. The patterns of disease in this so-called end-stage disease typically manifest with either restrictive physiology (noncompliant ventricles with relatively preserved systolic function) or transition to systolic dysfunction, usually accompanied by ventricular dilation. Heart transplantation has traditionally been reserved for patients with HCM who have progressed to end stage, defined as LV systolic failure with ejection fraction <50%.[89] Even in the absence of LVOT obstruction, diastolic dysfunction can cause symptoms of HF, necessitating invasive testing with or without exercise testing to identify the cause of functional limitation and to aid in the selection of patients for heart transplantation. Heart transplantation evaluation should also be considered in patients with HCM with intractable ventricular arrhythmias refractory to maximal antiarrhythmic therapy and ablation.[89] A subset of patients transition to severe restrictive physiology with a risk of developing pulmonary hypertension. These patients require frequent careful monitoring of pulmonary vascular resistance to ensure that they remain candidates for heart transplantation. In summary, cardiac transplantation is the only option for the small percentage of pediatric patients with HCM who manifest uncontrollable congestive HF secondary to systolic or diastolic dysfunction, and these patients require careful longitudinal monitoring for the potential development of pulmonary hypertension.

Rare Cardiomyopathies

Noncompaction Cardiomyopathy

Ventricular noncompaction is a spectrum of clinical profiles including an apparently normal variant in otherwise healthy individuals, including athletes and pregnant women. It is associated with underlying chronic health conditions (chronic polycystic kidney disease, sickle cell disease), congenital heart disease (eg, Ebstein anomaly), and cardiomyopathy of various phenotypes, including DCM, HCM, and RCM.[129–131] Although this spectrum has been observed in children and adults, children with ventricular noncompaction more commonly have associated congenital heart disease,[132] abnormal genetic findings, or both, including single pathogenic variants in sarcomere genes and multiple genetic abnormalities in single individuals.[133]

Treatment of LV noncompaction associated with cardiomyopathies generally follows treatment of the associated

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phenotype (dilated, hypertrophic, or restrictive).[131] The potential for thrombotic complications associated with LV complications had led to recommendations for antithrombotic therapy when LV noncompaction is associated with a cardiomyopathy phenotype but not LV noncompaction with normal cardiac structure and function.[134,135] Established echocardiographic or imaging features to stratify risk for thromboembolism for this patient population are limited,[135] making the timing to start antithrombotic therapy and the specific therapy unclear.

Information from genetic investigations may also identify opportunities for tailored management or potential therapies. For example, Barth syndrome has a form of ventricular noncompaction associated with DCM and severe HF. The syndrome is a common initial presentation of noncompaction,[136–138] with an undulating phenotype in some patients, so quickly proceeding to heart transplantation should be carefully considered.[137–139] Recognition of associated Barth syndrome and its effect on mitochondrial cardiolipin metabolism may lead to targeted therapy.[140]

Restrictive Cardiomyopathy

RCM is a rare form of heart muscle disease characterized by impaired ventricular filling leading to progressive elevation of pulmonary vascular resistance and nondilated biventricular failure with relatively preserved systolic function. Pediatric RCM is associated with poor prognosis, with more than half of children dying or requiring transplantation within 2 years of diagnosis.[141,142] Both sarcomeric and nonsarcomeric mutations are associated with pediatric RCM. In a PCMR study by Webber et al,[141] RCM accounted for 4.5% of cases of pediatric cardiomyopathies; a pure RCM phenotype was seen in approximately two-thirds of patients, whereas the rest had a mixed restrictive/hypertrophic phenotype. Webber et al[141] reported that survival did not differ between patients with pure RCM and those with mixed restrictive/hypertrophic phenotype; however, transplantation-free survival was superior in the mixed phenotype. Although idiopathic RCM is most common, secondary causes of RCM include infiltrative, iatrogenic, and oncological origins; fibrotic processes; and storage disorders. Although treatment for RCM should target the cause, in most cases, no apparent reason for RCM can be identified, leading to an individualized treatment approach. Cardiac transplantation is the preferred treatment that offers long-term survival, but the optimal timing for listing these patients is unknown.[143] The development of dysrhythmias, thromboembolic disease, diastolic and eventually systolic HF, and progressive pulmonary hypertension is associated with poor outcomes and can inform the timing of listing for transplantation. All children with RCM should undergo serial monitoring of their pulmonary vascular resistance, and any significant finding should prompt consideration of a transplantation evaluation.[144] Cynicism about offering LV assist device therapy to these patients is based on concerns about impaired LV assist device therapy function resulting from compromised diastolic filling due to restrictive pathophysiology and inflow cannula obstruction in a small LV cavity.[145] A national database study reported low VAD use in patients without DCM, with ≈4.5% of children with RCM listed for cardiac transplantation having a VAD compared with ≈24% of children with DCM.[146] Novel modifications to the LV cannulation techniques reported for patients without DCM include (1) transseptal left atrium–to-aorta VAD cannulation, (2) atrial cannulation, or (3) biventricular support with atrial cannulation of the right atrium and LV cannulation with excision of the mitral valve and papillary muscles.[145,147,148] The incidence of thrombosis in pediatric RCM is high; therefore, antithrombotic and anticoagulation therapy is recommended at diagnosis.[147] Management of volume status in patients with RCM can be challenging; they rely on high filling pressures to maintain cardiac output, and excessive diuresis may result in decreased perfusion to the body. β-Blockers or calcium channel blockers to increase filling time or to treat arrhythmias should be used with caution because these agents may not be well tolerated. Data supporting the beneficial effects of ACE inhibitors and angiotensin II receptor blockers in RCM are lacking, and these agents may not be well tolerated. The evolution of genomics may help characterize cellular and molecular mechanisms leading to myocardial restriction and identify targets for potential interventional strategies.

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy has been defined as an arrhythmogenic disorder of the myocardium not secondary to ischemic, hypertensive, or valvular heart disease.[149] According to this definition, arrhythmogenic cardiomyopathy incorporates a broad spectrum of genetic, systemic, infectious, and inflammatory cardiomyopathies. One of the best characterized of these cardiomyopathies is arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC), which shows pathologic fibrous and fibrofatty replacement of the right ventricular myocardium. The ventricular tachycardia with this entity shows a left bundle-branch pattern. Most ARVC is caused by variants in one of several genes encoding desmosomal proteins or proteins involved with the desmosome, or a desmosomopathy.

It is recognized that most patients with ARVC develop LV involvement, which can be observed with cardiac magnetic resonance imaging. LV involvement may result not only in LV arrhythmias but also in LV dysfunction leading a DCM phenotype and HF, which can lead to transplantation. These patients may present with a clinical and pathological diagnosis of acute myocarditis.[150,151] Although ARVC presents primarily in adulthood, recent studies[150–152] suggest that genetic disease affecting the desmosome that presents with HF and a DCM

phenotype may occur in children and adolescents more frequently than has previously been appreciated.

Therapeutic strategies for ventricular arrhythmias seen with desmosomopathies generally follow those used for similar complications in HCM. HF and LV dysfunction strategies in a similar fashion follow those used for DCMs. A unique therapeutic intervention for ARVC and other presentations of desmosomopathies is exercise limitation. Current consensus[149] states that exercise increases arrhythmic risk and structural dysfunction in patients with ARVC. Guidelines for the management of ARVC state that individuals with ARVC should not participate in competitive or frequent high-intensity endurance exercise.[149] Furthermore, it is recommended that clinicians counsel adolescent and adult individuals who have a positive test for ARVC but are phenotype negative that competitive or high-frequency endurance exercise is associated with an increased likelihood of developing ARVC and ventricular arrhythmias. Thus, exercise guidance for ARVC and perhaps all presentations of desmosomopathies is different from that for HCM. The potential to mitigate the development of the overt cardiomyopathy in these patients would also lead to an added importance of genetic testing of family members to initiate these exercise interventions for genotype-positive family members.

FUTURE DIRECTIONS

Investigational Management Strategies

Pulmonary Artery Banding

The use of a pulmonary artery banding has emerged as a potential therapeutic alternative in infants with advanced HF due to DCM with preserved right ventricular function. Schranz et al[153] from Germany originally described the application of pulmonary artery banding as an additional strategy to delay or even avoid heart transplantation in infants and young children with end-stage HF due to DCM. This study was expanded to a multicenter retrospective analysis with participants from 11 different nations (World Network Reports) and found that pulmonary artery banding was associated with significant improvement in patients with DCM.[154] A recent multicenter retrospective analysis by Spigel and colleagues[155] from the United States and the World Network Reports by Schranz et al[154] found pulmonary artery banding to be associated with myocardial functional recovery in approximately one-third to one-half of the children with DCM.

Although both the US and Germany series exhibited a high prevalence of achieving cardiac recovery or a transplantation, the recovery rate in the US series was lower (one-third) than in Germany (more than two-thirds).[153,155] A lower recovery rate in the United States could indicate a sicker patient population with advanced HF, suggesting selection bias, a limitation inherent to any retrospective case series.

Cell-Based Therapies

Some stem cell studies have reported improved function and LV dimension in adults. Preliminary data in animal models of DCM have shown improved cardiac function and reduced myocardial fibrosis.[156,157] However, the results of stem cell therapy for children with DCM are mixed. Although some pediatric case reports have not described strong benefits,[158,159] other studies have reported that stem cell therapy improved ejection fraction and decreased LV end-diastolic volume.[160,161]

Collaborative Networks and Registries

One of the challenges in studying rare diseases is establishing QI models that apply rigorous scientific methods to improve quality of care, building robust data infrastructures, and gaining insights into the high-impact research topics critical in eliminating health care gaps and disparities for children with cardiomyopathy.[162] The Quality in Pediatric Subspecialty Care workgroup, established by the American Board of Pediatrics, launched pediatric collaborative improvement networks in 2002.[162] These multisite, collaborative clinical networks provide a foundation for QI research into rare childhood diseases to translate evidence into best clinical practice.[162,163] The Children's Oncology Group and the Cystic Fibrosis Foundation are 2 successful collaborations that have produced spectacular results in collecting and using data to transform patient outcomes.[162]

This network approach has also been successful in pediatric cardiology, which now has collaborative networks that include the North American PCMR, the Pediatric Heart Transplant Society, and the Pediatric Heart Network. Specific to pediatric HF, ACTION (Advanced Cardiac Therapies Improving Outcomes Network) was developed in 2017.[164,165] ACTION involves the key stakeholders, including patients, families, clinicians, and researchers. This network provides invaluable support and education to families and patients.[165] One of the initial QI projects launched by ACTION was the "ABCs of stroke prevention." This project focused on preventing stroke in children with end-stage HF and VADs. Within 2 years, this project likely contributed significantly to stroke rates at participating sites dropping by 60%.[165,166] In particular, stroke rates among patients receiving pediatric durable VAD were significantly reduced from 30% to 11% in ACTION locations.[167] The Table displays the ongoing ACTION network HF-specific QI initiatives.

Linking large clinical registries is a popular strategy to broaden analytic options. Outcomes research using linked registries can set benchmarks in pediatric HF and support research into complex questions that individual databases cannot answer alone.[164,168] Large databases can be linked to indirect patient identifiers (probabilistic matching) or unique, direct identifiers (deterministic matching).[168–170] Furthermore, establishing a standardized global unique patient identifier to facilitate linkage across collaborating registries would allow integration of new data into existing

Table. The Ongoing ACTION Network HF-Specific QI Initiatives[165]

1.	Implantable pulmonary artery pressure monitoring in advanced pediatric heart failure	The implantable pulmonary artery pressure monitor protocol discusses patient selection, preimplantation, postimplantation follow-up, and outpatient monitoring after discharge. The implantable pulmonary artery pressure monitor protocol is in the data collection phase.
2.	DMD therapy harmonization	The DMD harmonization protocol helps harmonize dystrophin-related cardiomyopathy medications, especially early in the disease when significant practice variability exists across pediatric institutions.
3.	Inpatient rounding checklist to improve pediatric HF symptom assessment	The inpatient communication checklist helps improve pediatric heart failure symptom assessment and management.
4.	Inpatient and outpatient medication checklist to optimize goal-directed medical therapies	The inpatient and outpatient medication checklist discusses initiating and optimizing goal-directed medical therapy in inpatient and outpatient settings to reduce hospital readmission rates and outpatient medication titration harmonization.
5.	Discharge-standardizing processes to reduce hospital readmission rates in pediatric HF	

ACTION indicates Advanced Cardiac Therapies Improving Outcomes Network; DMD, Duchenne muscular dystrophy; HF, heart failure; and QI, quality improvement.

registries.[164] Given the challenges of conducting randomized trials in children with HF, a collaborative platform is particularly suited to this field of research. Integrated multimodality registries, including joint biorepositories with genomic and clinical data sets, could be leveraged to speed the translation of research findings into clinical practice guidelines.

In summary, pediatric collaborative networks are a successful model for sharing knowledge, providing a platform for research, and facilitating community engagement. However, adequate, long-term, reliable funding is essential to sustain these networks.

New Trial Designs and End Points

Legislative changes in the United States and European Union since the late 1990s have fostered an increase in the number of pediatric clinical trials though a combination of mandates and incentives.[171] Alternative trial formats or recruiting strategies may also help increase the number of higher-quality trials. Registry-based randomized trials can be conducted at lower costs with greater generalizability. Such trials could test approved medications for new pediatric indications when there is no financial incentive for industry to support such trials or when funding is available but not to the scale needed for clinical trials.[172,173] Registry-based trials may also decrease selection bias, particularly in studies of underserved populations.

Adaptive trial designs may help address inadequate sample sizes, dose selection, and comparators based on the questionable assumptions that plague pediatric clinical trials. Adaptive trials allow results from interim data analyses to modify the ongoing trial without undermining validity or integrity. Ongoing adaptive trials can refocus enrollment toward participants most likely to benefit from a treatment, alter trial arm allocation ratios, abandon less promising treatments or doses sooner, add new treatment arms, or stop a trial early for success or futility.[174] These designs save time and money, require fewer patients, protect patients from ineffective treatments, decrease the probability of inadequate statistical power, and lead to earlier and more precise conclusions.[175,176]

Death and transplantation are appropriate end points for clinical trials of adults with HF, but studies of children with HF rarely enroll enough patients to provide adequate statistical power for these end points. As a result, identifying surrogate end points for clinical trials is critical to test evidence-based therapies. Recently, the use of composite, global rank primary end points has gained favor in pediatric HF trials. The utility of circulating and imaging biomarkers and measures of exercise and functional capacity also needs to be assessed. In PANORAMA-HF, patients are ranked by their outcome from worst to best: death, need for mechanical life support, listing for heart transplantation, worsening HF, New York Heart Association/Ross scores, and patient-reported outcomes.[68]

Transition of Care

Regardless of the type of cardiomyopathy, it is vital to have a cohesive and stepwise transition from child to adult care to achieve optimal long-term outcomes.[177] Health care professionals must ensure that their adolescent and young adult patients with cardiomyopathy have the independence that enables them to navigate a new medical system, understand the need for and effects of their medications, and receive adequate medical education about their diagnosis. One systematic review of studies on children with congenital heart disease found that transition failed when patients were not explicitly told that specialized cardiac care was required, had not undergone cardiac surgeries, had less complex disease, had no specific adult health care professional, and had insufficient documentation of the need for a cardiac specialist who treated adults. In contrast, factors associated with successful transitions included the belief that specialized cardiac care was necessary, a history of cardiac surgery, multiple discussions in advance about the need for and the importance of transitioning to adult care, attendance of appointments without parents, older age, referral to an adult cardiac specialist, and a thorough understanding of their cardiac disease.[178–181] The literature on the transition of adolescents and young adults with cardiomyopathy is scarce. Given the additional complexity of transitioning asymptomatic but at-risk children, strategies are needed to determine best practices for transitioning this unique population.

CONCLUSIONS

This scientific statement emphasizes the important differences between the types of and treatments for cardiomyopathies and HF in children and adults. Nevertheless, treatments for children can be informed by the results from studies of adults, as well as by new mechanistic-based therapeutic targets identified through preclinical work and tested in humans through phased clinical studies. Efforts to promote learning networks and registries focused on pediatric cardiomyopathies and HF can optimize data collection and provide a platform for research and the infrastructure needed to implement quality initiatives. New clinical trial designs, validated clinically relevant surrogate and composite outcomes suitable for smaller and shorter studies in children, and advancements in precision medicine with the development of cause-specific therapies should advance our ability to diagnose and treat cardiomyopathies in children.

ARTICLE INFORMATION

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*Modest.

†Significant.

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†Significant.

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