

## Congenital Heart Disease in the Older Adult A Scientific Statement From the American Heart Association

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The population of adults with congenital heart disease (ACHD) has increased dramatically over the past few decades, with many people who are now middle-aged and some in the geriatric age range. This improved longevity is leading to increased use of the medical system for both routine and episodic care, and caregivers need to be prepared to diagnose, follow up, and treat the older adult with congenital heart disease (CHD). The predictable natural progression of CHD entities and sequelae of previous interventions must now be treated in the setting of late complications, acquired cardiac disease, multiorgan effects of lifelong processes, and the unrelenting process of aging. Despite the advances in this field, death rates in the population from 20 to >70 years of age may be twice to 7 times higher for the ACHD population than for their peers.<sup>1</sup>

This American Heart Association (AHA) scientific statement will focus on the older adult (>40 years old) with CHD. It is meant to be complementary to the 2008 American College of Cardiology (ACC)/AHA guidelines for ACHD and orient the reader to the natural history, ramifications of childhood repair, and late initial diagnosis of CHD in the older adult. This population with CHD is unique and distinct from both the pediatric and young adult populations with CHD. Much of the information we provide is from scientific research combined with clinical experience from longitudinal care. We emphasize that this is the beginning of a discussion regarding this rapidly growing population, and continued research aimed at the progression of disease and complications reviewed here is necessary to advance the field of ACHD with the scientific rigor it deserves.

ACHD encompass a broad range of presentations. There are people who are diagnosed for the first time in adulthood, as well as those with prior palliative repair and its consequences, new sequelae years to decades after childhood surgical repair, or residual lesions with delayed presentation.

It can become more complicated to care for middle-aged and older patients with residual hemodynamic abnormalities despite the success of their earlier operative intervention when acquired heart disease intervenes. The addition of acquired heart disease may lead to symptoms such as exercise intolerance with significant disability in a previously asymptomatic patient. The challenge that often faces the cardiologist is to sort out the relative contribution to symptoms of acquired heart disease and CHD.

In addition to the large number of patients with previously diagnosed CHD, there exists a population of adults whose CHD was not diagnosed during childhood. These adults may be symptomatic, leading to detection of the lesion. However, some lesions may escape detection until adulthood and become apparent because of superimposed acquired heart disease or as an incidental finding. Operative or catheter interventional therapy for these patients may be more complex than if the problem had been addressed in childhood and may have to be combined with additional procedures, for example, coronary artery bypass or coronary angioplasty, if advanced ischemic heart disease is present. On the other hand, newer percutaneous interventions may obviate surgery in cases in which it would have been required in the past.

This AHA scientific statement will address diagnosis and management of CHD in adults >40 years of age to summarize

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 2, 2014, and the American Heart Association Executive Committee on January 27, 2015. A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

The American Heart Association requests that this document be cited as follows: Bhatt AB, Foster E, Kuehl K, Alpert J, Brabeck S, Crumb S, Davidson WR Jr, Earing MG, Ghoshhajra BB, Karamlou T, Mital S, Ting J, Tseng ZH; on behalf of the American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;131:•••-•••.

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(*Circulation*. 2015;131:00-00. DOI: 10.1161/CIR.000000000000204.)

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIR.000000000000204

**Table 1. Applying Classification of Recommendations and Levels of Evidence.**

		SIZE OF TREATMENT EFFECT				
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit or CLASS III Harm</i>	
				Procedure/Test	Treatment	
				COR III: No benefit	No Proven Benefit	
				COR III: Harm	Excess Cost w/o Benefit or Harmful to Patients or Harmful	
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other
Comparative effectiveness phrases <sup>†</sup>		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

what is presently known and to outline areas in which additional knowledge is critical to their care. The focus of this scientific statement will be structural CHD, including coronary artery anomalies and aortopathy associated with bicuspid aortic valve (BAV) disease. We will exclude familial cardiomyopathies, degenerative mitral valve disease, genetically based arrhythmias, connective tissue disease, and familial aortic aneurysm. Issues related to contraception and pregnancy will not be addressed in this document, although we recognize that some women >40 years of age may still have child-bearing potential.

The writing group was charged with the task of performing an evidence-based assessment of the data and providing a class of recommendation and a level of evidence to each

recommendation according to the ACC/AHA classification system (Table 1).

### Prevalence of CHD in Adults

There is no database of adults with CHD in the United States that provides systematically collected population prevalence data. The Centers for Disease Control and Prevention recently funded 3 pilot projects for surveillance of congenital heart defects to begin to address this elusive question. In the province of Quebec, Canada, there was a prevalence of 4.09 cases of CHD per 1000 adults in 2000, with 9% of these people having diagnoses of severe CHD.<sup>2</sup> Extrapolated to the United States, there would have been ≈850 000 adults with CHD in

the year 2000. It has been estimated that the ACHD population increases at 5% annually<sup>3-6</sup>; thus, there would have been an additional 400 000 increase in this population from 2000 to 2012. These estimates in Canada include patients not receiving specific cardiac care.<sup>2</sup> The 32nd Bethesda Conference on "Care of the Adult With Congenital Heart Disease" in 2000 yielded similar population estimates, categorized according to severity of lesion as follows: 45% of adults had mild, 37% had moderate, and 14% had severe heart disease.<sup>7</sup>

The birth prevalence of specific congenital heart defects varies by ethnicity.<sup>8</sup> Mortality also varies by ethnic group, which raises the possibility of disparities in access to health care and education and in knowledge of care needs within the ACHD population.<sup>9</sup> Importantly, variations in ethnic makeup may limit comparability of data from other countries to the United States.

### Survival Into and in Adulthood of Patients With Known CHD

Although cardiac surgery for congenital heart defects began in the mid-1950s, surgery was initially often performed on older children and adults, often in multiple staged procedures. Complex cardiac defects were not approached with definitive infant surgeries until the mid and late 1970s, when infant cardiopulmonary bypass (CPB) was in common use. The contemporary adult population of people with CHD is therefore made up of myriad populations with unique natural histories: those who survived without surgery; those who had repairs with multiple procedures, with first surgeries after infancy; and those who had surgery in infancy. The last group includes an evolving set of diagnoses among patients who have not usually survived to adulthood, including hypoplastic left heart syndrome and dextro-transposition of the great arteries (D-TGA) with an arterial switch. An understanding of the expected course of this latter group after 40 years of age awaits the survival of larger numbers of such patients to that age.

When population-based data were used, the life span in patients with ACHD was shown to be similar to that of the general population of Quebec when assessed in 2004.<sup>2</sup> However, the CONCOR (Congenitale Cor Vitia [Congenital Heart Ailments]) database demonstrated that patients who sought care for ACHD were at risk of death compared with their peers; more patients of younger ages were represented in the CONCOR data. It is likely that as the ACHD population ages and has more severe comorbid disease, the excess death risk for patients with moderate or severe disease will be manifest in many countries.<sup>10,11</sup>

Survival to adulthood varies with severity of CHD, with 98% of patients with mild CHD, 96% of those with moderate CHD, but only 56% of those with severe forms surviving to adult ages. Survival of the population as a whole to adulthood was 81% in 1970 to 1974, increasing to 88.6% in 1990 to 1992. As far back as 1970, 36.4% of patients had undergone some surgical intervention, a proportion that was little changed through 1992, although the nature and timing of surgical interventions changed during that period. Survival to age 40 years was 84.1% for all CHD types combined.<sup>11</sup> For patients with CHD, the death registries of the United States

from 1999 to 2006 showed a sharp rise in mortality rates after 65 years of age.<sup>9</sup>

### Evaluation and Management of the Patient With Known CHD

#### Late Morbidities in ACHD That Are Not Diagnosis Specific

Nearly 80% of deaths in ACHD patients are associated with heart failure, sudden death, arrhythmias, and vascular complications.<sup>1</sup> Hospital admissions occurred in 50% of ACHD patients over 5 years of follow-up in the CONCOR database<sup>12</sup>; 61% of admissions were for cardiovascular causes. In the United States, 20% of hospital admissions of people with ACHD are for heart failure, and the prognosis is worse for these patients than for those with ACHD admitted for other reasons.<sup>13</sup> Heart failure occurs both with diminished and with preserved systolic function; on occasion, there is no clear pathogenetic hemodynamic load. Diastolic dysfunction is present without the usual comorbidities of obesity or hypertension in many of these patients.

Intra-atrial reentrant tachycardia (IART) is increasingly common in the ACHD population across diagnostic categories, with the estimate that 50% of all patients will manifest some atrial arrhythmia by 55 years of age. This reentry circuit often involves a prior atriotomy scar and may require specialized mapping for ablation.<sup>14</sup>

Vascular complications include the development of pulmonary hypertension, aortic root dilation, aneurysm formation, and venous insufficiency.

Importantly, with age, and in this older ACHD population, management will need to encompass acquired heart disease. In the general population, mortality rates for all cardiovascular disease, coronary heart disease, and stroke are, respectively, 10, 9, and 13 times higher in people  $\geq 65$  years old than in those 45 to 64 years of age. As people with ACHD approach these decades, the problems of acquired heart disease in this population will become manifest over time. This is already evident, because in the adult population with acyanotic CHD, since 1990, myocardial infarction has become the leading cardiovascular cause of death, consistent with improved longevity and the increasing impact of acquired heart disease.<sup>15</sup>

ACHD patients with heart failure, arrhythmia, acquired heart disease, and other acute morbidities are likely to present locally to hospitals that may not have established ACHD programs. Coordination of care between such facilities and ACHD regional programs is important.

#### Evaluation of the Older Adult With CHD

Evaluation of adults presenting with or known to have CHD should, within the initial evaluation, include the participation of a specialized center for the care of ACHD. It is recommended in the ACC/AHA guidelines for care of this population that each cardiovascular specialist, emergency department, and pediatric cardiology program have a relationship with a regional specialized program for the care of ACHD. In most ACHD patients, the history, progression of symptoms, and assessment of the relationship of symptoms

to the congenital lesion form the clinical foundation of the patient's care. Physical examination provides the most useful information, and chest radiography, ECG, and the use of simple laboratory tests (creatinine, sodium, liver function tests, brain natriuretic peptide, hematocrit, uric acid) can help assess the longevity and systemic effects of the disease. It is essential that patients' records, in particular previous cardiac catheterization reports and operative notes, be obtained from primary sources. Not only does this allow initial comprehensive evaluation of these patients, but it provides a medical center where, if needed, other illnesses can be managed in a setting that is also knowledgeable about CHD.

Evaluation should include expertise in appropriate imaging to allow planning for the care of that patient and determination of severity of illness. Imaging of CHD patients requires a specialized set of skills within echocardiography, magnetic resonance imaging (MRI), and cardiac catheterization. Echocardiography laboratories certified in CHD in the pediatric population may not always be appropriate for the adult population if additional skills are not available to evaluate superimposed acquired heart disease. After an initial evaluation, patients can be considered as having mild, moderate, or severe disease.

In centers dedicated to ACHD care, cardiopulmonary exercise testing can be used for quantitative assessment of cardiopulmonary efficiency in both the presence and absence of symptoms. Routine exercise testing will assess for arrhythmias and ischemia as well, and stress echocardiography may be of use to assess worsening valvular disease or pulmonary hypertension, especially if exertional symptoms are out of proportion to resting imaging results. Obstructive sleep apnea may coexist in select diagnoses within this population and may be worth evaluating. For the ACHD patient, multidisciplinary ACHD team review is essential in patient care and prudent before recommendations are made.

After a definitive diagnosis and treatment plan are evolved at a specialized center, collaborative relationships with community cardiologists are essential to the ongoing care of patients with mild disease and some with moderate disease. The model of 2-way conversation about patient management over the years is not well established in US medical practice; such collaborative patient-centered care would be of benefit to this ACHD population.

## CHD Diagnosed and Treated in Childhood

### *Simple Shunts*

Patients with repaired atrial septal defects (ASDs) or ventricular septal defects (VSDs), or with closed ductus arteriosus, can anticipate excellent quality of life in general, with a near-normal lifespan.<sup>16</sup> Late structural complications in simple shunt lesions may include aortic cusp prolapse after VSD repair (or in unrepaired restrictive VSD) with aortic insufficiency and, rarely, development of a subaortic membrane or right ventricular (RV) muscle bundle hypertrophy and a double-chambered RV.

Electrophysiological concerns late in life can include IART after ASD closure or patch repair for partial anomalous pulmonary venous return and sinus venosus atrial defect. Sick

sinus syndrome or low atrial rhythms can also be seen late after sinus venosus and anomalous pulmonary venous return repair. Atriotomy incisions, performed in myriad CHD surgeries, can lead to atrial flutter, whereas other times, surgery may disrupt the sinus node arterial branch.

Some patients with shunt lesions may be at risk of pulmonary arterial hypertension (PAH) later in life, and of note, in patients with large shunts who may have had pulmonary artery (PA) banding to limit pulmonary blood flow in childhood, some may present later in life with supralvalvular pulmonary stenosis.

### *Atrioventricular Septal Defect*

In patients with an atrioventricular septal defect (AVSD), there is often late left-sided atrioventricular (AV) valve regurgitation that necessitates reintervention. Overall freedom from reintervention at 10 years may be as low as 67.2% or as high as 86%<sup>17</sup> or 89%.<sup>18</sup> Independent risk factors for need for reoperation may include associated cardiovascular anomalies ( $P<0.001$ ), left AV valve dysplasia ( $P<0.001$ ), and non-closure of the cleft ( $P=0.027$ ) or primary cleft closure rather than patch augmentation. Survival is higher after left AV valve repair than after replacement ( $P=0.010$ ), and cardiomyopathy may be more likely after replacement; however, both repair and replacement are associated with a high incidence of reoperation. Fortunately, overall survival of patients who undergo reoperation for left AV valve regurgitation is favorable (88.1% at 10 years in a recent study).<sup>17,19</sup>

### *Tetralogy of Fallot*

An as yet unknown proportion of patients with repaired tetralogy of Fallot (TOF) develop pulmonary insufficiency, which can progress to enlargement of the right side of the heart and heart failure that requires pulmonary valve replacement (PVR). Criteria for optimal timing of valve replacement are evolving, with the goal of maintaining RV size and function after valve replacement.<sup>20</sup>

### *RV to Pulmonary Artery Conduits*

The use of conduits between the RV and PA is an intrinsic part of many CHD repairs, including pulmonary atresia with VSD, Rastelli repair of D-TGA with VSD, and truncus arteriosus. In all cases in which a valve is present in the conduit, that valve may develop stenosis or insufficiency over time. RV to PA conduits are notorious for requiring reintervention, often for combined stenosis and insufficiency.<sup>21</sup> PVR may be accomplished with the use of percutaneously implanted valves. Bioprosthetic valves are usually chosen for placement in the RV outflow tract (RVOT) and have a finite, unpredictable life span such that multiple replacements are anticipated. Recurrent pulmonary stenosis, either at the annulus or in the branch PAs, occurs in these patients and is often approachable and addressed by interventional means. RV and left ventricular (LV) failure, ventricular tachycardia (VT), and atrial tachycardia occur in this population as well.<sup>14</sup>

### *Obstruction of the Left Side of the Heart*

Congenital aortic stenosis (AS) and coarctation of the aorta and BAV all occur in congenital forms and often in combination. BAV carries with it the risk of aortic root dilation and aortic dissection in an unknown proportion of cases.<sup>22</sup> BAVs

may develop progressive stenosis or insufficiency that requires repair or replacement.

Recurrent or residual coarctation of the aorta with hypertension may be responsive to further dilation and stent placement in the narrowed site. A high percentage of patients with coarctation repair develop aortic valve disease as well.<sup>23</sup>

The role of adult weight gain and obesity as they relate to functional obstruction of the original coarctation is not clear. Patients with coarctation have often been thought to have increased risk of coronary artery disease (CAD); however, this appears to reflect the presence of known risk factors in the coarctation population (eg, male sex, hypertension, and hyperlipidemia).<sup>24</sup>

LV outflow tract obstruction may develop late after initial AVSD repair. Lesions that lead to obstruction may include subaortic membrane, fibromuscular obstruction, tunnel obstruction, hypertrophic cardiomyopathy/muscular obstruction, or anomalies of the mitral subvalvar apparatus, including attachments from the mitral valve to the septum, which are important to recognize in surgical decision making. There are multiple potential operative strategies, most of a complex nature, that should be performed by a surgeon with experience treating the adult with CHD in an ACHD center, in whose hands there are favorable early and midterm outcomes.<sup>25</sup>

Most patients with isolated thin, discrete subaortic stenosis treated with transluminal balloon tearing of the membrane in childhood had sustained relief at subsequent follow-ups without restenosis, the need for surgery, progression to muscular obstructive disease, or an increase in the degree of aortic regurgitation.<sup>26</sup> However, in the older adult with CHD with a history of repair of subaortic stenosis in childhood as described above, moderate to severe aortic regurgitation (16%) or progressive valvular AS requiring surgery (26%) may develop. In 1 long-term follow-up study of older adults with a history of subaortic stenosis after childhood surgery, valve surgery for AS was more common in patients with concomitant BAV disease ( $P=0.008$ ), coarctation of the aorta ( $P=0.03$ ), and supra-valvular stenosis ( $P=0.02$ ). Careful clinical follow-up of the discrete subaortic stenosis population to monitor aortic valve status continues to be warranted even after a successful surgical resection.<sup>27</sup>

In people with Williams syndrome, there may be late presentation of supra-valvular AS in those who were not diagnosed at an earlier age.

#### **Transposition of the Great Arteries (D-TGA and L-TGA)**

Transposition of the great arteries in the older adult will generally represent either D-TGA after atrial switch (Mustard or Senning) repair or levo-transposition (L-TGA), also known as congenitally corrected transposition (CCTGA), both of which have a morphological RV as the systemic, subaortic ventricle. In 1 multicenter study, among patients who had undergone L-TGA, heart failure developed by age 45 years in 67% of those with associated lesions (eg, VSD, tricuspid insufficiency, or pulmonary stenosis) and in 25% of those with no associated lesions.<sup>28</sup>

After atrial switch for D-TGA, the 20-year survival rate is  $\approx 80\%$  to  $85\%$ , with nearly equal survival after the Senning and Mustard procedures. Because these studies were first

performed in the early 1960s, there are an increasing number of patients who have survived to age 40 and beyond.<sup>29-32</sup> Sudden death has been the most common cause of death in the D-TGA patients.<sup>33</sup> In the systemic RV associated with atrial baffle repair (Mustard or Senning operation) of dextro-transposition of the great vessels, RV failure is uncommon,<sup>33</sup> although many RVs are enlarged. Complications in the older adult may include obstruction of systemic or pulmonary venous pathways created by baffling of the atria, sinus node dysfunction or marked bradycardia (potentially requiring pacemaker placement), and atrial reentrant tachyarrhythmias (which may benefit from radiofrequency ablation by an experienced electrophysiologist with knowledge of their complex anatomy). The change to the arterial switch operation in the 1980s will mean that there will be fewer of these patients in coming years.

Longstanding subpulmonic stenosis in L-TGA (or D-TGA after atrial switch) may be observed and in fact may play a protective physiological role in maintaining subpulmonary LV pressures and preventing systemic RV annular dilation and progressive systemic tricuspid valve regurgitation.

#### **Single-Ventricle Physiology**

This includes a diverse group of anatomic diagnoses such as tricuspid atresia, double-inlet LV, malaligned AV canal, and hypoplastic left heart syndrome. The morbidity of these diagnoses are expected to vary with the type of single ventricle, for example, anatomic LV or anatomic RV.

Very few patients with Fontan palliation of single ventricle have reached 40 years of age; those who have most likely had late Fontan operations, that is, were natural survivors of their single-ventricle status. In younger patients, cirrhosis is markedly more frequent in single-ventricle patients hospitalized for any cause than in others, with a rapidly increasing number of admissions and diagnoses of ascites and portal hypertension.<sup>34</sup> In the older Fontan patient, risk factors for cirrhosis are being investigated, but prospective assessment of liver disease will be necessary to better understand the progression and potential avoidance of or treatment for liver complications. Atrial reentrant tachycardias are very common in this population and may benefit, temporarily or potentially long-term, from radiofrequency ablation.

#### **CHD Diagnosed in Childhood but Not Treated**

The proportion of patients with known but unrepaired CHD not undergoing surgery appeared stable from 1970 to 1992 at  $>60\%$ , during which time patients with more complex disease underwent surgery, but their survival to adulthood remained significantly below that of others.<sup>11</sup> In a multicenter European study of 5 years of follow-up of 4110 patients surveyed from 79 centers in 29 countries, 57% of ASD and 56% of VSD patients had not undergone closure of the defects. Approximately 10% of patients with coarctation of the aorta had not had previous repair. Of the 4110 patients, 390 had Eisenmenger syndrome and therefore may not have had surgery.<sup>35</sup>

It is estimated that at least half of all children born with CHD may not need surgical intervention in their lifespan.<sup>11</sup> These data must be reconciled with the known occurrence of atrial tachycardia, endocarditis, heart failure, and other

associated problems of ACHD patients that are not limited to the operated patients.

## CHD Diagnosed in Adulthood

### *Atrial Septal Defect*

ASD is one of the most commonly diagnosed CHDs among adults. The anatomy of the septal defect that presents in adulthood will most often be a classic ostium secundum defect or a patent foramen ovale, or it can be a sinus venosus defect, which often coexists with partial anomalous pulmonary venous return. The secundum ASD will often have a right axis and right bundle-branch block on the ECG, as well as a pulmonic flow murmur and widely split  $S_2$  on physical examination. The physiology that leads to symptoms in adulthood may be multifactorial. Adult comorbidities such as ischemic heart disease, hypertension, or development of diabetes mellitus can all result in a reduction in LV compliance and an increase of LV diastolic and left atrial pressure compared with right atrial pressure, leading to increased left-to-right shunting with pulmonary overcirculation. In extreme cases, this may accelerate RV failure. Superimposed pulmonary disease, including interstitial disease or obstructive sleep apnea, may adversely affect the RV as well.

The mechanism of adult presentation is relevant to all atrial level shunts. Sinus venosus defect, with or without partial anomalous pulmonary venous return, may present additionally with sinus node dysfunction, a low atrial rhythm, or atrial arrhythmias (also seen in secundum ASD). Any adult presenting with atrial arrhythmia and a dilated RV should be investigated for an atrial level shunt lesion.

With age, pulmonary arteriolar remodeling will lead to increased pulmonary vascular resistance; however, the late presentation of Eisenmenger syndrome, with right-to-left shunting leading to cyanosis, is rare. It is more common with associated genetic syndromes or in people in rural or underserved areas without adequate access to health care who may be living with a large unrepaired shunt (often AVSD, VSD, or patent ductus arteriosus).

Although ASD closure is known to improve morbidity and mortality in children and young adults, data on older adults are more recent and sometimes controversial. However, recent research suggests that in patients >60 years of age, ASD repair has few if any procedure-related deaths and low major complication rates (lower with percutaneous than surgical closure in some series) and results in improved quality of life and New York Heart Association (NYHA) class, as well as decreased RV size with increased biventricular function. These benefits are demonstrated with percutaneous and surgical closure. The prevalence of atrial arrhythmia in this age group may remain stable, perhaps secondary to the additional causes for atrial arrhythmia by this decade of life.<sup>36</sup> In general, with repair at any age >25 years, the risk of atrial arrhythmias is not abolished, although it may be attenuated.<sup>37</sup> Mitral valve competence also may deteriorate after ASD repair in older patients with a large ASD and should be monitored.<sup>38</sup>

### *Bicuspid Aortic Valve*

BAV has a bimodal distribution of progression of AS. These patients may present in their fourth decade of life with

progressive AS, or they may do well into late adulthood. Aortic insufficiency may be a concomitant or primary lesion. Aortic dilation does not have a predictable pattern of progression, and routine follow-up and echocardiography are recommended. Unicuspid aortic valve may progress with AS at a slightly younger age, and quadricuspid aortic valve is diagnosed rarely, but the approach to assessment and surgical correction is similar to that for BAV. In patients diagnosed in late adulthood with BAV, associated lesions should not be overlooked, including aortic dilation, coarctation of the aorta, and, occasionally, other left-sided obstructive lesions (although patients with multiple left-sided obstructive lesions generally will have presented at a younger age).

### *Complex CHD (eg, TOF, CCTGA, Double-Chambered RV, and Coronary Artery Anomalies)*

Initial surgery in adulthood for some of these CHD lesions carries a low complication rate; however, in-hospital complication and surgical mortality rates remain higher than those reported for similar lesions if repaired during childhood. These data emphasize the importance of prompt attention on diagnosis and avoidance of loss to follow-up even in developed countries to decrease procedure-related complication and mortality rates.<sup>39</sup>

### *Tetralogy of Fallot*

TOF is the most common cyanotic CHD in adulthood. Most patients with TOF who present in adulthood have had a complete repair; however, there are some who may present having only undergone palliative surgery or who have had no surgery at all. Those who have had no prior repair may have had an excellent balance of VSD flow with pulmonic stenosis that offered protection from pulmonary overcirculation but no significant cyanosis, may have developed Eisenmenger syndrome from an unrestrictive VSD and minimal pulmonic stenosis, or may have severe pulmonic stenosis or atresia with multiple aortopulmonary collaterals. They may also present with congestive heart failure and systolic dysfunction caused by volume overload from collateral flow or previously placed systemic-to-pulmonary shunts.

In the noncyanotic population >40 years of age, surgical repair, most commonly PVR, with RVOT or transannular patch revision can be performed, with improved functional class in most patients; however, survival is lower than expected, and the need for reoperation does exist. Repair in patients >40 years old is rarely possible or even desirable in those with pulmonary atresia and multiple aortopulmonary collaterals, a number of whom have symptoms related to pulmonary hypertension, which is treatable. Additional surgical concerns are addressed in a subsequent section.

The importance of long-term follow-up should be emphasized at the time of original repair to avoid poor outcomes with a missed opportunity for surgical correction.<sup>40</sup> Those who present after years of pulmonary overcirculation, with Eisenmenger physiology or chronic cyanosis, have unique issues covered in the section on pulmonary vascular disease in the older adult with CHD. Patients with pulmonary overcirculation caused by high multiple aortopulmonary collateral flow or by palliation with systemic pulmonary shunt operations



may have heart failure and systolic dysfunction, discussed under heart failure.

#### *Congenitally Corrected Transposition of the Great Arteries (L-TGA)*

CCTGA or L-TGA is a complex CHD that, although rare, can present initially in adulthood. These patients have ventricular inversion and transposed great arteries, which results in normal blood flow with systemic venous return directed to the PA and pulmonary venous return directed to the aorta; however, the ventricular inversion results in a systemic RV. Although its incidence is low (<1% CHD), if diagnosed secondary to symptoms of heart failure, this group may require frequent hospital visits and use increased healthcare resources. Those who present at a younger age may present with fatigue or dyspnea on exertion or be diagnosed with complete heart block. L-TGA may be associated with VSD, pulmonary stenosis, and apical tricuspid displacement. Although patients with L-TGA have had other associated lesions (ie, VSD treated in childhood),<sup>41</sup> it is important to recognize that late presentation may also occur and will be more easily diagnosed with a high index of suspicion if there are specific presenting findings. The physical examination in L-TGA reveals a single loud S<sub>2</sub>, at times with a holosystolic murmur consistent with systemic AV valve (tricuspid valve) regurgitation. If a VSD or pulmonic stenosis is present, these murmurs (holosystolic or systolic ejection, respectively) may be identified and lead to an echocardiogram. The ECG in L-TGA is classic and reveals absent Q waves in the left precordial leads and their presence in V<sub>4</sub>R (reversed septal depolarization). Complete heart block is another form of presentation of L-TGA in adulthood.

With age, systemic hypertension, and eventual development of systemic AV valve regurgitation (which occurs in more than half of patients by the time of diagnosis), classic orthopnea, paroxysmal nocturnal dyspnea, and dyspnea on exertion may lead to a “heart failure evaluation” and the diagnosis of a systemic RV that may be dilated or depressed secondary to the pressure load of systemic arterial pressure, with heart failure presentation usually secondary to the additional burden of volume load from systemic AV valve regurgitation. Management may include classic heart failure medications, although their benefit in systemic morphological RVs continues to be assessed and may not be the same as in a morphological LV. Coronary angiography also documents inversion of the coronary circulation with a left-sided right coronary artery tree. Surgical intervention for L-TGA is discussed in the Surgery in ACHD for Patients >40 Years of Age section.

#### *Double-Chambered RV*

Double-chambered RV is a rare form of RVOT obstruction consisting of an anomalous muscle bundle that divides the RV, usually between the sinus (inlet) and the infundibulum (outlet). The hemodynamic obstruction of the RVOT is usually an acquired phenomenon, and therefore, double-chambered RV often has a late presentation. In some instances, it is misdiagnosed for many years as pulmonary hypertension, because there is an elevated tricuspid regurgitant jet velocity to the high-pressure inflow portion of the RV chamber. RV outflow obstruction may lead to RV failure symptoms and exertional intolerance and may require surgical correction.

It often occurs in conjunction with VSD or discrete subaortic membrane. Depending on the location of a residual VSD, there may be a high-velocity jet seen from the LV to the low-pressure outflow portion of the RV, or a lower-pressure jet to the inflow portion where right-to-left shunting can occur, especially during exercise. In the setting of palpitations or documented arrhythmia, additional investigation, monitoring, and an electrophysiological study may be warranted in the later decades as in older adulthood; after the sixth decade, ventricular arrhythmias become of concern.

#### *Coronary Artery Anomalies*

Coronary artery anomalies occur in 1% to 1.3% of patients who undergo coronary angiography<sup>42</sup> and are seen in 0.3% of all patients at autopsy.<sup>43</sup> Anomalous courses of the coronary arteries may be benign (such as a retroaortic circumflex artery) or malignant. For the purposes of this discussion, we will focus on potentially malignant lesions in older adults. These anomalies are important to recognize because they may carry a risk of myocardial ischemia, ventricular dysfunction, VT or ventricular fibrillation, and sudden death in some anatomic subtypes. Coronary anomalies are the second most common cause of sudden death associated with strenuous exercise in competitive athletes after hypertrophic cardiomyopathy; however, the risk in the general adult population is not as well defined. When these subtypes of coronary artery anomalies were assessed, the presence of a left coronary artery from the right sinus was thought to be more strongly associated with risk of sudden cardiac death (SCD); however, there is increasing recognition that a dominant right coronary artery from the left sinus of Valsalva with high-risk anatomic features may pose an equal risk.<sup>44-46</sup>

At older ages, several factors must be taken into account when determining the potential level of risk from an anomalous coronary artery and indications for surgery. Symptomatic documented ischemia or ventricular arrhythmia is an indication for surgical repair. A slit-like coronary ostium, an acutely oblique proximal coronary course (particularly with a high takeoff as occurs with the anomalous right coronary artery), and a longer segment running within the arterial wall (“intra-arterial”) are all high-risk features. Additionally, ventricular arrhythmia elicited on exercise testing, unexplained syncope, or a dominant anomalous vessel should prompt further evaluation and discussion. The single coronary ostium, although less common, also is a concern for SCD risk.<sup>47</sup>

Identification and assessment of anomalous coronary arteries can be achieved with multiple imaging modalities. Echocardiography frequently has excellent resolution in children and young adults but may be less sensitive in older adults. The right coronary artery is generally harder to image than the left, although visualization in the parasternal long-axis view next to the aorta may be helpful. Coronary angiography has traditionally been used to delineate arterial course and branches, determine dominance, and assess a patient for atherosclerosis, although much of that can now be achieved with coronary computed tomographic angiography (CTA). The use of coronary angiography for assessment of ischemia with exertion in the laboratory, as well as pressure wire measurements, fractional flow reserve, and intravascular ultrasound,

may be of help in particularly challenging cases with unclear symptoms, poor ostial imaging on echocardiography, or computed tomography (CT) to assess the anatomy and physiology of proximal segment narrowing. The risk of coronary occlusion, ischemia, or arrhythmia should be recognized by the operator when these studies are undertaken.

Coronary CTA has become the “gold standard” for assessment of anomalous coronary origin and course in the older adult. In experienced hands, it offers anatomy and coronary course assessment in a cross section of the coronary ostium and determination of coronary atherosclerosis. Intramural coronary length was recently reported as a potential additional measure in a younger group of patients, in whom intramural coronary length as measured intraoperatively correlated with preoperative symptoms (angina, VT, syncope, SCD), with longer segments noted in the symptomatic patients.<sup>48</sup> This has not been assessed systematically in the older adult population; however, clinical observation supports this finding, and it is likely that in the future, CT may provide more data, which can influence management.

The current ACHD guidelines<sup>49</sup> recommend 3 criteria for Class I indications for surgical intervention: (1) an anomalous left main coronary artery coursing between the aorta and PA, (2) ischemia caused by coronary compression (when coursing between great arteries or in intramural manner), and (3) an anomalous right coronary artery origin between the aorta and PA with evidence of ischemia.

#### *Aortic Dilation in ACHD*

Aortic enlargement may occur in patients with conotruncal abnormalities (TGA, double-outlet RV, truncus arteriosus, TOF) regardless of whether they have undergone intervention. Patients who have undergone Damus-Kaye-Stansel procedures may have neo-aortic dilation, and patients with a Jatene arterial switch for D-TGA may also present with significant aortic dilation (although the oldest of these patients are a decade away from being an “older” adult [ $>40$  years old]). Management is challenging because aortic dissection is rare; therefore, observation may be an appropriate course in some of these patients. In patients who have had aortic valve repair/replacement, moderate aortic enlargement may be encountered in those with conotruncal abnormalities, and the management approach should be discussed for each case individually with a multidisciplinary ACHD team. Although few women will contemplate pregnancy after the age of 40 years, the management of these dilated aortas is challenging in this population and similarly necessitates preconception counseling, as well as intrapartum and postpartum close follow-up.<sup>50</sup>

#### **Recommendations in the Adult $>40$ Years of Age With Newly Diagnosed ACHD**

- 1. In adults with a new presentation of a simple shunt or valve lesion with no hemodynamic concerns, evaluation by a general cardiologist in consultation with an ACHD cardiologist is reasonable (Class IIIa; Level of Evidence C).**
- 2. In adults with moderate or complex lesions or those with simple lesions with associated cyanosis, pulmonary hypertension, or significant or complicated valve**

**disease, patient evaluation at an ACHD center annually and then coordinated care with a general cardiologist are recommended (Class I; Level of Evidence C).**

- 3. For patients with simple lesions, interval follow-up can be determined by the cardiologist, ensuring loss to follow-up does not occur. However, with any moderate to complex disease, at least annual ACHD visits with testing as recommended by the ACHD specialist and in the ACHD guidelines should be followed to ensure the best possible long-term outcomes for these patients (Class I; Level of Evidence C).**
- 4. Atrial level shunts with RV enlargement and without PAH are recommended for closure to prevent the development of RV failure, improve exercise capacity and likely decrease future burden of atrial arrhythmia (Class I; Level of Evidence B).**
- 5. Intervention for coarctation of the aorta with obstruction should be considered for palliation of hypertension and possibly heart failure (Class I; Level of Evidence C).**
- 6. Patients with newly diagnosed coronary artery anomalies should be evaluated by an ACHD team with expertise in imaging, CAD management, intervention, and surgical revascularization for coronary anomalies (Class I; Level of Evidence C).**
- 7. Complex ACHD will rarely present de novo in adulthood, but when recognized, patients should receive comprehensive care at an ACHD center with multidisciplinary input (Class I; Level of Evidence C).**

#### **Impact of Acquired Heart Disease Management of Cardiovascular Risk Factors**

The relationship between the risk factors of hypertension, hyperlipidemia, and diabetes mellitus with cardiovascular disease is well established.<sup>51</sup> As the CHD patient ages, exposure to these risk factors may be considered no less problematic than with the non-CHD population. The ACHD individual may have abnormal myocardial substrate, abnormal cardiovascular physiology, abnormal anatomy, or any combination of the 3. The adverse impact of superimposed cardiovascular risk factors may well be amplified in this group, who also may already be at risk for systemic ventricular dysfunction, rhythm disturbances, and heart failure. It has been reported that  $\approx 80\%$  of adults with CHD had at least 1 cardiovascular risk factor.<sup>52</sup> Primary prevention, with a thorough assessment and approach to risk factor management, is imperative in this population. We explore the prevalence and relationship of these risk factors to CHD and appropriate CHD subsets and suggest appropriate screening strategies and therapeutic goals.

#### *Hypertension*

##### *Prevalence*

Approximately one third of US adults have hypertension (blood pressure  $>140/90$  mm Hg).<sup>53</sup> The prevalence increases with age, and there is a progressive rise in systolic pressure that averages 20 to 30 mmHg between early and late adulthood. The prevalence at age 45 to 54 years is 36% in men and women, and by age 75 or older, 65% in men and 80% in women.<sup>54,55</sup> There is a relative paucity of data on the prevalence of hypertension in the ACHD population. There may be an increased



risk of hypertension in the ACHD population compared with the general population,<sup>56</sup> especially among men.<sup>52</sup> Quebec CHD database figures showed a prevalence of 47% in a CHD population comprising people >65 years of age.<sup>57</sup> The pathogenesis of hypertension in this population may be multifactorial and may extend beyond traditional risk factors and age. Select groups who may be at increased risk include those with renal abnormalities (such as the renal disease associated with cyanotic CHD)<sup>58</sup> and patients with coarctation of the aorta, who may have systemic hypertension despite abolition of a coarctation gradient. In patients with coarctation of the aorta, the prevalence of hypertension is higher with later repair.<sup>59,60</sup> Obesity is associated with development of hypertension, insulin resistance, dyslipidemia, sleep apnea, autonomic imbalance, and increased inflammatory cytokines. The prevalence of obesity in the general population has been increasing dramatically, and this trend does not appear to spare the ACHD population. Increased body mass index (BMI) is common in ACHD, with a pooled study of ACHD outpatients >18 years of age showing that 54% had BMI >25 kg/m<sup>2</sup> and 20% had BMI >30 kg/m<sup>2</sup>.<sup>61</sup>

### Treatment

Hypertension is a leading risk factor for heart disease and stroke, the leading and third-leading causes of death in the United States, respectively. Appropriate treatment in any population is imperative. The ACHD patient may be particularly vulnerable because many already have abnormal hemodynamics. Changes in aortic stiffness, diameter, and wave reflection that can occur with aging may lead to increased ventricular afterload, resulting in potential adverse effects in late systolic ejection and diastolic relaxation. The single or systemic ventricle, which may poorly tolerate increased afterload, may be particularly sensitive to these changes, resulting in detrimental effects. Therefore, monitoring and appropriate treatment according to available guidelines are indicated in all ACHD patients. Standard diagnostic workup of hypertension is indicated, including assessment of target organ damage and exclusion of identifiable causes of hypertension. Urinalysis, blood glucose levels, hematocrit, lipid panel, basic metabolic panel, and calcium levels should be obtained. Identifiable causes of hypertension, such as sleep apnea, nonsteroidal anti-inflammatory drug use, chronic kidney disease, endocrine causes, renovascular disease, and coarctation, should be considered.

The current recommendations for hypertension management in the general population are to treat to <140/90 mmHg or <130/80 mmHg in patients with diabetes mellitus or chronic kidney disease. There is concern about overaggressive blood pressure lowering in people >80 years old, with guidelines indicating <140/90 mmHg as a goal in most but 140 to 145 mmHg as acceptable, with avoidance of a diastolic pressure <65 mmHg.<sup>62,63</sup> These recommendations can be extrapolated to the ACHD population with consideration given to lower blood pressure goals in those with lesions, who would benefit from lower afterload (ie, single ventricle, systemic RV) and aortic dilation.

Lifestyle modification is recommended in all patients, individualized as to their specific circumstances. In patients with coarctation of the aorta who are at risk for hypertension and premature CAD, strict blood pressure control is of utmost importance. In all patients, obesity increases the risk

of several comorbidities, including premature development of vascular disease, diabetes mellitus, hypertension, and stroke. Attainment of ideal body weight, with a BMI goal of 18.5 to 24.9 kg/m<sup>2</sup>, healthy eating, and a healthy lifestyle should be stressed and monitored. This would include sodium restriction, a DASH (Dietary Approaches to Stop Hypertension)-type eating plan, and regular physical activity, as determined by the underlying cardiac situation. Moderation of alcohol consumption should also be discussed.

Pharmacological therapy should be initiated per current published guidelines.<sup>53</sup> In most cases, at least 2 agents will be necessary to reach goals. Specific subgroups, however, deserve special mention. In cyanotic CHD, nephropathy has long been recognized as a potential complication.<sup>58,64</sup> The renal glomeruli are hypercellular and congested and eventually become sclerotic. There is a reduction in the glomerular filtration rate, increased creatinine levels, and proteinuria. Medications such as angiotensin-converting enzyme (ACE) inhibitors, diuretic agents, and nonsteroidal anti-inflammatory drugs may affect renal function, and their use should be limited to necessary instances with close monitoring of creatinine, glomerular filtration rate (GFR), or both. In patients with Eisenmenger physiology, extreme caution should be used when giving any vasodilating agent, which could result in accentuation of right-to-left shunting.<sup>65</sup> Coarctation of the aorta is now known to be a lifelong process related to underlying aortopathy and possible vasculopathy.<sup>59,60,65</sup> Even with adequate repair, a significant number of patients remain hypertensive, with the incidence of hypertension directly related to age at repair. Sequelae and associations also include ascending aortic aneurysm, aneurysm at the repair site, and premature CAD. Lifelong follow-up is therefore mandatory. Treatment of hypertension in a patient with repaired coarctation without a significant residual gradient would include the standard Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure approach. When a recurrent or residual gradient is present, stenting of the obstruction may relieve hypertension or reduce the need for medication. In cases of aneurysm, it is unclear whether initiation of an ACE inhibitor or angiotensin II blockade would be of benefit beyond the blood pressure-lowering effects of these medications. Angiotensin receptor blockers may have a protective effect for the patient with a dilated Marfan aorta, possibly related to the inhibition of excessive transforming growth factor- $\beta$  signaling.<sup>66</sup> Whether these data are applicable to the coarctation or bicuspid valve associated aneurysm is unknown. Significant coarctation of the aorta can mimic the renal physiology of severe bilateral renal artery stenosis. Administration of ACE inhibitors in this setting has been reported to precipitate acute renal failure because of already restricted flow via the renal arteries downstream of the coarctation, and ACE inhibitors should be used with vigilance in the presence of significant hemodynamic coarctation.<sup>67</sup>

### Diabetes Mellitus

#### Prevalence

The prevalence of diabetes mellitus in the general population is 4% for those aged 20 to 44 years, 14% for ages 45 to 64, and 30% for those >65 years old.<sup>55</sup> Type 2 diabetes mellitus

accounts for 90% to 95% of all diagnosed cases of diabetes mellitus in adults. On the basis of data in the general population, it may be inferred that at least 1 in 5 adults with CHD will be affected with diabetes mellitus.

The prevalence data for diabetes mellitus in the ACHD population are sparse. A report from the United Kingdom demonstrated that when adjusted for smoking and deprivation, there was a significantly increased risk of diabetes mellitus in the ACHD population compared with control subjects.<sup>56</sup> However, another European study of risk factor prevalence in the ACHD population found no difference in incidence of diabetes mellitus compared with the general population.<sup>52</sup> Average age was not given in that study, and one could surmise that if younger patients were included, the prevalence may not reflect the older ACHD population. Special populations may be at increased risk for diabetes mellitus; for instance, the prevalence of type 1 diabetes mellitus in patients with Down syndrome is estimated at 1.4% to 10.6%, significantly higher than in the general population.<sup>68</sup>

Development of premature CAD has been correlated not only with diabetes mellitus but also with cardiovascular risk factors such as elevated total cholesterol or low-density lipoprotein (LDL) cholesterol and, importantly, impaired glucose tolerance.<sup>51</sup> There is evidence for abnormal glucose metabolism in ACHD patients.<sup>69</sup> Abnormal glucose metabolism is recognized as a powerful predictor of cardiac morbidity and mortality. The pathogenesis is probably multifactorial and lesion specific. A high prevalence of abnormal glucose metabolism has been shown in patients with complex ACHD and appears to be associated with central obesity, hepatic and renal dysfunction, diuretic use, and increased plasma renin activity.<sup>70</sup> It would therefore be expected that a significant percentage of the population with moderate or complex ACHD will have diabetes mellitus or abnormal glucose metabolism. Of note, with regard to glucose management, the fasting glucose level in cyanotic patients may be lower because of the high resting catecholamine state and impaired nutritional status<sup>71</sup>; however, there may concomitantly be increased clearance of insulin by the lung in right-to-left shunts.

Because diabetes mellitus and glucose intolerance are such potent risk factors for cardiovascular morbidity, appropriate screening and treatment strategies are increasingly an important part of the care of the ACHD patient.

#### *Diagnosis and Treatment*

The detailed treatment strategy for the adult with diabetes mellitus is outside the scope of this scientific statement. Surveillance and anticipation of metabolic risk are essential. As noted, 1 in 5 ACHD patients may be affected, and these numbers may increase in the face of the escalating incidence of obesity. The current published guidelines suggest all patients with BMI  $\geq 25$  kg/m<sup>2</sup> with  $\geq 1$  risk factors for diabetes mellitus be screened for abnormal glucose tolerance, and all those  $>45$  years old should be screened as well.<sup>72</sup> These recommendations should be applied in the ACHD population with consideration for diabetes mellitus screening in all those  $>40$  years of age with BMI  $\geq 25$  kg/m<sup>2</sup>, with or without risk factors. Appropriate screening would include hemoglobin A<sub>1c</sub>, fasting plasma glucose, or 2-hour 75-g oral glucose tolerance

test. If tests are normal, repeat testing at 3-year intervals is reasonable.

Other cardiovascular risk factors need to be treated aggressively. A goal blood pressure  $<130/80$  mmHg should be targeted. If lifestyle modification alone does not achieve this goal, then pharmacological therapy is appropriate. For pharmacological therapy in the diabetic patient, an ACE inhibitor or angiotensin receptor blocker should be included, except in a subset of patients with cyanotic heart disease, in whom its use may be contraindicated, as discussed previously.

Finally, patients with diabetes mellitus are considered in the high-risk category for treatment of dyslipidemia as described in the subsequent section. Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, in all diabetic patients  $>40$  years of age who have  $\geq 1$  cardiovascular risk factors and in any patient with established vascular disease. The goal for LDL treatment is  $<100$  mg/dL in the absence of vascular disease and  $<70$  mg/dL for the high-risk patient with established vascular disease and diabetes mellitus.

### *Hyperlipidemia*

#### *Prevalence*

The age-adjusted prevalence of high LDL cholesterol in US adults from 1999 to 2004 was 25.3%. The percentage of the population aged 45 to 54 years and 55 to 64 years with total cholesterol  $>240$  mg/dL (2003 to 2006) was 21% and 16%, respectively.

There is a paucity of prevalence data on dyslipidemia in the adult with CHD. The Quebec Congenital Heart Disease Database noted a 27% incidence of dyslipidemia in patients  $>65$  years of age.<sup>57</sup> In a study from the United Kingdom, dyslipidemia was present in 19% of all ACHD patients and in 15% and 10% with intermediate and complex lesions, respectively.<sup>73</sup> These data are from registries or single centers outside the United States and may not be accurately extrapolated to the US ACHD population, although available data suggest that at a minimum, the prevalence of dyslipidemia is likely similar to the general population.

#### *Treatment*

Current guidelines for lipid management in both primary and secondary prevention are well established in the general population.<sup>74</sup> In the Adult Treatment Panel III, LDL was identified as the primary target of therapy. The optimal LDL level was defined as  $<100$  mg/dL, with therapeutic goals of treatment outlined. Since that report, new data from clinical trials have been reported, resulting in the "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults."<sup>75</sup>

In the ACHD population, the presence of comorbid risk factors, in the setting of a high incidence of residual hemodynamic, arrhythmic, and heart failure issues seen in this population, mandates an aggressive approach to risk factor modification. The application of these guidelines or of upcoming treatment recommendations should be adhered to in the adult with CHD.

Certain subsets of ACHD patients may be considered to have potentially higher cardiovascular risk for the purpose of lipid treatment. Although few patients  $>40$  years of age have

undergone arterial switch operation for transposition of the great vessels, this surgery is now routinely performed, and an older population will be emerging. The great arteries are transected, and the coronary arteries are translocated to the opposite arterial root. This translocation involves injury of the sympathetic nerves that supply the coronary arteries, with attendant denervation.<sup>76</sup> Abnormal vasoreactivity has been documented in these arteries, as well as increased intimal thickness and rare coronary events.<sup>77,78</sup> Whether this seemingly increased risk would qualify as the “high-risk” category with regard to statin therapy is unclear at this time. A target of “optimal” LDL of  $\leq 100$  mg/dL would not seem unreasonable in this group. Coarctation of the aorta is another group with increased cardiovascular risk. Whether this is caused by a primary vasculopathy or related risk factors (hypertension) is unclear, but consideration of an optimal LDL level in this population should also be considered. The use of statin therapy to prevent structural valve degeneration of bioprosthetic valves, specifically aortic, has been considered. The data regarding their long-term use for this purpose are somewhat conflicting, although they have pleiotropic properties that may be beneficial in the perioperative period.<sup>79,80</sup>

### Hyperlipidemia Recommendations

1. **The ACHD patient may have abnormal myocardial substrate, abnormal coronary physiology, abnormal coronary anatomy, or any combination of the 3 conditions. Primary prevention for acquired CAD with a thorough assessment for and approach to risk factor management is recommended in this population (Class I; Level of Evidence C).**
2. **In the treatment of the hypertensive patient with cyanotic CHD, ACE inhibitors, angiotensin receptor blockers, and diuretic agents should be used cautiously,<sup>64</sup> and care should be coordinated at an ACHD center (Class I; Level of Evidence C).**
3. **The patient after arterial switch operation represents a potentially higher long-term coronary risk, so it is reasonable to optimize CAD risk factors from young adulthood (Class IIa; Level of Evidence C).<sup>76,77</sup>**

### Heart Failure in the Adult With CHD

#### Prevalence

As the ACHD population ages, heart failure admissions and mortality are increasing. The Dutch CONCOR national registry identified a greater rate of mortality in ACHD patients than in the general population, with 77% of deaths being of cardiovascular origin and 45% caused by chronic heart failure, with a mean age at death of only 48.8 years.<sup>1</sup>

The pathophysiology of heart failure in ACHD is multifactorial. For example, systolic dysfunction of the systemic ventricle is common in patients with D-TGA after atrial switch and in patients with L-TGA. In the Fontan population, the systolic function of the single ventricle may be normal, and heart failure may result from a combination of diastolic dysfunction with increasing Fontan pressures, which leads to systemic venous congestion. Although patients with ACHD often

do not report significant symptoms (82.4% NYHA class I or II in the single-ventricle and systemic RV population), clinical heart failure is documented in 22.2% of patients with TGA who have had a Mustard procedure, 32.3% of L-TGA patients, and 40% of patients who have had a Fontan procedure, with symptomatic patients demonstrating a significantly lower peak  $\dot{V}O_2$ , systemic ventricular ejection fraction, and higher mortality rate.<sup>81</sup>

#### Treatment

The challenge of how to stem the progression of heart failure in these populations remains. Trials of proven heart failure therapies used in non-ACHD heart failure do not report the same resounding success in the ACHD population. Whereas some studies (double-blind randomized controlled trials<sup>82</sup>) have revealed no significant change in exercise capacity or neurohormones with  $\beta$ -blockade,<sup>83,84</sup> others reported improvement in NYHA class and smaller systemic RV end-diastolic area (in D-TGA Mustard patients), which correlated with higher doses of  $\beta$ -blockade.<sup>85</sup> In similar D-TGA atrial switch populations, ACE inhibitor use has also been assessed with mixed results,<sup>86–88</sup> and in a randomized controlled trial with the angiotensin receptor inhibitor valsartan, there was no significant treatment effect on RV ejection fraction, exercise capacity, quality of life, or clinical events.<sup>89</sup>

In conditions with systemic RVs, including L-TGA, D-TGA with atrial switch, and hypoplastic left heart syndrome, heart failure is seen with older age. To stem the progression of ventricular decline, relieving systemic AV valve regurgitation can positively alter the course of disease in these patients, especially when performed before the systemic RV ejection fraction declines. In patients undergoing late operation for L-TGA (systemic tricuspid valve repair or replacement), long-term survival correlates with preoperative ejection fraction. There is nearly 100% survival at 10 years in patients with RV ejection fraction  $>44\%$  on preoperative echocardiography who undergo surgery with an ACHD surgeon compared with 19.5% survival with lower RV ejection fraction. Early deaths do occur in 10% of operated patients, and 25% of patients will need reoperation.<sup>90,91</sup>

Novel electrophysiological techniques such as cardiac resynchronization or multisite pacing have been applied in ACHD as well. Initial studies suggest that the addition of an LV lead (epicardial or coronary sinus) may benefit the chronically paced adult with CHD; multisite RV pacing has been described in CHD patients with RV dysfunction; and cardiac resynchronization therapy has been used in patients with TOF with LV dysfunction, all in small studies. Patients with surgically related complete heart block and RV pacing from childhood onward may be particularly appropriate candidates for cardiac resynchronization. The anatomy for multisite pacing can be challenging, with abnormal coronary venous drainage in some populations. Placement of thoracoscopic (systemic) RV leads and endocardial placement of an atrial lead have enabled cardiac resynchronization to be performed in select D-TGA Mustard patients.<sup>92,93</sup> However, longer-term nonanecdotal data in larger ACHD populations are not yet available.

Finally, the challenge exists of deciding when to list ACHD patients for consideration for transplantation. Patients born

in the 1950s and 1960s and those with unrecognized cyanotic disease have already declared themselves to often need dual-organ transplant (heart-liver or heart-lung), with increasing presentation for this in the past decade. In a 2003 report from a registry of the International Society for Heart and Lung Transplantation, 32.2% of patients who underwent transplantation secondary to heart failure were adults with CHD (1.7% of all candidates).<sup>94</sup> Heart transplantation was successful in 79% of ACHD patients, with a survival rate of 79% at 1 year and 60% at 5 years, similar to the overall rate. However, the 10-year survival rate was only 62% in Fontan patients after heart transplantation. In a study of 605 heart-lung or lung transplantations for Eisenmenger syndrome, interestingly, VSD had a better prognosis than ASD or patent ductus arteriosus.<sup>94–97</sup> The challenge of transplantation in the ACHD population includes the fact that ACHD is a multisystemic disease, and renal, pulmonary, and hepatic dysfunction, as well as the effects of chronic cyanosis in a subset of patients, can lead to many immediate postoperative complications, as well as long-term concerns. A history of multiple prior interventions in some patients may result in a significant burden of antibodies and require the use of desensitization protocols. The close interaction of ACHD programs with adult heart failure programs will be necessary in upcoming years to ensure a structured approach to end-stage heart failure in ACHD, and ideally, an early approach to consideration for listing for transplantation when appropriate. Where appropriate, end-of-life discussions should not be avoided in this relatively young population and should certainly be addressed in the older ACHD population.

### Recommendations for Heart Failure in the Adult With CHD

1. Patients with moderate to complex ACHD are at risk for development of heart failure, and clinicians should emphasize early referral to an ACHD center to initiate a plan for heart failure prevention or treatment (*Class I; Level of Evidence C*).
2. Evaluation at an ACHD tertiary care center with a heart failure service and electrophysiological service allows for multidisciplinary care of these complex patients. The ACHD specialist should lead the direction of care, because these patients are not directly comparable to heart failure patients with acquired disease (ischemic and nonischemic) (*Class I; Level of Evidence C*).
3. Transplant evaluation, when considered, should include in the risk-benefit assessment not only the mortality or morbidity of transplantation but also the presence of antibodies secondary to multiple prior surgeries in some patients and the coexistence of multisystem dysfunction (ie, renal, hepatic, pulmonary hypertension) (*Class I; Level of Evidence C*).

### Arrhythmias: Diagnosis and Treatment

With improved survival to older adulthood, arrhythmias have emerged as a major cause of morbidity and mortality in the ACHD population.<sup>98</sup> Arrhythmias can occur as a direct result of the specific CHD anomaly or as sequelae of prior corrective/palliative surgery. The interaction of suture lines, conduits,

baffles, and patches with chamber dilation, hypertrophy, fibrosis, abnormal hemodynamics, and direct trauma to the specialized conduction system forms the complex substrates for the spectrum of arrhythmias encountered.<sup>99</sup> In particular for the older adult with ACHD, later age of reparative surgery is associated with increased incidence of arrhythmias.<sup>100,101</sup> Catheter ablation has emerged as an excellent early therapeutic option in experienced ACHD centers. With standard incorporation of 3-dimensional mapping technology for precise localization of tachycardia circuits<sup>102–104</sup> and the routine use of irrigated-tip radiofrequency ablation catheters,<sup>105</sup> acute success rates of  $\approx 80\%$  can be achieved.<sup>104,106</sup> Specific issues, by arrhythmia and congenital lesion, are addressed below.

### Tachyarrhythmias

#### *Wolff-Parkinson-White Syndrome and Accessory Pathway-Mediated Tachycardia*

Wolff-Parkinson-White syndrome is associated with certain forms of CHD, particularly Ebstein anomaly.<sup>107</sup> For the older adult, because of progressive atrial dilation and scarring, the burden of tachycardia episodes increases as the incidence of atrial fibrillation (AF) increases, which poses risk for rapid conduction over the accessory pathway(s). Standard of care is catheter ablation as curative therapy, although the distorted anatomy (including location of AV node) and frequent presence of multiple pathways lead to lower acute and chronic success rates for patients with CHD than for patients with structurally normal hearts.<sup>107–109</sup> For patients with Ebstein anomaly undergoing surgical treatment of tricuspid valve disease, intraoperative ablation of accessory pathways is safe and effective.<sup>110</sup> The addition of the atrial maze procedure to surgical repair for patients with AF can be beneficial. Supraventricular tachycardias caused by accessory pathways may also be identified in patients with L-TGA and Ebstein anomaly of a left-sided tricuspid valve.<sup>109</sup>

#### *Intra-Atrial Reentrant Tachycardia*

The most common arrhythmia facing older adults with CHD is recurrent IART, a macroreentrant circuit within atrial tissue that has been disrupted by patches, atriotomy incisions, and scars.<sup>111–113</sup> Multiple IART circuits are often present in the same patient.<sup>102</sup> Cavotricuspid isthmus-dependent atrial flutter that revolves around the tricuspid annulus may be a common circuit; however, unusual circuits are often present, particularly when the tricuspid valve is not present or is distorted. Unlike the classic sawtooth flutter waves at  $\approx 300$  beats per minute that are observed in typical atrial flutter in structurally normal hearts, P-wave morphology and rates in IART are variable and typically slower because of the unpredictable paths, ranging from 170 to 250 beats per minute.<sup>99,110</sup> These slower rates may allow for 1:1 AV conduction, which can result in hypotension, syncope, or even sudden death.<sup>114–116</sup> In the older ACHD patient, slower conduction of IART with 2:1 or 3:1 block may be misinterpreted as sinus rhythm; therefore, the index of suspicion should always be high.<sup>117</sup> Vagal maneuvers can be helpful to uncover P waves obscured by QRS or T waves. Atrial thrombi have been noted in a subset of CHD patients with IART; therefore, screening with transesophageal echocardiography (TEE) should be discussed for each individual situation.<sup>118</sup>

Although any patient who has undergone an atriotomy, including repair for ASD or TOF,<sup>119</sup> may be at risk for IART, its incidence is highest in those who have undergone Mustard or Senning repair for D-TGA<sup>110</sup> or the Fontan procedure for single ventricle. In particular for the older Fontan patient, >50% of those with older atriopulmonary connections will develop IART within 10 years of repair<sup>100,120</sup> compared with <10% for those with newer cavopulmonary connections.<sup>121</sup> Other risk factors for development of IART are concomitant sinus node dysfunction (tachy-brady syndrome) and older age at the time of Fontan repair.<sup>100</sup> Often, multiple circuits are present because of the dilated and thick atria. Up to one third of patients with D-TGA after atrial baffling will develop IART as well.<sup>110</sup>

Treatment options for IART depend on frequency, patient recognition and tolerance, and whether accompanying tachy-brady syndrome or atrial thrombus is present. If IART is well tolerated and infrequent, elective direct current cardioversion with preprocedural TEE to rule out atrial thrombus (unless anticoagulation has been established for several weeks) is favored. For such patients, chronic AV nodal blockade with digoxin, a  $\beta$ -blocker, or a calcium channel blocker to reduce rapid ventricular conduction and chronic anticoagulation are prescribed. Although class IC and III antiarrhythmic agents may be considered in those without sinus node or systolic dysfunction, efficacy has been limited in the ACHD population.<sup>99,114</sup>

For those with sinus node dysfunction, a pacemaker will provide atrial rate support, which itself may reduce IART episodes and allow for treatment with agents that may otherwise exacerbate bradycardia.<sup>122</sup> Although atrial antitachycardia pacing may be beneficial,<sup>115,123</sup> because of the risk for acceleration of atrial rates, these treatments should be used with caution and typically in conjunction with AV nodal blocking agents. In the appropriate patient with both IART and VT or at high risk for SCD, implantable cardioverter-defibrillators (ICDs) with atrial antitachycardia features, including low-energy shocks, may be considered.

For patients with more frequent IART episodes or significant associated symptoms, catheter ablation has emerged as an excellent early therapeutic option in experienced ACHD centers, with a high success rate. Access to the atrial area that requires ablation and adequate ablation without resulting complications with conduction may necessitate that the procedure be performed in ACHD centers with high-volume electrophysiology laboratories.

Later recurrence of clinical IART or new circuits after catheter ablation is observed in approximately one-third of patients, with higher risk in patients who have undergone the Fontan procedure.<sup>104</sup> Overall, ablation results are superior to those with antiarrhythmic medications, and even if not entirely successful, ablation often substantially reduces the burden of IART episodes. As technology advances and experience accumulates, ablation success is expected to continue to improve.

For patients with refractory IART, or if surgery is planned for hemodynamic indications, surgical ablation with the atrial maze procedure can be beneficial. This is most commonly used as an adjunctive procedure in the Fontan patient undergoing revision from atriopulmonary to newer cavopulmonary connection.<sup>124</sup> Although recurrence rates have been

very favorable at  $\approx 12\%$ , for the older patient with increased comorbidities, surgical risks should be considered carefully against potential benefit.

#### *Atrial Fibrillation*

Much less common than IART, AF is most often observed in patients with mitral valve disease, congenital AS, or palliated single ventricle.<sup>125</sup> Anticoagulation with warfarin is generally recommended in older ACHD patients with sustained AF, regardless of the presence of traditional risk factors (congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior cerebrovascular accident). The new oral anticoagulant agents have not yet been studied in the ACHD population. Other management strategies mirror those for AF in other forms of heart disease: Ventricular rate control is the mainstay, and electrical cardioversion is indicated for sustained or symptomatic episodes. Antiarrhythmic therapy with class III agents may be considered but often has limited efficacy. Pacemaker implantation, when indicated for concomitant tachy-brady syndrome, may also reduce AF episodes. Catheter ablation for AF has not yet been studied in the ACHD population; however, if a patient is undergoing surgery for hemodynamic indications, it may be reasonable to consider an adjunctive atrial maze procedure.

#### *Ventricular Tachycardia*

In the older ACHD population, VT is prototypically seen in patients with TOF, but ventricular arrhythmias may also develop in a spectrum of lesions, including congenital AS, D-TGA or L-TGA, severe Ebstein anomaly, single ventricle, and VSD with PAH. A decline in hemodynamic status often heralds the occurrence of VT.<sup>126</sup> The classic presentation is macroreentrant VT as a late postoperative complication of ventriculotomy or VSD patch, with the circuit(s) revolving around these regions of scar in the RVOT. Most VTs are rapid, resulting in syncope or cardiac arrest. Some VTs may be slow and thus hemodynamically tolerated; however, because IARTs are also common in this population,<sup>119</sup> patients experiencing palpitations may have either or both.

For older adults with repaired TOF, SCD is the most common cause of late mortality, with an incidence of 2% per decade<sup>117</sup> and approaching 10% by 35 years after surgical repair.<sup>127,128</sup> Cohort studies have identified older age at time of repair, advanced RV dilation, presence of RVOT patch, QRS interval  $\geq 180$  ms, and annual increase in QRS duration as independent risk factors.<sup>101,129,130</sup> Predictive strategies for future VT risk in these patients, including the use of Holter monitoring and exercise testing, have limited accuracy. Electrophysiological testing with programmed ventricular stimulation has shown promise in distinguishing high- and low-risk patients<sup>131,132</sup>; however, because it is invasive, it is currently reserved for patients with rapid palpitations, dizziness, unexplained syncope, or significant Holter findings (ie, rapid or frequent nonsustained VT). For asymptomatic patients, no consensus strategy exists for surveillance or risk stratification. Beyond the annual ECG and periodic Holter monitor, selected testing is guided by the patient's symptoms and hemodynamic status.

Predictors of SCD after the Mustard or Senning procedure include documented arrhythmias (VT, AF, or IART) and symptoms referable to arrhythmias or heart failure.<sup>133</sup> Most

SCD events occur during exercise. Although electrophysiological study and catheter ablation may be useful in defining and treating arrhythmias, prospective studies have yet to be performed to define their impact on future SCD risk. Pacing has not been found to be protective.

For patients with documented sustained VT or cardiac arrest, definitive therapy including catheter ablation, ICDs, or arrhythmia surgery has replaced pharmacological management, which now plays a largely supplemental role. Because VT and cardiac arrest often coincide with hemodynamic derangements, hemodynamic evaluation is recommended along with electrophysiological testing to identify the need for possible surgical intervention, such as valve replacement, which would allow intraoperative VT ablation.<sup>134</sup> In the older adult with CHD, acquired disease may also be present; therefore, ensuring coronary ischemia is not contributing to ventricular arrhythmia should be part of the evaluation.

Catheter ablation of hemodynamically tolerated VT has favorable acute success in experienced centers<sup>135–138</sup>; however, because late recurrence occurs in  $\approx 20\%$  of cases,<sup>138</sup> ICDs should still be considered as primary therapy for most ACHD patients with VT or in whom there is a high suspicion for VT.<sup>139</sup> Therefore, catheter ablation as sole therapy for VT should be reserved for the few ACHD patients with excellent hemodynamic status and slow, solitary VTs on electrophysiological testing, as well as lack of inducibility on follow-up ventricular stimulation. Catheter ablation may be valuable adjunctive therapy in patients with a high burden of ICD shocks.

Transvenous ICD systems can be implanted in the majority of ACHD patients. The exceptions are patients with single ventricles, stenoses in venous pathways, or significant residual intracardiac shunts, for whom an endovascular lead would increase thromboembolic risk; epicardial systems are implanted in these cases. Defibrillation thresholds are similar to those for other adult patients with acquired heart disease. However, lead revisions are commonly needed because of relatively high lead failure rates in the ACHD population.<sup>139</sup>

### **Bradycardias**

#### *Sinoatrial Node Dysfunction*

True congenital sinoatrial node dysfunction is limited to rare forms of heterotaxy syndrome in patients with single ventricle, with dual sinus nodes seen in the asplenia type and lack of sinus node in the polysplenia type.<sup>117</sup> Only the latter type results in clinically significant bradycardia that requires pacemaker implantation. Sinoatrial node dysfunction may also be seen in patients with sinus venosus defects. More commonly, sinus node dysfunction is acquired as a complication of Mustard, Senning, Glenn, or Fontan operations that compromise the node itself or its artery and increase the risk of IART or AF.<sup>100,110,140,141</sup> Sinus node dysfunction and tachy-brady syndrome are observed in more than half of D-TGA patients after the atrial switch operation.<sup>110</sup> Surgical trauma and suture lines during atrial baffling are responsible, because this issue is rarely observed in patients who have undergone an arterial switch operation. Chronotropic incompetence may compound symptoms for those with hemodynamic problems.

In an adaptation from recent ACC/AHA pacemaker implantation guidelines, implantation of an AAIR or DDDR

pacemaker is recommended as a Class I indication in symptomatic older ACHD patients with sinoatrial node dysfunction, including tachy-brady syndrome, and those with pause-dependent VT.<sup>122</sup> Pacemaker implantation is recommended as a Class IIb indication for asymptomatic ACHD patients with resting heart rates  $< 40$  bpm or sinus pauses  $> 3$  seconds. Because of the risk of pacing-induced ventricular dysfunction, programming in dual-chamber pacemakers should aim to maintain native AV conduction.

Several technical considerations unique to the ACHD population merit mention. Lead positions and adequate pacing and sensing thresholds are often limited by the anatomic lesion, fibrosis, and scar, and particularly for the older ACHD patient, obstructed or stenotic vascular channels. Although transvenous systems are possible in most adult patients with CHD, as with ICDs, certain cases (eg, single ventricle, cavopulmonary Fontan, and significant intracardiac shunts) require epicardial leads because of lack of access or risk of thromboembolism. Review of specific anatomy and all surgical records, in addition to defined imaging with echocardiography, CT, or magnetic resonance to define possible obstructions or stenosis in vascular pathways, is key in planning device implantation.

#### *AV Block*

L-TGA and AVSD both carry risk of AV block with age in ACHD. The AV node and His bundle are congenitally displaced, with compromised function in patients with L-TGA, particularly those with Down syndrome.<sup>142–144</sup> Complete AV block occurs at birth in 3% to 5% of patients with L-TGA, and because of anterosuperior displacement of the AV node, progressive deterioration of the conduction system occurs in older adult patients with L-TGA, with an estimated 2% yearly risk of complete heart block<sup>145</sup> or an additional 20% incidence of AV block by adulthood.<sup>145,146</sup> Surgical trauma can further exacerbate compromised AV conduction. Older adults with repaired AVSD are also at risk for progressive conduction disease, including paroxysmal complete heart block, caused by an inferiorly displaced AV node and bundle of His in the Koch triangle.<sup>144</sup> Therefore, adult patients with these lesions should be monitored with serial ECGs and Holter monitoring.

More commonly in the older adult with CHD, certain surgical procedures such as those for valve repair or replacement may result in trauma to the AV conduction tissues and AV block. In the majority of cases, AV conduction recovers within 7 to 10 days,<sup>147</sup> but pacemaker implantation is recommended as a Class I indication for any patient with postoperative Mobitz II second- or third-degree AV block that is not expected to resolve or that persists beyond this period.<sup>122</sup> Pacemaker implantation is also recommended by some as a Class IIb indication when AV conduction recovers postoperatively but the patient has bifascicular block.<sup>148</sup>

### **Arrhythmias: Diagnosis and Treatment Recommendations**

- 1. Adult patients with D-TGA subsequent to atrial switch, L-TGA, or AVSD should be monitored with annual ECG and periodic monitoring for dysrhythmias (Class I; Level of Evidence C).**

2. Annual surveillance of patients with repaired TOF, including taking a history, ECG, assessment of RV function, periodic monitoring for dysrhythmias, and periodic exercise testing, is recommended for asymptomatic patients (*Class I; Level of Evidence C*).
3. Evaluation for baffle pathway abnormalities (ie, in D-TGA atrial switch and Fontan circulations), ventricular dysfunction, and atrial thrombus should be performed in patients with new incident IART (*Class I; Level of Evidence C*).
4. Anticoagulation with warfarin generally is recommended in older ACHD patients with sustained AF, regardless of the presence of traditional risk factors (*Class I; Level of Evidence C*).
5. Effective anticoagulation is recommended in older ACHD patients with sustained AF, whether or not those patients meet the usual criteria for anticoagulation of patients with atrial flutter/AF in acquired heart disease (eg, CHADS<sub>2</sub> scoring) (*Class I; Level of Evidence C*).
6. AAIR or DDDR pacemaker implantation is recommended in symptomatic older ACHD patients with sinus node dysfunction, including tachy-brady syndrome, and those with pause-dependent VT (*Class I; Level of Evidence C*).
7. Pacemaker implantation is recommended for any patient with postoperative Mobitz II second- or third-degree AV block that is not expected to resolve (*Class I; Level of Evidence C*).
8. Pacemaker implantation may be reasonable for asymptomatic ACHD patients with resting heart rates <40 bpm or sinus pauses >3 seconds (*Class IIb; Level of Evidence C*).
9. Because of the risk of pacing-induced ventricular dysfunction, programming in dual-chamber pacemakers should aim to maintain native AV conduction (*Class I; Level of Evidence C*).
10. In the patient with sustained VT or cardiac arrest, hemodynamic catheterization and coronary angiography are recommended, as well as electrophysiological testing, to identify the need for possible surgical intervention such as valve replacement, which may allow intraoperative VT ablation (*Class I; Level of Evidence C*).
11. ICD implantation is recommended for cardiac arrest survivors and patients with sustained VT discovered on electrophysiological study (*Class I; Level of Evidence C*).

### Device Implantation and Management

Transvenous pacemaker and ICD systems can be used in most ACHD patients, although certain cases (eg, single ventricle, cavopulmonary Fontan, significant intracardiac shunts) require epicardial leads because of the lack of access or risk of thromboembolism. However, lead revisions are commonly needed because of relatively high lead failure rates in the ACHD population.<sup>139</sup>

ICDs have been used with increasing frequency for primary prevention of SCD in patients with CHD.<sup>149</sup> Recent ACC/AHA/Heart Rhythm Society guidelines reviewed data for this

practice.<sup>150</sup> Although randomized clinical trials have not been performed, systemic ventricular dysfunction in CHD patients has been consistently identified as the risk factor most predictive of subsequent SCD or appropriate ICD shock.<sup>151,152</sup> Although limited results have been promising,<sup>153</sup> insufficient data exist to make specific recommendations about cardiac resynchronization therapy in patients with CHD.<sup>154</sup>

For all electrophysiological procedures, specifically device implantation, use of surgical records and advanced imaging is essential in defining anatomy and pathways for lead placement. Venous occlusion is a particular consideration for older adults with transvenous leads in place for many years. Risk factors for venous thrombosis after lead implantation are history of prior thrombosis, lack of anticoagulation, use of hormone replacement therapy (HRT), and multiple leads.<sup>155</sup>

Embolitic stroke can result from lead placement in the patient with intracardiac right-to-left shunts or inadvertent implantation in the systemic circulation.<sup>156</sup> Intracardiac shunts can occur at the atrial or ventricular level, including venovenous collaterals after Fontan repair caused by high central venous pressure. Epicardial leads are typically considered if significant intracardiac shunts are present, although in some cases, shunt closure by covered stents or septal occluders<sup>157</sup> can be performed before transvenous lead implantation. For those with residual shunts, anticoagulation is usually prescribed if transvenous leads are implanted, although there is no firm evidence in support of this action.

In patients who have had a Mustard or Senning operation for D-TGA, baffle obstruction is fairly common and may require endovascular stenting to facilitate lead implantation. Because of significant scarring and baffling, adequate atrial pacing parameters typically are limited to regions in the left atrial appendage, anterior left atrial roof, or superior vena cava–right atrial junction.<sup>117</sup> Furthermore, ventricular lead placement and achievement of adequate lead parameters can be challenging in the morphological LV. In patients with CCTGA, ventricular pacing may also be associated with septal shift, which may exacerbate systemic ventricular dilation and cause worsening of systemic AV valve regurgitation.

### Recommendations for Device Implantation and Management

1. In planning procedures, clinicians should review specific anatomy and all surgical records, in addition to detailed imaging with echocardiography, CT, or magnetic resonance to define possible obstructions or stenosis in vascular pathways (*Class I; Level of Evidence C*).
2. Comprehensive evaluation of shunts by echocardiography or angiography should be undertaken before transvenous lead implantation (*Class I; Level of Evidence C*).
3. In patients with CCTGA and a permanent pacemaker, regular echocardiographic monitoring is recommended because of the risk of worsening of systemic AV valve regurgitation with ventricular pacing (*Class I; Level of Evidence C*).

### Progressive Pulmonary Vascular Disease

The development of progressive pulmonary vascular disease is increasingly recognized as a complication in the older adult with CHD. The prevalence may be higher than previously thought (6% at 67 years of age), and the diagnosis of pulmonary hypertension leads to a 2-fold increase in all-cause mortality and a 3-fold increase in risk of heart failure admissions and arrhythmia in adults with CHD.<sup>1</sup> The presence of pulmonary vascular disease with ACHD also increases resource use.

The pathogenesis of pulmonary vascular disease is often multifactorial in older adults with CHD. Left-sided heart disease, including congenital lesions, cardiomyopathy, and progressive diastolic dysfunction, can all raise LV end-diastolic pressure and pulmonary capillary wedge pressure and secondarily cause pulmonary venous and subsequent arteriolar hypertension. In disease states with a tendency toward thrombosis, chronic thromboembolic disease can superimpose on existent left-sided heart disease or pulmonary vascular disease to worsen pulmonary hypertension. Obstructive sleep apnea and pulmonary interstitial disease may contribute to pulmonary vascular disease as well. The gold standard for diagnosis is hemodynamic assessment with cardiac catheterization to assess pulmonary vascular resistance directly, delineate the contribution of left-sided heart disease, include the effects of intracardiac shunting, and allow for pulmonary angiography when necessary. However, in the older ACHD patient, reluctance to undergo procedures, challenging vascular access, intracardiac wires, and hardware may pose challenges to assessment. In these cases, initial evaluation with echocardiography performed by a sonographer with experience in ACHD can be informative, and cardiac MRI and CT may help assess valve gradients, ventricular function, distal pulmonary vasculature, and pulmonary parenchyma in detail. All patients with risk of pulmonary hypertension may also develop pulmonary or tricuspid regurgitation, which should be identified on echocardiographic imaging.

The classic Eisenmenger presentation will generally occur in the presence of a previously undiagnosed shunt lesion, such as an ASD, VSD, AV canal, patent ductus arteriosus, surgical shunt (more likely with a central, Potts, or Waterston shunt than with a Blalock-Taussig shunt). The Potts shunt is often difficult to reverse and may be more likely to be associated with pulmonary vascular disease secondary to incomplete or failed closure. The presence of a significant shunt (whether native or surgical) for an extended period of time may lead to late pulmonary hypertension, even if pulmonary vascular resistance was normal at the time of shunt takedown. Complex CHD with a shunt may also lead to Eisenmenger syndrome, although patients with these complex lesions present with elevated pulmonary vascular resistance at a younger age.

Therapy for pulmonary vascular disease has been investigated beginning with the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) in straightforward ASD, VSD, or patent ductus arteriosus with Eisenmenger syndrome. Further studies suggest a benefit of sildenafil in patients with left- and right-sided heart disease. Most recently, ACHD patients treated with endothelin antagonists were demonstrated to have improved mortality rate in a retrospective analysis.<sup>158</sup> It should be emphasized that Eisenmenger syndrome is a chronic disease with prolonged

survival, with 87% of patients surviving 20 years after diagnosis in a contemporary era.<sup>159</sup> However, rates of mortality remain high, and although long-term therapy with pulmonary arterial vasodilator drugs is effective, there is often a plateau in improvement after optimal dosing with 1 agent, and escalation to dual vasodilator therapy can improve objective exercise capacity and symptoms even further.<sup>160</sup>

There are additional considerations for treatment in cyanotic CHD, including identification of iron deficiency; initiation of replacement therapy is safe and results in early improvement in exercise tolerance and quality of life.<sup>161</sup>

Research regarding the use of pulmonary arterial vasodilator drugs in the Fontan patient consists of small and conflicting studies. In the older Fontan patient, although it is unlikely that pulmonary vascular resistance is increased significantly, there is some preliminary discussion as to the role of lowering existing pulmonary vascular resistance to aid forward flow. Treatment with bosentan was not beneficial at 6 months in a population of Fontan patients with elevated N-terminal pro-B-type natriuretic peptide.<sup>162</sup> However, sildenafil in children and adults improved ventilatory efficiency and exercise in Fontan patients.<sup>163</sup> Further study will be necessary before pulmonary arterial vasodilator drugs can be considered part of the armamentarium for treatment of the Fontan patient.



### Recommendations for Pulmonary Vascular Disease

1. **Clinicians should have a low threshold for assessing a patient for PAH in ACHD, notably in shunt lesions, left-sided obstructive disease, or complex CHD. Initial evaluation should include echocardiography, followed by hemodynamic cardiac catheterization at an experienced ACHD center (Class I; Level of Evidence C).**
2. **Patients with Eisenmenger syndrome should be followed up closely by an ACHD specialist (Class I; Level of Evidence C).**
3. **Treatment of ACHD with PAH with pulmonary arterial vasodilator drugs, in appropriate settings, can be useful and can lead to functional improvement in many diagnoses (Class IIa; Level of Evidence B).**

### Impact of Noncardiac Disease

With increased survival into older age, there is growing recognition of noncardiovascular morbidities in the ACHD population. These may be related to the initial CHD or to subsequent repair and medical treatment and are often caused by the longstanding alterations in hemodynamics, physiology, neurodevelopment, and psychosocial development seen in this population. These possible complications can adversely affect a patient's quality of life and mortality.

### Neurological Issues

The neurological complications of CHD may be manifest in childhood and early adulthood. There are no data to suggest that they increase in incidence over the age of 40 years. The complications include ischemic embolic stroke, brain abscess, and intracranial hemorrhage. Ischemic stroke may be a result



of paradoxical embolization of venous thrombi crossing an ASD or patent foramen ovale. The indications for closure of patent foramen ovale remain controversial and are beyond the scope of this document. Ischemic stroke can also result from thrombi in the setting of AF or atrial flutter. The indications for antithrombotic therapy are discussed elsewhere in this document. Brain abscess is relatively uncommon and most often seen in the setting of cyanotic heart disease with a right-to-left shunt. Intracranial aneurysms in the circle of Willis are found in patients with coarctation of the aorta; hemorrhage can occur even in the absence of hypertension. Intracranial aneurysms can be detected in as many as 10% of patients with coarctation, which is  $\approx 5$  times higher than the general population.<sup>164</sup> Some practitioners advocate routine screening for aneurysms in patients with both repaired and unrepaired coarctation.

## Pulmonary Disease

### Prevalence

Several studies have reported that pulmonary function abnormalities are common in the ACHD population.<sup>165–169</sup> In 475 adult patients with various forms of CHD, spirometry revealed that in most patients, the forced vital capacity was significantly lower than predicted for healthy subjects ( $P < 0.0001$ ), a finding that is highly suggestive of abnormal pulmonary mechanics.<sup>166</sup> Significantly reduced forced vital capacity and forced expiratory volume in 1 second ( $FEV_1$ ) was also found in 335 adults with various forms of CHD.<sup>168</sup>

Additional studies have suggested that the pulmonary abnormalities in the ACHD population are primarily those of a restrictive lung disease (RLD) pattern based on spirometry and formal pulmonary function testing.<sup>169,170</sup> The estimated prevalence of RLD in adults with CHD has been reported to be as high as 44% to 56%, with an even higher prevalence in the setting of certain lesions, particularly patients with a history of Fontan palliation (prevalence of 89%) and TOF (prevalence of 76%).<sup>170,171</sup> These studies suggest that the prevalence of spirometry-diagnosed RLD in the ACHD population is markedly higher than in the general adult population, where it is reported to be  $\approx 9.2\%$ .<sup>172</sup>

### Pathogenesis

The increased prevalence of a restrictive lung pattern in ACHD patients is likely multifactorial. RLDs are a group of conditions characterized by reduced lung volume, either because of an intrinsic cause, such as an alteration in lung parenchyma, or because of an extrinsic cause, such as a disease of the pleura, chest wall, or neuromuscular apparatus. The higher prevalence of restrictive lung physiology in the ACHD population may be secondary to extrinsic pulmonary causes, including diaphragmatic weakness, respiratory muscle weakness, and restrictive thoracic cage. Spinal deformities, including scoliosis and kyphosis, are significantly more common in patients with CHD and may be related to previous thoracotomy or sternotomy.<sup>173</sup> Cardiomegaly may also contribute to restriction of lung capacity.

RLD may also occur in ACHD patients as a result of intrinsic lung factors and abnormalities of lung development. Congenital heart lesions characterized by decreased pulmonary blood flow may hinder the growth and development of lung parenchyma and result in pulmonary hypoplasia, which

may account for the restrictive pattern observed on spirometry.<sup>174,175</sup> Parenchymal lung disease and amiodarone-induced lung toxicity for the treatment of chronic arrhythmias are other potential intrinsic causes for the development of RLD in the ACHD population.

### Prognostic Implications

Abnormal lung function may be a common but underrecognized cause of long-term morbidity in adults with CHD, particularly in relation to reduced exercise tolerance and decreased functional capacity. Exercise intolerance is common in this population<sup>165–169</sup> and is associated with an increased risk for hospitalization and death.<sup>168,176</sup> Reduced exercise capacity is often attributed to an underlying cardiac pathogenesis, including abnormal heart rate response to exercise and cardiac dysfunction. However, one of the most powerful predictors of exercise capacity in ACHD is pulmonary function, in addition to peak heart rate.<sup>168</sup>

Until recently, the impact of RLD on long-term mortality in the ACHD patient was undefined. Previous studies in adults with acquired heart disease have clearly identified abnormal lung function as a significant predictor of long-term mortality, independent of smoking status.<sup>172,177</sup> Recently, however, in a large series of 1188 ACHD patients, the presence of moderate to severe impairment of lung function as measured by spirometry was an independent predictor of survival.<sup>178</sup>

Recently, several small series have been published that examined the utility of training and cardiac rehabilitation in the ACHD patient.<sup>179,180</sup> Preliminary data are encouraging and indicate that many determinants of exercise capacity may demonstrate improvement.<sup>179,180</sup>

## Recommendation on Impact of Noncardiac Disease

1. It is reasonable to consider serial evaluations of lung function in all adults with CHD (*Class IIa; Level of Evidence C*).

## Liver Disease

### Prevalence

Congestive hepatopathy is a known potential complication in patients with significant right-sided heart failure. There are many forms of either repaired or unrepaired CHD that may result in liver dysfunction because of passive congestion, decreased cardiac output, or hepatitis attributable to transfusions or medications.<sup>181</sup> Despite this, the majority of the literature regarding liver disease in patients with CHD focuses on those who have undergone Fontan palliation.

In various small case series, the presence of liver disease in the Fontan population is ubiquitous. A small study by Kieswetter et al<sup>182</sup> involving 12 Fontan patients demonstrated some degree of change in liver histology in each patient. In a small cohort of 16 Fontan patients, all had at least 1 abnormal liver finding on CT scan, including heterogeneous enhancement, varices, and liver nodules.<sup>183</sup>

### Pathogenesis

The pathological changes in the livers of Fontan patients share similarities with those seen in cardiac cirrhosis secondary to other acquired cardiac diseases. The mechanisms of

pathological change, however, are very different. These may include prolonged episodes of hypoxia and low cardiac output that are often experienced in patients with single ventricular physiology, perioperative insults, the obligatory elevation of central venous pressure in the Fontan circulation, the passive slow flow in the Fontan circuit without a subpulmonary ventricle, and the distention of the hepatic veins seen with atrial contractions.<sup>182</sup> Other potential mechanisms of liver injury include thrombosis of intrahepatic vessels, hepatotoxic medications, and infections.<sup>183–186</sup> These insults can result in increased inflammatory activity in the liver and subsequent fibrosis.<sup>186</sup> These structural changes may then lead to functional changes in the liver, with subsequent liver dysfunction and failure.

### Diagnosis

Liver biopsy remains the gold standard to assess the severity of liver disease, and hepatic venous pressure gradient (HVPG; the difference between the wedged and the free hepatic venous pressures, which provides an estimation of the difference in pressure between the portal vein and inferior vena cava) may also be a useful marker to assess the degree of liver injury in Fontan patients. As chronic passive congestion progresses to liver fibrosis and cirrhosis over time, one would expect the HVPG to increase. The normal HVPG value is between 1 and 5 mmHg, whereas HVPG  $\geq 10$  mmHg is predictive of development of complications of cirrhosis, including death.<sup>187</sup> However, 1 study found no correlation between HVPG and the extent of pathological liver injury in Fontan patients.<sup>183</sup>

### Imaging

CT scan of the liver is a rapid, noninvasive method to evaluate the liver in patients after a Fontan operation. Findings on CT scan that represent liver damage include hepatomegaly, zonal enhancement, inhomogeneous parenchymal enhancement (reticular pattern), and hypervascular nodules. Several studies have shown that these abnormalities on CT scan are common among Fontan patients,<sup>182,183</sup> and they correlate with hepatic vein and Fontan pressure.<sup>182,188</sup> Hypervascular liver lesions are concerning findings in this patient population, because these lesions may be seen in hepatocellular carcinoma.<sup>187</sup> In fact, there have been cases of hepatocellular carcinoma reported in Fontan patients with cardiac hepatopathy.<sup>188,189</sup>

Diffusion-weighted MRI and ultrasonography can both be used to image the liver. Contrast-enhanced ultrasound has been shown to improve the diagnosis and assessment of liver cirrhosis.<sup>190</sup> However, both diffusion-weighted MRI and ultrasonography have difficulty distinguishing between earlier stages of fibrosis.<sup>184,191</sup>

Transient elastography, performed with ultrasound or MRI, is a noninvasive method of assessing liver stiffness in patients with liver disease<sup>192</sup> or acute decompensated heart failure<sup>193</sup> and in pediatric patients with the Fontan circulation.<sup>186</sup> Transient elastography can be performed with either ultrasound or MRI. This methodology may overestimate fibrosis secondary to increased vascular stiffness in the liver from increased blood volume. For now, serum fibrosis markers are independent of liver congestion and are becoming the standard of care for liver assessment in the Fontan population.<sup>186</sup>

### Serum Tests

Synthetic hepatic function is usually well preserved as liver fibrosis develops, and evaluation of liver function in Fontan patients who are asymptomatic can be challenging. However, at the time when patients present to adult congenital heart centers, or in those who have complications related to their Fontan physiology, numerous abnormalities found on liver function testing are often seen.<sup>184,194</sup> At midterm follow-up (median of 10–12 years after initial Fontan operation), the most common laboratory abnormalities are elevated levels of  $\gamma$ -glutamyltranspeptidase, alkaline phosphatase, and total bilirubin, consistent with cholestasis.<sup>194–196</sup> Abnormalities in coagulation are commonly seen that involve both procoagulant factors and anticoagulant factors.<sup>195,196</sup> Serum protein and albumin and prealbumin levels are usually normal in most patients unless they have protein-losing enteropathy.<sup>194–196</sup>

Some biochemical markers may be used as surrogates for liver biopsy to estimate the degree of liver fibrosis. There are composite blood tests that combine the quantitative results of 6 serum biochemical markers to provide a numerical quantitative estimate of liver fibrosis that corresponds to the Metavir scoring system.<sup>183</sup> However, there is no study that directly correlates these scores with liver biopsy findings. Length of time since Fontan surgery correlates significantly with biochemical markers of fibrosis, which suggests they may be elevated in most patients  $>40$  years of age in the Fontan population.<sup>183</sup>

### Prognostic Implications

Although liver disease has a clear impact on morbidity and mortality in various disease states, the impact of liver fibrosis on long-term outcomes in the Fontan patient is not well defined. In patients with cardiac cirrhosis and chronically elevated central venous pressure, the portohepatic vein pressure gradient is reduced, and liver perfusion relies more heavily on cardiac output and hepatic arterial flow. These patients are more susceptible to ischemic hepatitis during times of hemodynamic instability and cardiovascular shock.<sup>197</sup> Liver disease may also result in coagulation abnormalities and immunodeficiency. The extent of liver fibrosis in Fontan patients being evaluated for cardiac transplantation has been shown to be associated with outcomes after transplantation<sup>198</sup> and may be used in pretransplantation risk assessment.<sup>199</sup> Future studies will be needed to assess whether ventricular assist devices, Fontan conversion, or cardiac transplantation affect the progression of, or improve, liver fibrosis.

Clearly, further exposure to liver injury needs to be avoided in this high-risk population. This is particularly true for viral hepatitis. There is a growing body of evidence that patients who underwent cardiac surgical repair before 1992, which required CPB, are at an increased risk of having acquired hepatitis C. Before July 1992, there were no universal screening practices for the hepatitis C virus (HCV) in blood donation centers. A few studies have been performed in large urban cities to determine the prevalence of HCV in this patient population.<sup>200,201</sup> In 1994, CHD patients in Munich, Germany, were screened, and 14.6% of their patients were positive for anti-HCV, compared with 0.7% of control subjects.<sup>200</sup> In 2007, an evaluation of CHD patients in Atlanta, Georgia, revealed 8.6% of their patients were positive for the HCV antibody, with 4.0% having positive HCV RNA results.<sup>201</sup> This was a

5-fold increase in the prevalence over the age-matched general population in that location.

### Recommendations for Liver Disease

1. Serial evaluation of liver function should be performed for all patients with a history of previous palliation with the Fontan procedure (Class I; Level of Evidence B).<sup>184,194</sup>
2. All ACHD patients with a history of previous surgical palliation of CHD before 1992 should undergo screening for hepatitis C (Class I; Level of Evidence B).<sup>201</sup>
3. There is an increased frequency of gallstones and need for cholecystectomy in ACHD, especially in the cyanotic and Fontan populations. Vigilance should be high for diagnosis, and ACHD clearance may be needed for operative management (Class I; Level of Evidence B).<sup>202</sup>

### Renal Disease

#### Prevalence

Renal dysfunction is a common finding in the ACHD population. Nearly half of adults with CHD have some degree of renal dysfunction, with 1 in 5 having moderate or severe dysfunction.<sup>203</sup> Renal dysfunction was present in just over 50% of patients who had a history of prior palliation of TOF. Furthermore, the rate of decline of renal function was more rapid in the palliated TOF cohort than in the general population.<sup>204</sup> Renal function was worse in adults who had more complex CHD, particularly those with cyanotic heart disease. Compared with the general population, renal dysfunction in the ACHD population has been found to be 18-fold higher in acyanotic patients and 35-fold higher in cyanotic patients.<sup>203</sup>

#### Pathogenesis

An important risk factor relating to renal dysfunction in ACHD is cyanosis. More than 65% of cyanotic ACHD patients may have renal dysfunction, and 16% of those had at least moderate renal dysfunction in 1 study.<sup>201</sup> Cyanosis is thought to affect renal function both directly via chronic hypoxia and ischemia and indirectly through erythrocytosis and increased blood viscosity, which can affect glomerular arteriolar resistance, filtration, and renal perfusion.<sup>203,204</sup>

Other important risk factors for renal dysfunction in the ACHD population relate to multiple cardiac surgeries that require CPB. Clinically relevant renal injury develops in  $\approx 30\%$  of cardiac surgery patients. CPB is an established risk factor for the development of postoperative acute kidney injury.<sup>205–207</sup> Theories to explain the mechanism for acute kidney injury at the time of CPB include cellular ischemia from transient episodes of low arterial perfusion and a systemic inflammatory response. Factors such as preexisting anemia, perioperative need for blood transfusions, and the need for reexploration have also been shown to be independently associated with acute kidney injury after cardiac surgery.<sup>205</sup>

Other potential causes of renal dysfunction in the ACHD patient include traditional risk factors such as hypertension, diabetes mellitus, cardiac dysfunction, advancing age, and use

of diuretic drugs and nephrotoxic medications (including contrast agents during prior catheterizations and CT scans).<sup>203–205</sup> Increased central venous pressure has been shown to be associated with impaired renal function in various cardiovascular diseases<sup>208</sup> and to be an important hemodynamic factor behind worsening renal function in patients with decompensated heart failure.<sup>209</sup> Because increased central venous pressure is a common finding in many forms of CHD, this may play an important role in renal dysfunction in the ACHD population. In ACHD patients with LV dysfunction, the mechanism of renal dysfunction is similar to that of patients with acquired heart disease, namely, a low cardiac output state resulting in an increase in catecholamines and neurohormonal activation that results in decreased renal perfusion and a decline in renal function.<sup>203</sup>

#### Diagnosis

Measuring serum creatinine and estimating the GFR with any of a number of available equations are traditional methods of assessing renal function; however, these methods have inherent limitations. Creatinine levels are impacted by nonrenal factors such as weight, race, sex, total body volume, age, drugs, muscle metabolism, and protein intake.<sup>210</sup> GFR cannot be measured directly; rather, it is measured by determination of urinary clearance of filtration markers, which may be cumbersome and expensive. Also, many formulas used to estimate GFR have not been evaluated in special populations such as ACHD patients.<sup>211</sup> Biomarkers, including urinary interleukin 18 and neutrophil gelatinase-associated lipocalin, may be predictive of acute kidney injury, and novel mechanisms to estimate renal function may eventually allow for better assessment of risk of complications during cardiac procedures.<sup>212</sup>

#### Impact on Outcomes

Impaired renal function can impact length of stay in the intensive care unit and hospital, as well as healthcare resource expenditures, for patients after cardiac surgery.<sup>205,213</sup> Acute kidney injury after cardiac surgery confers an 8-fold increase in the odds of death and is independently associated with a marked increase in morbidity and mortality.<sup>205</sup> Similarly, renal dysfunction is a poor prognostic marker in the ACHD population. Mortality risk over 6 years was 5-fold higher in those with moderate to severe renal impairment in 1 study and 2-fold higher in those with mild renal impairment than in those with normal renal function.<sup>203</sup>

Renal dysfunction is also related to higher NYHA class and moderate or severe systemic ventricular dysfunction in ACHD patients.<sup>203</sup> Although poor systemic ventricular function can play a role in the pathogenesis of renal dysfunction as described above, renal dysfunction can also promote maladaptive cardiac remodeling and progression of cardiac dysfunction through the loss of sodium balance, volume overload, hypertension, and anemia.<sup>203</sup>

### Recommendations for Renal Disease

1. Routine assessment of renal function should be performed in all adults with moderate to complex CHD (Class I; Level of Evidence B).<sup>203</sup>

**2. In the setting of existing renal dysfunction, efforts should be made to avoid future episodes of acute kidney injury (Class I; Level of Evidence A).<sup>205</sup>**

### Cancer Risk

Excessive exposure to radiation in children with CHD has raised the concern about increased risk for adult malignancy. Children are more susceptible to the effects of ionizing radiation than adults.<sup>214,215</sup> There is wide variability in the radiation dose received during childhood catheterization procedures, ranging from 2.2 to 12 mSv.<sup>216</sup> The total dose received over 12 years in patients with 6 different lesions who received multiple examinations was lowest in those with aortic coarctation (mean of 9.53 mSv) and highest in those with tricuspid atresia (mean of 33.31 mSv).<sup>216</sup> During interventions in the current era, the dose of radiation received varies significantly. Although better equipment and shielding methods may reduce exposure to children studied currently, it is likely that longer procedures with interventions may increase exposure.

There is limited information on the risk of cancer in adults with CHD who were studied as children. A Toronto-based study showed no excess of cancer among almost 4000 patients with at least 1 catheterization before the age of 18 years during the years of 1950 and 1965.<sup>217</sup> In contrast, an Israeli study of 674 children, with catheterizations performed from 1950 to 1970, found an excess risk of cancer according to registry data in 1996, with lymphoma and melanoma being most common.<sup>218</sup>

To determine the risk for malignancy, a French cohort study is being initiated to examine the current population of children exposed to radiation for the diagnosis and treatment of CHD.<sup>219</sup> Additional data would be extremely useful in the current population of older adults with CHD. Until more information becomes available, these patients should be considered at increased risk. Patients with ACHD may not be undergoing screening in the United States as frequently as recommended<sup>220</sup>; therefore, although no specific recommendations can be made for this population at this time, practitioners should strive to meet the screening recommendations of the US Preventative Health Services Task Force for the general population.

### Recommendation for Cancer Screening

- 1. Routine screening for cancer should follow guidelines for the general population according to the US Preventive Health Services Task Force (Class I; Level of Evidence C).**

### Issues of Aging

#### Gynecologic Issues

The majority of women experience menopause, defined as complete absence of menses for 12 months, at  $\approx$ 50 years of age. Menopause before the age of 40 years is considered primary ovarian failure; however, many women have the onset of vasomotor symptoms, so-called hot flashes and menstrual irregularities, before true menopause. There are no studies on the onset of menopause in women with CHD. Hypoestrogenemia

and elevated levels of follicle-stimulating hormone are associated with symptoms of vaginal dryness, sleep disturbance, and mood swings. There are changes in lipids and bone density with increases in total cholesterol and LDL and decreases in high-density lipoprotein.<sup>221</sup> Increased risks of stroke and pulmonary embolism were observed in the Women's Health Initiative when women were treated with combined estrogen/progestin therapy.<sup>222</sup> Although unopposed estrogen therapy does not appear to be associated with increased cardiovascular risk, it is not recommended in women with a uterus because of the increased risk for breast cancer. In newer data on women between the ages of 50 and 59 years, there appears to be a higher risk of stroke and venous thromboembolism but a lower risk of CAD when HRT is administered over a 5-year period.<sup>223</sup>

The use of HRT in women with CHD must take into account both the overall risk for venous thromboembolic disease and the severity of menopausal symptoms. For example, women with Fontan surgery have a high risk of venous thromboembolism and should avoid HRT, whereas women with TOF repair and good RV function have a low risk and could probably receive HRT for symptoms.<sup>224</sup> The lowest dose of estrogen required to alleviate symptoms should be used. Transdermal estrogen therapy may be associated with lower risk and can be considered. Symptoms of vaginal dryness can be treated with vaginal estrogen therapy, and mood disorders can be treated with selective serotonin reuptake inhibitors.<sup>224,225</sup>

### Recommendations for Gynecologic Issues

- 1. Thrombotic risks associated with hormone replacement should be weighed carefully against the benefits for symptoms associated with menopause (Class I; Level of Evidence C).<sup>225</sup>**
- 2. Vaginal estrogen therapy can be useful in most women for symptomatic vaginal dryness (Class IIa; Level of Evidence C).<sup>225</sup>**

### Sexual Dysfunction in Older Adults With CHD

Although sexuality is widely regarded as an important aspect of quality of life, there is very little information about sexuality in ACHD. This is especially true of adults in their fifth decade and beyond. A survey of Belgian adults with CHD<sup>226</sup> found that up to 20% of patients reported at least occasional agreement with statements such as "being insecure about having sex," "being afraid of having sex," or "worrying about your sex life." More than 80% of those patients experienced psychological distress related to their sexual concerns. The participants in this study ranged from 18 to 57 years of age; 53% were men; and 94% were in NYHA functional class I or II.

A survey of 86 US men with CHD was performed to assess sexual health, specifically erectile dysfunction.<sup>227</sup> The mean age of this cohort was 34 years. Erectile dysfunction was reported by 38% of respondents and did not vary significantly with congenital lesion severity. Approximately 40% of patients in this study were prescribed  $\beta$ -blocker therapy, either alone or in combination with an ACE inhibitor. Not

surprisingly, treatment with a  $\beta$ -blocker conferred 3 times the risk of erectile dysfunction.

Vigl and colleagues<sup>228</sup> surveyed 332 German men with CHD who ranged in age from 18 to 59 years with a median age of 23 years. Using multiple tools, including the International Index of Erectile Function, the authors determined that men with CHD between the ages of 21 and 40 years were less likely to be living in a sexual relationship than normal control subjects. Erectile dysfunction was diagnosed in 10% of patients. Interestingly, the incidence of erectile dysfunction did not correlate with congenital lesion severity or with functional class.

In a subsequent study, Vigl's group investigated issues of sexuality and reproduction among 536 women with CHD aged 18 to 75 years, with a median of 29 years.<sup>229</sup> In women, symptoms of menstrual discomfort and cardiac symptoms during sexual activity were associated with functional class, congenital heart lesion severity, and cyanosis. Menstrual discomfort occurred in 29% to 49% of survey respondents; cardiac symptoms with sexual activity occurred in 6% to 26% of women. Winter et al<sup>230</sup> reported a survey of 133 Dutch patients with CHD and 74 partners; the study found that compared with the general Dutch population, patients were less likely to be in a relationship. Both patients and their partners reported a higher level of relational satisfaction than the general population. Erectile dysfunction was reported by 42% of male patients; difficulty with adequate vaginal lubrication was reported by 66% of female patients. Neither of these findings varied significantly from either partners or the general population. The recent AHA scientific statement concluded that phosphodiesterase type 5 inhibitors are useful for the treatment of erectile dysfunction in men with cardiovascular disease and are safe for most patients, as long as they are not taking nitrate therapy.<sup>225</sup> The safety of phosphodiesterase type 5 inhibitors has not been established in the presence of severe LV outflow tract obstruction. Dyspareunia in women can be treated with nonsystemic estrogen therapy, which has not been shown to increase cardiovascular risk.

Sexuality is an important aspect of human quality of life. A recent AHA scientific statement on "Sexual Activity and Cardiovascular Disease" made the following Class IIa recommendation: "Sexual activity is reasonable for most CHD patients who do not have decompensated or advanced heart failure, severe and/or significantly symptomatic valvular disease, or uncontrolled arrhythmias (...Level of Evidence C)."<sup>225</sup>

However, there is very limited evidence to guide patient counseling and care. Existing evidence is consistent only in identifying the presence of sexual function concerns among both men and women with CHD and in recognizing an adverse impact on quality of life for patients with concerns about sexual health. There is a need for additional research using both quantitative and qualitative methodology to better understand the prevalence of sexual dysfunction among the older adult with CHD, as well as the experience of sexuality in the older adult with CHD.

## Recommendations for Sexual Dysfunction in Older ACHD Patients

1. Anxiety and depression regarding sexual activity should be assessed in ACHD patients (Class I; Level of Evidence B).<sup>225</sup>
2. Patient and spouse/partner counseling by healthcare providers is useful to assist in resumption of sexual activity after an acute cardiac event, new cardiovascular disease diagnosis, or ICD implantation (Class I; Level of Evidence B).<sup>225</sup>
3. Sexual activity is reasonable for most ACHD patients who do not have decompensated or advanced heart failure, severe and/or significantly symptomatic valvular disease, or uncontrolled arrhythmias (Class IIa; Level of Evidence C).<sup>225</sup>
4. Phosphodiesterase type 5 inhibitors are useful for the treatment of erectile dysfunction in men with cardiovascular disease and are safe for most patients in whom sexual activity is reasonable, as long as they are not taking nitrate therapy (Class I; Level of Evidence C).<sup>225</sup>
5. The effectiveness of phosphodiesterase type 5 inhibitors has not been established in the presence of severe ventricular outflow tract obstruction (Class IIb; Level of Evidence C).<sup>225</sup>
6. It is reasonable to treat dyspareunia in women with nonsystemic estrogen therapy, which has not been shown to increase cardiovascular risk (Class IIa; Level of Evidence C).<sup>225</sup>

## Cognitive Decline

Examination of the Quebec Congenital Heart Disease Database for predictors of all-cause mortality in 3239 ACHD patients  $\geq 65$  years of age interestingly revealed that the complexities of CHD and CHD-related complications were not significant predictors of mortality.<sup>57</sup> The strongest predictors included dementia, gastrointestinal bleeding, and chronic kidney disease. Dementia, the strongest predictor of mortality in ACHD patients  $> 65$  years of age, warrants a closer examination.

On the basis of data from the Aging, Demographics, and Memory Study (ADAMS), the incidence of new onset of dementia and cognitive impairment with dementia in the United States among 456 adults  $\geq 72$  years of age followed up for an average of 5 years was reported.<sup>231</sup> The incidence of dementia was estimated to be 33.3 cases per 1000 patient-years, and the incidence of cognitive impairment with dementia was reported to be 60.4 cases per 1000 patient-years. The likelihood of progressing from cognitive impairment with dementia to dementia was 7 times greater than progression from normal baseline cognitive function to dementia.

The Cardiovascular Health Study–Cognition Study followed 532 patients (mean age, 77 years) who had normal cognitive function or mild cognitive impairment at baseline.<sup>232</sup> During an average follow-up of 4.6 years, 76 of 396 normal patients developed dementia, and 99 developed mild cognitive impairment. Of the 136 patients who had mild cognitive impairment at baseline, 69 patients progressed to dementia.

In the Quebec cohort, 20 of the 3239 patients carried a diagnosis of dementia. The median follow-up in the analysis was 6.9 years.<sup>57</sup> Although dementia accounted for only 1% of all deaths, it conferred the greatest predictive strength, with a hazard ratio of 3.24. Estimating the ACHD population of the United States at 1.3 million<sup>2</sup> and using the prevalence findings from Quebec leads to an estimated 5000 geriatric ACHD patients in the United States.<sup>57</sup> Extrapolating from the ADAMS data, there could be 165 new cases of dementia and 300 new cases of cognitive impairment present among the US population with ACHD each year.<sup>231</sup>

A consistent finding of descriptions of patients with moderate or severe complex CHD is lower educational and career achievement.<sup>233</sup> Lower educational achievement and low occupational achievement significantly increased the risk of incident dementia in a sample of at-risk people from the general population.<sup>234</sup> Whether this translates to an increased incidence of dementia among ACHD patients is unknown.

### ***Dementia and Cognitive Decline in Adults With Neurodevelopmental Syndromes***

Approximately half of patients with Down syndrome are born with a congenital heart defect. The life expectancy of a patient with Down syndrome is now estimated at 60 years.<sup>235</sup> Patients with Down syndrome are often believed to have accelerated aging and premature dementia, which offers an opportunity for exploration into the interactions of CHD and cognitive decline.

To further explore differences in typical aging effects among adults with Down syndrome compared with adults with other forms of intellectual disability, Burt and colleagues<sup>236</sup> conducted a cross-sectional study of clients in 4 age groups: 30s, 40s, 50s, and 60s. Subjects received annual evaluations for up to 5 years. The findings indicated specific changes consistent with premature aging only on tests of verbal fluency. The overall conclusion from this study was that multiple factors were likely contributing to decline but that no aging-related typical changes could be identified.

Zigman and Lott<sup>237</sup> reported that although the neuropathological substrate for Alzheimer-type dementia was virtually ubiquitous by 30 years of age in Down syndrome patients, the clinical diagnosis was not present until at least a decade later and then in only half the patients studied. The rate of appearance of Alzheimer dementia in Down syndrome patients paralleled that of the typically developing population but preceded the appearance by  $\geq 2$  decades. The authors summarized the data on various risk factors for dementia of the Alzheimer type, including age, sex, baseline mental retardation, genetic factors, and apolipoprotein E gene allele subtype. They concluded that the utility of biomarkers to predict the risk of development of Alzheimer-type dementia holds great potential but is in a very preliminary stage.

Cognitive changes in the older adult with CHD are a virtual unknown at this time. It is clear that adults with CHD are reaching older adulthood with increasing frequency. Existing research in the pediatric cardiology literature has shown us that there are neurodevelopmental delays associated with CHD, with CPB, and with circulatory arrest during reparative surgery.<sup>238</sup> How this will manifest in ACHD and its impact on

ACHD in the fifth and sixth decades and beyond remains to be seen. Opportunities for research surrounding these issues are abundant.

### **Psychosocial Issues in Older ACHD Patients**

Adults with CHD have been shown to have significant psychological and social challenges for several decades. As early as 1991, 25-year follow-up on patients treated for CHD at the Mayo Clinic<sup>239</sup> identified that 1 in 3 adults with CHD had evidence of psychological distress. This was significantly greater than the prevalence in the normal comparison population. More recent studies<sup>240,241</sup> have reaffirmed these findings. Most of the existing research on ACHD patients has involved study subjects with mean ages in their 30s.<sup>242–244</sup> Similar psychosocial findings exist among ACHD patients in Japan.<sup>241,242</sup>

Adults with CHD reaching their fourth or fifth decade are often confronted by unexpected declines in health status, because they perceived themselves to have been “cured” by childhood operations and interventions. The misperception of “cure” carries several important considerations for the ACHD patient,<sup>245</sup> among them the potential for psychological distress when the ACHD patient’s health declines unexpectedly. Patients with chronic illness may develop an “illness career.”<sup>246</sup> In this model, patients experience a dynamic process of psychosocial adjustment throughout their lives that is modulated by wellness, illness, and interactions with medical and behavioral providers. Patients who do not receive regular specialized care may be more vulnerable to significant and debilitating psychosocial disruption when their health declines or they face an unexpected need for intervention. Therefore, the importance of ongoing assessment and intervention for the psychosocial needs of ACHD patients cannot be understated.

The existing knowledge base of psychosocial issues among older adults with CHD provides a good foundation for future research. Although there is consistent evidence demonstrating a significant incidence of anxiety and depression among adults with CHD, there is a need for interventional studies to identify best practices in the treatment of mood disorders and an exploration of strategies for early intervention to minimize the development of anxiety and depression. Programs need to be designed and tested and may include early assessment of vulnerability to psychological issues and developmentally appropriate education to prepare for confronting social issues later in life.

### **Recommendations for Psychosocial Issues in Older ACHD Patients**

- 1. Individual and family psychosocial screening should be part of the care of ACHD patients. Advanced practice nurses, physician assistants, psychologists, and social workers should play an integral role in assessing and providing for the psychosocial needs of ACHD patients, along with their physicians (Class I; Level of Evidence C).<sup>49</sup>**
- 2. A psychological evaluation should be obtained if an adult’s mental competency is in question, if there is no need for urgent care, and no appointed adult surrogate is available (Class I; Level of Evidence C).<sup>49</sup>**

## Genetic Screening and Counseling of the Older ACHD Patient

The genetic contribution to CHD ranges from classic mendelian inheritance to complex gene-environment interactions. The older CHD patient presents unique challenges, because family history may be lacking and the patient's parents may be unavailable to assess inheritance patterns. Phenotypic abnormalities suggestive of syndromic CHD are often subtle and may be missed, and late-onset systemic disorders associated with these syndromes may only manifest in older patients. Finally, patients with negative genetic test results may need retesting in the future as more sensitive genetic tests are developed. The genetic basis of acquired cardiovascular disorders such as hypertension and CAD are beyond the scope of this review and will not be discussed.

### Potential Utility of Genetic Screening and Counseling in the Older ACHD Patient

Although the indications for genetic testing have been described for children and young adults with CHD,<sup>247,248</sup> genetic screening of the older ACHD patient is less well established. Genetic screening of the older ACHD patient helps patients to better understand the biological basis of their cardiac defects. Second, knowledge of genetic pathogenesis can inform the risk of recurrence in children and other family members.<sup>249</sup> Finally, identification of a genetic syndrome can help identify other organ system involvement that can guide management strategies and inform prognosis for outcomes.<sup>250</sup>

The majority of adults with CHD have not had genetic testing or counseling. Even those found to have a genetic variation in childhood may not have received genetic counseling, either because they were too young to participate in the counseling process or the service was unavailable. Barriers that limit access to genetic counseling include low income, low education, racial background, and lack of medical insurance.<sup>251</sup> Genetic testing and counseling should therefore be revisited in all adults with CHD in whom a genetic origin is suspected. In North America, genetic counseling is provided by board-certified counselors, in collaboration with clinical geneticists. The National Society of Genetic Counselors recognized cardiovascular genetic counseling as a specialty in 2006, yet only 4% of counselors at the time had cardiovascular specialist training.<sup>252,253</sup> This increases the burden of counseling on the CHD specialist.

### Assessment of Genetic Risk

A comprehensive evaluation for genetic risk factors is indicated in all CHD patients regardless of age, particularly in those with no previous evaluation.

### Recommendations for Genetic Screening and Counseling of the Older ACHD Patient

1. **A detailed family history for CHD and other birth defects that spans at least 3 generations is recommended to identify familial inheritance. Parental consanguinity should be documented, along with a history of miscarriages and stillbirths (Class I; Level of Evidence C).**

2. **Detailed history and physical examination should be performed for dysmorphic features, extracardiac malformations, and other organ system involvement, including neuromuscular abnormalities, mental retardation, psychiatric abnormalities, short stature, visual or hearing loss, immune deficiency, endocrine disorders, and other systemic disorders (Class I; Level of Evidence C).**
3. **Family member screening through history, physical examination, and/or echocardiographic screening is reasonable, particularly in patients reporting a positive family history (Class IIa; Level of Evidence C). This may aid in the detection of clinically silent defects such as ASDs, small VSDs, BAV, and right aortic arch in asymptomatic family members and establish a familial basis for CHD in the patient.**

### Indications for Genetic Testing

All CHD patients with genetic risk factors should be offered genetic counseling and genetic testing if clinically available. Two consensus statements from the AHA<sup>247</sup> and the Canadian Cardiovascular Society<sup>254</sup> provide important information related to genetic testing in CHD in the young and have useful insights into genetic screening for the older CHD patient.

The absence of typical phenotypic features does not exclude a genetic syndrome, because dysmorphic features are often subtle, and extracardiac manifestations can be of late onset.<sup>255</sup> Approximately half of all women with Turner syndrome are diagnosed after their 15th year of age.<sup>256</sup> Typical phenotypic features may be equally subtle in milder forms of 22q11.2 microdeletion syndrome,<sup>255</sup> with some patients identified only after the diagnosis of an affected child.<sup>257</sup> In suspected or confirmed genetic syndromes, a targeted search for other system involvement should be considered because of the important medical and prognostic implications of identifying a genetic syndrome in a patient with CHD. Patients with 22q11 deletion syndrome can have other abnormalities that require management, including hypocalcemia, immunodeficiency, renal anomalies, and behavioral and neuropsychiatric disorders that are often late in onset. Patients with Williams-Beuren syndrome should be screened for hypercalcemia, nephrocalcinosis, systemic hypertension, and cognitive disabilities. Early diagnosis of other organ involvement can facilitate timely interventions, with improvement in clinical outcomes.

### Genetic Screening Techniques for Evaluation of CHD

Genetic testing usually begins with the index patient, or "proband," because this gives the greatest likelihood of finding a genetic abnormality. Targeted gene testing of the proband and "cascade" screening of at-risk family members are customary to help clarify mode of transmission and transmission risks. Cytogenetic testing gives a positive yield in 10% to 20% of probands with a genetic risk factor. Fluorescent in situ hybridization (FISH) is the current test of choice to detect 22q11 deletion syndrome and 7q11.23 deletion in Williams-Beuren syndrome. Multiplex ligation-dependent probe amplification is an alternative quantitative multiplex polymerase chain reaction approach to determine the relative copy number of a

genomic target sequence, which can diagnose these deletions, although it remains largely in the research realm at this time.

In a small subset of CHD patients, targeted gene sequencing can help identify mutations in the coding sequences of candidate genes. Examples include Holt-Oram syndrome, Noonan syndrome, Alagille syndrome, and Marfan syndrome. More than 90% of patients with Alagille syndrome have either 20p12 rearrangement or deletion or a *JAG1* mutation. Noonan syndrome is characterized by pulmonic stenosis or hypertrophic cardiomyopathy and additional systemic manifestations. Mutations in the RAS signaling pathway involving *PTPN11*, *SOS1*, *RAF1*, and *KRAS* genes account for >60% to 70% of Noonan syndrome cases.<sup>258–261</sup> Holt-Oram syndrome is characterized by ASD or VSD, sometimes with limb anomalies, usually caused by *TBX5* mutations. Availability of clinical genetic tests can be found at the GeneTests Web site (<https://www.genetests.org>), a public access Web site. Up-to-date knowledge of both the clinical criteria for genetic conditions and their molecular basis is of vital importance for ACHD specialists.

### Genetic Counseling

The counselor must integrate family and medical histories to assess the risk of disease occurrence or recurrence; educate the patient about inheritance, testing, management, prevention, resources, and research; and provide counseling to promote informed choices and adaptation to the risk or condition.<sup>250,253</sup> Genetic counseling typically starts before genetic testing and includes a discussion of the purpose, nature, limitations, and consequences of the genetic test in question. Positive consequences of genetic testing include relief of uncertainty surrounding a diagnosis, more accurate estimation of transmission risk, and identification of asymptomatic at-risk family members. Genetic confirmation may also enable preemptive screening and treatment of complications such as hypertrophic cardiomyopathy in Noonan syndrome<sup>262</sup> and neuropsychiatric disease in 22q11.2 microdeletion syndrome.<sup>263</sup> Potential harms, which have been addressed through legislation in the United States, include difficulty in acquiring insurance, potential job discrimination, and negative self-image, although this is less relevant in patients with diagnosed or manifest CHD.<sup>264–266</sup> Also, it is important to be aware of the limitations of genetic test results. Although a positive result is informative, negative results do not always rule out a genetic cause, particularly in cases in which the family history and clinical phenotype are highly suggestive. Many patients with CHD exhibit marked locus heterogeneity, with causative mutations occurring across many different genes, as in Noonan syndrome. In addition, mutations in >1 gene may be required to cause CHD in many cases. A genome- or exome-wide approach may facilitate the search for compound mutations; however, it may also uncover genetic variants of unknown significance. Until technical accuracy and clinical validity improve, genome-wide analysis remains in the research realm.

### Estimating Recurrence Risk

Estimating recurrence risk in family members is often an important concern even in the older CHD patient who is beyond the reproductive age range. Recurrence risk can be more easily predicted for patients with CHD who have mendelian

patterns of inheritance, although these represent a relatively small proportion of familial CHD cases. The majority of patients with CHD for which there is a definite genetic basis have an autosomal-dominant inheritance, with a transmission risk of 50%. Autosomal-recessive conditions are less prevalent but may be suspected in the context of consanguineous parenthood. Recurrence risk prediction is more challenging in sporadic CHD that arises de novo in the affected individual with no prior family history. In general, for sporadic CHD, the risk of recurrence in offspring is ≈3%, with the recurrence risk being highest for siblings, followed by first-degree relatives, then second-degree relatives.<sup>267</sup> This is consistent with the results of a recent large Danish population-based study of 18708 people with CHD that reported a 3-fold higher recurrence risk in a first-degree relative.<sup>268</sup> Cardiac defects associated with higher recurrence risks include heterotaxy, AVSD, and left-sided outflow tract obstructive lesions.<sup>269,270</sup> Despite a familial basis, prediction of CHD type or severity in family members can be difficult because of variable phenotypic expression within families secondary to gene-gene or gene-environment interactions.<sup>271–275</sup> Significant intrafamilial phenotypic variability despite inheritance of the same genetic mutation is observed in 22q11.2 microdeletion syndrome and Holt-Oram syndrome.<sup>276–278</sup> Nonetheless, reproductive counseling can provide useful guidance to family members of CHD patients even in the absence of a confirmed genetic diagnosis.

### Future Directions

The search for disease-causing variants has moved from candidate gene approaches to genome-wide approaches.<sup>278</sup> The success of next-generation or high-throughput sequencing in identifying the causes of mendelian diseases is being broadened to more complex diseases, such as CHD.<sup>279–281</sup> This approach is particularly attractive for patients with CHD, in whom large phenotypic effects are likely to be caused by ≥1 rare genetic variants that have been difficult to detect by use of current platforms.

In summary, as genomic advances lead to possible identification of more genetic causes of CHD, genetic evaluation and counseling will gain importance in the management of CHD patients. Genetic counseling can help patients understand and adapt to the medical, psychological, and familial implications of a genetic defect that causes CHD. Given the complexity of the medical and ethical issues surrounding a genetic diagnosis in CHD, close collaboration between cardiologists, genetic counselors, and geneticists is recommended.

### Recommendations for Genetic Testing

1. Patients with a history of parental consanguinity or a family history of CHD that includes frequent miscarriages or stillbirths should be referred for genetic evaluation (*Class I; Level of Evidence C*).
2. Genetic evaluation may be useful in patients with associated clinical features suggestive of an underlying genetic syndrome, such as facial dysmorphism, extracardiac malformations, cognitive impairment, neuropsychiatric disorders, or multisystem involvement (eg, hepatic, renal, hematologic, immunologic,



**Table 2. Imaging Modalities in the Diagnosis and Management of CHD in the Adult**

Modality	Availability*	Scan Time†	Cost	Radiation‡	Contrast	Notes
Echocardiography	+++	+++	\$\$	None	None	Widely available; requires dedicated expertise for ACHD
MRI	++	+++	\$\$\$	None	Necessary for late gadolinium enhancement	Requires expertise to perform, interpret; long scan and postprocessing times. Preferable to evaluate known diagnoses where echocardiography is inadequate.
MRA	+++	+	\$\$	None	Preferred for shorter examination time; can be combined with MRI	Although images can be rapidly acquired, dedicated expert readers are necessary; cannot reliably exclude significant CAD
Noncontrast CT	+++	+	\$	+	None	Limited beyond calcification assessment; calcium scores alone do not exclude significant CAD
Thoracic CTA	+++	+	\$\$	++	Yes	May be sufficient for noncoronary questions; may still require MD supervision in complex lesions
ECG-gated cardiac CT/CTA	++	++	\$\$\$	Variable	Yes	Requires experts and advanced equipment; in the proper hands, can be performed at low doses. Can assess function and scar, but never phase-velocity mapping. Preferred method of CAD exclusion in ACHD. May be preferable in cases of unknown diagnosis to survey entire thorax.

ACHD indicates adults with congenital heart disease; CAD, coronary artery disease; CHD, congenital heart disease; CT, computed tomography; CTA, computed tomographic angiography; MD, medical doctor; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; and \$, \$\$, \$\$\$, progressively increasing cost.

\*“Widely available” is indicated with 3 plus signs and “Available” with 2 plus signs.

†“Longest time” is indicated with 3 plus signs, “Standard time” with 2 plus signs, and “Least time” with 1 plus sign.

‡“More” is indicated with 2 plus signs, and “Less” with 1 plus sign.

**endocrinologic, and sensorineural abnormalities) (Class IIa; Level of Evidence C).**

**3. Genetic testing is reasonable in patients with certain types of isolated cardiac defects commonly associated with genetic syndromes even in the absence of syndromic features (Class IIa; Level of Evidence C). Common examples are screening for 22q11.2 deletion syndrome in patients with interrupted aortic arch, truncus arteriosus, TOF, VSD with aortic arch anomaly, right aortic arch, or discontinuous branch PAs and screening for 7q11.23 deletion or Williams-Beuren syndrome in patients with supravalvar AS, coronary stenosis, and supravalvar and peripheral pulmonary stenosis.**

### Diagnostic Testing in the Older Adult

#### Echocardiography

Echocardiography is the primary imaging tool in the diagnosis and management of CHD in the adult<sup>49,282</sup> (Table 2). It is used to establish segmental anatomy; measure and follow up valve and ventricular function; and calculate pulmonary, RV, and other intracardiac pressures. It can be useful in identifying arterial and venous vascular anomalies and connections. Echocardiographic evaluation of ventricular function and hemodynamics guides management and offers prognostic insights. Transthoracic echocardiography/Doppler in ACHD is complemented by TEE and specialized techniques, including contrast imaging, myocardial strain imaging, real-time 3-dimensional/4-dimensional imaging, and stress echocardiography with or without Doppler. Special

competency in ACHD is essential when interpreting echocardiograms in an ACHD patient.<sup>283,284</sup> For all echocardiography and other imaging modalities, competency requires an adequate volume and diversity of cases, which comes by training or experience, and a demonstration of mastery.<sup>285,286</sup> Fundamental to all CHD imaging is a segmental approach, with development of an anatomic diagnosis based on the most complex condition present. The anatomic diagnosis requires determination or confirmation of atrial situs and morphology, AV valve number and morphology, ventricular number and position, infundibular presence and connections, and great vessel number and relationships. The connections and relationships between the segments, presence and size of shunt lesions, and identification and quantification of regurgitant and stenotic lesions must be established as much as the images allow. Complete anatomic and functional assessment is often best achieved in moderate or severely complex ACHD by use of transthoracic echocardiography complemented by TEE or MRI/CT. For intracardiac and hemodynamic/valvular questions, TEE is favored, whereas MRI or CT excel for extracardiac questions, particularly those that involve complex intracardiac connections and the great veins and arteries.<sup>287</sup> MRI has also become the reference standard for RV volumes and ejection fraction.

The superimposition of acquired heart disease, particularly disease of the left side of the heart, including CAD, hypertension, and acquired aortic and mitral valve disease, complicates the interpretation of echocardiograms in older ACHD patients. Thus, echocardiographers must be skilled in the interpretation of acquired heart diseases. Additional time for a study should be allotted to perform a complete congenital and acquired heart

disease assessment in a single study. Sonographers should be trained in the segmental approach and familiarized with the array of ACHD conditions, interventions, and surgeries that will be encountered. Imaging should routinely include all parasternal and apical, subcostal, and suprasternal views. Pulmonary venous anatomy, branch PAs, and coronary arteries will require concerted efforts to image; this may not always be successful with TTE in the older adult. Frequently, imaging from unusual locations is necessary to compensate for malposition of the heart and changes in accessible imaging windows with aging. Prior surgeries, obesity, and lung disease may degrade image quality. Direct supervision by or access to an ACHD echocardiographer during these studies can aid in diagnosis, help to avoid commonly overlooked or misinterpreted entities, and spare the ACHD patient return visits or repetitive imaging.

For all imaging studies, access to the medical and surgical history; identification of anatomy first, then physiology; and comparison of imaging to prior study images rather than reports will all improve the accuracy of imaging diagnosis and its utility in management. For example, a VSD is inherent in the diagnosis of TOF; therefore, VSD would not be a separate diagnosis. However, findings must be reported based on accepted nomenclature<sup>288</sup> and seek simplicity and clarity of language. Unanswered questions after the initial echocardiogram in new referrals are common in complex ACHD. Complete initial diagnosis will often be predicated on complementary MRI or CT imaging and often will be accompanied by review in a conference setting with ACHD clinicians and imagers. Rarely today is catheterization necessary for anatomic diagnosis; even most hemodynamic information will be available from echocardiography/Doppler and MRI, although cardiac catheterization remains the gold standard for assessment of pulmonary vascular resistance, aortopulmonary collateral arteries, and venovenous collaterals, particularly in the single-ventricle patient.

Serial quantitative assessment of valvular and ventricular function is one of the principle uses of echocardiography in the long-term follow-up of ACHD patients with chronic volume and pressure overload. After repair and many subsequent years, ACHD lesions tend to resemble acquired heart disease in that chronic overload and its resulting impact on chamber sizes and function become major determinants of cardiac morbidity and mortality. Standard American Society of Echocardiography (ASE) criteria for chamber sizes and valvular function are often applicable in older ACHD patients who have mostly simple or moderately complex disease, using the ASE/European Association of Echocardiography guidelines available for adults with acquired heart disease for the assessment of the LV, RV, and other chambers,<sup>289,290</sup> native valves<sup>291,292</sup> and prosthetic valves,<sup>293</sup> and diastolic function.<sup>294</sup> In many complex ACHD conditions, such as D-TGA, CCTGA, or single ventricle, there are no chamber measurement conventions with proven reproducibility. Ventricular measurements from a short-axis view, as in the ASE pediatric echocardiography recommendations,<sup>295</sup> may be more useful than long-axis measurements in D-TGA with atrial switch and CCTGA.

LV size and systolic function are central tools in the management of left-sided heart disease and carry powerful prognostic information in CAD,<sup>296</sup> congestive heart failure, LV hypertrophy,<sup>297</sup> and CHD.<sup>298</sup> Quantification of LV size, systolic and

diastolic function, and LV hypertrophy should be performed with published normal data from adult patients in hand. The LV should be indexed to height or body surface area. Z scores generally are not used in adult patients. Quantification of LV global function with a biplane Simpson rule algorithm is considered the standard. Visual estimation of ventricular function alone is still in common usage by all echocardiographers but is suboptimal, particularly in patients with complex right- and left-sided heart disease and in distinguishing intermediate degrees of dysfunction. Ventricular shape and interventricular septal motion should be noted. Wall motion abnormalities should be reported consistently. Interpretation of wall motion abnormalities may be complicated by the presence of conduction abnormalities, abnormal septal motion caused by pressure or volume overload of the RV, surgical scars, and the impact of RV pacing. Reporting of all LV abnormalities should follow ASE cut points for mild, moderate, and severe abnormalities, particularly in 4-chambered hearts.<sup>289</sup> The optimal method for measuring function in the single ventricle has not been well established.

Atrial dilation reflects LV systolic and diastolic function, as well as chronic volume overload. Left atrial volume index is a reliable indicator of cardiovascular risk in adults with all forms of acquired heart disease, more sensitive and specific than linear or area measures of the left atrium. Left atrial volume index is an indicator of overall mortality, cardiovascular mortality, severity of diastolic dysfunction, stroke risk, AF risk, and embolic risk.<sup>299</sup> Similarly, right atrial dilation indicates elevation of right atrial or RV end-diastolic pressure<sup>300</sup> or chronic volume overload.

### *Echocardiography and the RV*

Improved echocardiographic quantification of RV size and function would be particularly useful in CHD. The RV may be subpulmonic or systemic in CHD. Unlike the LV, RV shape is not easily reduced to a simple geometric model, and there is not a single 2-dimensional echocardiographic view that allows use of a Simpson rule method of quantifying its volume. RV volume may be better estimated by use of linear or area measures from several more reproducible measurements using RV anatomic landmarks such as the RV base in the 4-chamber view and the RVOT in short-axis views. Although not developed for CHD, the 2010 ASE recommendations<sup>290</sup> for quantification of the RV should be useful in 4-chambered hearts. The traditional M-mode and 2-dimensional measurements of the RV are poorly correlated with RV volumes by MRI.<sup>295</sup> Measures of longitudinal RV function such as RV free wall velocity by tissue Doppler and the tricuspid annular peak systolic excursion are more accurate than visual assessment in distinguishing abnormal from normal RVs compared with MRI in acquired heart disease.<sup>301</sup> No criteria exist for separating mild or moderate from severe RV dilation or dysfunction by 2-dimensional echocardiography/Doppler. The presence of RV regional wall motion abnormalities, ventricular patches, or conduction disturbances may invalidate tricuspid annular peak systolic excursion and RV free wall velocity for systolic RV function in TOF.<sup>302,303</sup> Even without well-established cutoff points for mild and moderate dilation and dysfunction, serial evaluations may offer the ACHD clinician clues to declining ventricular performance

or loss of preload reserve, which may lead to a change in management. Real-time 3-dimensional echocardiography is a promising method for measurement of RV volume and function in the ACHD patient and has been validated against MRI.<sup>304,305</sup> Normal values for RV volumes and function indexed for sex and patient size have been published.<sup>306</sup> Whether technical challenges involved in imaging the RVOT from the apex or the problem of the very large ventricle can be overcome remains to be seen.

### ***Echocardiography and Single Ventricle***

No conventions exist for echocardiographic quantification of the variety of conditions that result in single-ventricle physiology. The condition is further heterogeneous in consisting of single left, single right, and single primitive ventricles. Visual assessments of echocardiography images are usually relied on and often found wanting compared with MRI.<sup>307</sup> The single-ventricle patient is a challenge for all imaging modalities. No commercially available echocardiographic or MRI equipment has algorithms designed for quantification of volumes and function of the anatomically varied single ventricle, although LV algorithms should be applicable in tricuspid atresia. Simple linear measures may be used as a rough analogue of volume in single-ventricle patients and offer opportunities for serial comparison. Measures of longitudinal function (tricuspid annular peak systolic excursion, RV free wall velocity, and longitudinal strain) are likely improvements over simple visual assessment of single ventricular function, but these measures lack outcome data.

### ***Strain Imaging***

Promising early data with strain imaging have identified ventricular dysfunction in many congenital conditions, including systemic RVs, single ventricles, and other CHDs; however, commercial software available for measurement of ventricular strain is designed for the LV, and it may be more difficult to use in the thinner-walled RV. There is less independent validation of the information acquired. No industry-wide standards exist for strain and strain rate imaging with either Doppler or 2-dimensional speckle-tracking methods. Nonetheless, global longitudinal strain has been shown to have prognostic utility in assessing the systemic RV in D-TGA after atrial switch and the LV in repaired TOF.<sup>308,309</sup>

### ***Echocardiography With Contrast***

Poor image quality may require the use of alternate strategies to complete a patient's echocardiographic assessment. Ultrasound contrast agents used with harmonic imaging are indicated to opacify the LV chamber and enhance endocardial borders of the LV. Ultrasound contrast agents have also been found to be useful in rest and exercise assessment of the single ventricle and systemic RV.<sup>310</sup> Ultrasound contrast agents are not approved by the US Food and Drug Administration for use in patients with right-to-left shunts, bidirectional shunts, or suspected transient right-to-left shunts; however, these agents can still be useful in many ACHD patients.

Saline contrast echocardiography was adopted early in CHD echocardiography<sup>311,312</sup> and remains a useful tool in ACHD. Well-agitated saline, including a few drops of the patient's blood, provides dense opacification of the right side of the heart without introduction of "air." Unlike commercially

available ultrasound contrast agents, it does not pass through the normal pulmonary circulation; hence, it can be used to identify the presence of an intracardiac or transpulmonary right-to-left shunt. Saline contrast is more sensitive than Doppler echocardiography for detection of low-velocity right-to-left shunts such as ASDs or baffle leaks in patients with atrial switch surgery for D-TGA. It is most frequently used for detection of a patent foramen ovale in adults. It is also useful to detect unusual venous connections, such as a vena cava to the left atrium,<sup>313,314</sup> diagnose the presence of a persistent left superior vena cava,<sup>313</sup> establish shunt level (eg, atrial versus ventricular), identify coronary sinus ASDs,<sup>315</sup> and establish whether late-onset cyanosis in the adult is attributable to a cardiac or intrapulmonary shunt.<sup>316</sup> In Glenn shunt and Fontan patients with cyanosis, saline contrast can identify the presence of acquired intrapulmonary shunts caused by venous collaterals or AV malformations, the latter often associated with lack of hepatic blood flow to 1 lung.<sup>317,318</sup>

### ***Transesophageal Echocardiography***

TEE is an important tool in the assessment of ACHD in the older patient. Use of TEE in ACHD is classified as a highly appropriate application of TEE.<sup>282</sup> For patients unable or unwilling to enter the magnet for MRI, TEE offers an alternative means of assessing ventricular function and size and valvular function in patients with poor transthoracic image quality. When transthoracic image quality is poor, TEE provides essential intracardiac information, some not available from MRI or CT. TEE is especially useful for assessing the intrathoracic aorta, native and prosthetic valves, and ventricular function; detecting atrial level shunts; diagnosing and managing endocarditis and its complications; and identifying cardiac sources of emboli. Specific applications in ACHD include ascertainment of mechanisms of cyanosis, assessment of baffle leaks and obstruction in D-TGA/atrial switch patients, and guidance of closure of atrial level shunts and other interventional procedures. Great vessel relationships can typically be established. TEE is required before cardioversion or ablation in all unanticoagulated patients with atrial flutter/AF that persists >48 hours to exclude atrial thrombi. TEE permits visualization of the main PA and its proximal branches and interrogation for pulmonic stenosis and insufficiency. Systemic and pulmonary venous connections can often be established. It is the echocardiographic procedure of choice for identification of sinus venosus ASDs, which are visible by transthoracic imaging in only 25% of cases,<sup>319</sup> and for identification of anomalous pulmonary venous connections associated with this defect or in isolation.<sup>320</sup> Use of intraoperative TEE is considered standard of care in the surgical repair or palliation of congenital heart conditions. TEE may be used in lieu of a pulmonary arterial catheter in ACHD surgery for monitoring of ventricular volume and function. Its use in skilled hands alerts the surgical team to problems with repairs, may discover previously unsuspected defects, and detects the presence of coronary ischemia. Consistent experience in the interpretation of regional wall motion abnormalities allows identification of serious intraoperative coronary arterial complications in CHD and ACHD surgeries.

### **Stress Echocardiography**

Exercise echocardiography and pharmacological stress echocardiography are well-established tools for the detection of coronary ischemia infarction and provide powerful prognostic information in any patient with CAD, including those with ACHD.<sup>321</sup> Additionally, stress echocardiography is useful for assessment of the ventricular response to exercise in aortic and mitral insufficiency<sup>292,322</sup> and the assessment of PAH.<sup>323</sup> There is an emerging population of patients with D-TGA arterial switch, anomalous coronaries, or conditions with an increased prevalence of premature CAD, such as coarctation. The interpretation of stress echocardiography in these patients requires expertise in differentiating the regional wall motion abnormalities from an ischemic versus a myopathic (global) response. It is also important to recognize that a high percentage of operated ACHD patients have preexisting right bundle-branch block, and abnormal septal motion may complicate the interpretation of stress echocardiography.

### **Aging and Echocardiographic Variables**

Cardiac structure and function change predictably with aging. The aortic root and ascending aorta become larger with age, sex, and patient size.<sup>324</sup> LV and RV filling is dominated by the E wave in youth, but after 20 years of age, E-wave peak velocity and the E/A ratio decline and then invert between the ages of 20 and 60 years. Pulmonary venous flow patterns shift from diastolic to systolic dominance with aging.<sup>294</sup> Assessments of ventricular diastolic performance in the adult must incorporate the factor of age.<sup>294</sup> Longitudinal strain values for both LVs and RVs may decline with age, but the data are inconsistent,<sup>325</sup> whereas ventricular systolic function appears to be preserved with aging. PA pressure and pulmonary vascular resistance rise with age, and in normal hearts, top normal PA systolic pressure rises from 30 to 40 mm Hg by catheterization.<sup>326</sup> Echocardiographic cut points for systolic pulmonary hypertension increase with age, rising from 38 mm Hg in a younger population to 44 mm Hg in an older population.<sup>327</sup> In the evaluation of PAH, the impact of pulmonary blood flow on the level of pulmonary hypertension should be considered. The pulmonary flow velocity interval should be routinely measured and compared with the flow velocity interval in the LV outflow tract. RVOT obstruction of any cause precludes use of the tricuspid insufficiency jet for calculation of PA systolic pressure, although RV systolic pressure may still be calculated. The impact of age on PA pressure may be one mechanism of the increasing prevalence of PAH in older ACHD patients.<sup>328</sup>

### **Echocardiographic Reporting**

Standards for echocardiographic reporting for ACHD patients have not been established; however, methodical anatomic reporting is readily used in pediatric cardiac echocardiographic evaluation and should be adopted in any ACHD report.<sup>295</sup> Serial evaluation is a great strength in echocardiography, and reports should enable serial quantitative comparisons. A focus on acquired adult heart disease, ranging from CAD to diastolic dysfunction, by a trained adult echocardiography team is equally important to the identification of congenital anatomy. Training sonographers and echocardiographers to approach these studies with a systematic anatomic and physiological approach and the use of advanced techniques when

applicable can truly aid in determining progression of disease, timing of therapy, intervention, and surgery.

### **Recommendations for Diagnostic Testing in the Older Adult With CHD**

- 1. Echocardiography in the older adult with CHD should be interpreted by physicians with expertise in both congenital and acquired heart disease (Class I; Level of Evidence C).**
- 2. Echocardiography in the older adult with CHD should take full advantage of all specialized techniques and technologies available for adults (Class I; Level of Evidence C).**
- 3. Echocardiography reporting in older adults with CHD should include both the anatomic diagnosis and quantitative assessment of chambers, valves, and great vessels in a format accessible to physicians caring for adults (Class I; Level of Evidence C).**

### **Advanced Imaging Techniques in ACHD**

Advanced cardiac imaging with MRI and CT is exceedingly useful in the new diagnosis of ACHD in addition to the evaluation of established or previously palliated ACHD (Table 2). The use of cardiac imaging should provide additional information rather than merely confirm abnormalities already diagnosed with another imaging modality. Echocardiography remains a cost-effective, ubiquitous tool for cardiovascular imaging in the ACHD patient. Because of moderately higher cost<sup>329</sup> or the need for radiation exposure,<sup>330-332</sup> MRI and CT, respectively, are usually reserved for problem solving and specific indications. However, when a specific imaging question is clearly outlined before image acquisition, in addition to careful review of previous images and operative reports (when available), and when the patient is studied properly and the images are processed carefully, cardiac MRI and CT are powerful diagnostic tools in the evaluation of the older adult with CHD. Ideally, people with a strong working knowledge of CHD in the adult should acquire and interpret the images; if this is not possible, early collaboration between cardiologists and radiologists should be forged for optimum image acquisition and interpretation.

### **Cardiac MRI**

Benefits of cardiac MRI include limitless angles of acquisition and evaluation of cardiac structure and function with high spatial and temporal resolution in addition to tissue characterization of the myocardium. In the absence of ferromagnetic objects or dense calcification, which causes susceptibility artifacts within the image, cardiac MRI is not limited by acoustic windows or shadows. Visualization of structures that are immediately posterior to the chest wall or sternum, including unparalleled views of the RV, great vessels, and associated semilunar valve anatomy, is improved. Comprehension of the cardiac anatomy in situ within the mediastinum can benefit the interventional cardiologist considering implantation of a percutaneous valve, the electrophysiologist planning an ablation procedure, and the surgeon planning a redo sternotomy in a patient with complex conotruncal anatomy with or without anomalous coronary arteries. Those who image these patients using cardiac MRI need

to effectively communicate their findings to their colleagues to safely streamline treatment planning. Careful attention should be given to additional extracardiac findings, including unexpected soft tissue findings or hepatic findings, which also need to be reported accurately.

The use of cardiac MRI in CHD assessment has burgeoned. However, local and regional expertise may vary, and echocardiography and cardiac CT may be preferable depending on institutional experience.

Strengths of MRI include unparalleled views of the RV and its function (via short-axis, long-axis, or phase-contrast imaging) in nearly all cases. Phase-contrast imaging also allows for shunt fraction assessment. The most specialized function of MRI, tissue characterization, sets MRI above many other cardiovascular imaging modalities with the exception of nuclear medicine techniques that can assess cardiac metabolism or adrenaline activity. The most important of these in ACHD is the identification of scar and fibrosis; the presence of late gadolinium enhancement (scar or fibrosis) is predictive of major adverse cardiac events in both acquired heart disease and CHD in the adult and can be incredibly useful when risk stratifying a new patient in an ACHD practice. Weaknesses of MRI include its inability to reliably assess the coronary arteries, although techniques are improving, and indirectly, MRI can assess for coronary disease via stress perfusion MRI (pharmacological stress).<sup>333</sup> However, MRI cannot image calcification, and metallic artifacts may obscure adjacent anatomy (including small stent lumens). There are also numerous challenges to MRI, which include patient factors such as claustrophobia, the need for repeated breath holds, anxiety or inability to follow directions because of developmental delay, and long scan times. Patient arrhythmias can make image acquisition more challenging and must be discussed with the imager before the patient arrives at the MRI scanner for proper planning or so another more useful test can be chosen. Those with low GFR ( $<35 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ) should not receive gadolinium contrast given the potential risk for nephrogenic systemic fibrosis. Lastly, implanted pacemakers, much metallic hardware, and foreign bodies are usually strict contraindications to cardiac MRI.<sup>334</sup> The ongoing MagnaSafe Registry, a multicenter collaborative registry that includes the US Food and Drug Administration, is carefully evaluating the effects of magnetic resonance on device function in adults undergoing nonthoracic imaging but still will not change current contraindications to thoracic MRI.

Acquisition sequences in cardiac MRI include 5 essential techniques. Knowing which techniques provide the anatomic and functional assessment necessary for patient management is helpful:

1. Segmented balanced steady-state free-precession images are cine images analogous to echocardiographic projections of the heart (eg, 3-chamber view or parasternal long axis, 4-chamber view or apical 4-chamber view, 2-chamber view). These images demonstrate wall motion abnormalities and are used for volume assessment.
2. Dark-blood T2-weighted images are static images obtained in similar projections that display myocardial edema.
3. Velocity-encoded images provide information similar to that of pulsed-wave Doppler in echocardiography

but also offer flow volumes; processing of these images can provide shunt fraction, differential pulmonary blood flow, diastolic function, regurgitant fraction of valves, and a surrogate for ejection fractions.

4. Late gadolinium enhancement images are still images that display areas of fibrosis. The pattern of late gadolinium enhancement can distinguish between previous infarct, myocardial inflammation, or surgical residua depending on the pattern within the myocardium.
5. Dynamic magnetic resonance angiography with gadolinium may also be used to characterize great vessel dimensions and identify collateral venous or arterial circulation.

### **Cardiac CT**

Cardiac CT offers noninvasive coronary artery imaging. This may be important regardless of other CAD assessments because of the ability to visualize anomalous coronary origin, course, and reimplanted coronary ostia (ostial or balanced disease can be missed on indirect stress myocardial perfusion imaging). Although CT depicts calcification with high sensitivity, calcium scoring alone is not sufficient evidence to exclude significant CAD.

Larger centers may offer significantly lowered radiation doses while still providing thorough anatomic and functional assessment. For ACHD patients in whom MRI is contraindicated or not tolerated, CT can be equally useful, although it also requires dedicated expertise to correctly perform and interpret scans. CT can provide quantitative measurements of RV and LV volume and ejection fraction, which is useful in patients who are not candidates for MRI. CT is routinely used in some centers before redo sternotomy to delineate the relationship of the cardiovascular structures to the sternum and the presence of adhesions. One common pitfall is the assessment of pulmonary vascular blood flow in the setting of known shunt lesions or circulations (the frequent misdiagnosis of pulmonary embolism in Fontan circulation in inexperienced hands). CT can assess late contrast enhancement, but it is a second-line test to MRI late gadolinium enhancement and cine myocardial functional assessment.

### **Peripheral Vascular Imaging**

As with acquired vascular disease, ultrasound serves a screening role, and many lesions require further characterization with CTA, magnetic resonance angiography, or invasive angiography. Peripheral vascular imaging is especially useful in the patient with multiple prior cardiac catheterizations or surgeries, to evaluate vascular patency before upcoming procedures. Some equipment may allow simultaneous acquisition of cardiac CTA with peripheral CTA, but not all vendors provide this time- and contrast-saving feature.

### **Other Imaging**

Some lung diseases are exacerbated or caused by ACHD lesions, such as pulmonary arteriovenous malformations, or chronic venous hypertension. Chronic passive congestion of the liver attributable to right-sided heart overload can lead to cirrhosis and may require advanced CT or MRI for surveillance imaging. Neurovascular lesions can occur (such as circle of Willis aneurysms in coarctation of the aorta) and may require collaboration with neuroradiology services.

The utility of advanced imaging is best when radiological expertise is coupled with a multidisciplinary panel of experts so that findings and diagnoses are considered in their proper context. Multidisciplinary conferences are highly encouraged. Direct physician supervision by a radiologist or cardiologist with advanced cardiac imaging training is encouraged in most cases of cardiac CT and MRI. This is often better accomplished at high-volume centers.

### **Cardiopulmonary Exercise Testing**

Exercise intolerance has been documented in all ages of CHD<sup>165–169,335</sup> and is associated with an increased risk for hospitalization and death.<sup>168,176</sup> Early data suggest that cardiopulmonary exercise testing, especially peak oxygen consumption (peak  $\text{VO}_2$ ) and heart rate reserve, may provide prognostic information in ACHD.<sup>336</sup> Most studies of exercise testing and of cardiopulmonary rehabilitation and exercise programs to improve capacity are in young adults (20–40 years of age) but show significant benefit.<sup>180,337,338</sup> Prospective data regarding exercise testing, prognosis, and the impact of cardiac rehabilitation in older adults need to be a focus of ACHD study in the coming years as this population continues to age.

## **Recommendation for Advanced Imaging Techniques in ACHD**

- 1. Training and cardiac rehabilitation should be recommended for ACHD patients found to have significantly reduced exercise tolerance (especially if in conjunction with abnormal lung function) (Class I; Level of Evidence C).**

### **Cardiac Catheterization**

Cardiac catheterization, because of the development and refinement of other imaging modalities such as magnetic resonance and CTA, is currently reserved to resolve specific anatomic or physiological questions or for interventional treatment.<sup>49,339</sup> Diagnostic cardiac catheterization in an older adult with CHD requires specific planning. This includes establishment of the presence or absence of vascular access, which may be limited by previous procedures or be altered by congenital anatomy, including azygous continuation of the inferior vena cava or left superior vena cava to the coronary sinus. Operators should review existing imaging, including vascular duplex, and plan the case in conjunction with the ACHD clinician and be prepared to use alternative routes of access. The condition in question may determine the most appropriate operator for the case. Patients with simple or moderately complex disease with symptomatic CAD and no need for intervention for CHD are best served by coronary angiography performed by an experienced operator. Conversely, patients with severe complex disease who require catheterization in preparation for surgery or to establish pulmonary vascular resistance should have the case performed by an operator experienced in complex CHD and PAH. In some cases, skills essential for both acquired heart disease and CHD will be necessary. Very few operators have sufficient skill to address all these issues. In many cases, institutions would be well served to use a team approach in which a congenital cardiologist and an experienced coronary angiographer work as a

team to ensure that adequate data are collected. The ACHD clinician plays an important role in determining the individual or team most appropriate for each individual case.

Diagnostic cardiac catheterization may be performed to assess pulmonary vascular resistance, RV or LV diastolic function, and pressure gradients; for evaluation and possible device closure of either aortopulmonary, arteriovenous, or venovenous collaterals; and for quantification of shunt volume when other noninvasive techniques are equivocal. In shunt lesions with echocardiographic evidence of elevated PA pressures (PA pressure  $>50\%$  systemic), cardiac catheterization should be performed to determine the feasibility, timing, and conduct of surgical repair. Patients with pulmonary hypertension may be candidates for fenestrated closure of ASDs or VSDs, but they often benefit from a period of preoperative treatment with pulmonary vasodilator drugs.<sup>340,341</sup>

Operators must have a firm grasp of the coronary anatomy. Azotemia is prevalent in severe CHD and in older patients.<sup>203</sup> In these cases, the use of as much ventricular and vascular imaging as possible noninvasively will minimize the dye load necessary to delineate coronary anatomy and will minimize renal toxicity. Biplane imaging, not available in many adult catheterization laboratories, may be helpful in minimizing contrast requirements. In cases of PAH or transplant evaluation, other team members may be recruited, such as a pulmonary hypertension heart failure specialist who may perform some cases or may assist in other cases to ensure adequate data collection. Evaluation of intracardiac shunts is typically much less familiar to an operator who mainly evaluates left-sided heart disease and coronary disease. In the case of shunt lesions, operators skilled in the evaluation of CHD should perform this aspect of the case.

In the case of superimposed CAD, it is essential that the operator have specific skills in coronary angiography and percutaneous coronary intervention, when indicated. Coronary angiography, especially in those with defined risk factors for CAD (eg, postmenopausal women, hypertension, cigarette smoking, hyperlipidemia), is reasonable before surgery in ACHD patients. Although previous guidelines have suggested an age threshold of 40 years for preoperative cardiac catheterization, recent consensus guidelines from the AHA/ACC and the Canadian Cardiovascular Society have not supported these age cut points in the absence of other predisposing factors.<sup>49,342</sup> Recent meta-analyses in the general population indicate that 64-slice CTA can be used in lieu of coronary angiography to exclude important CAD when the pretest probability is low.<sup>343</sup> Patients who are symptomatic or who have positive signs suggestive of CAD should undergo invasive angiography to facilitate endovascular treatment of lesions preoperatively.<sup>344</sup>

## **Recommendations for Cardiac Catheterization**

- 1. We recommend that diagnostic cardiac catheterization in the older adult with CHD use a team approach that includes interventionalists skilled in the evaluation of the physiology associated with CHD, as well as those skilled in selective coronary angiography (Class I; Level of Evidence C).**

2. Coronary angiography, especially in those with defined risk factors for CAD (eg, postmenopausal women, hypertension, cigarette smoking, hyperlipidemia), is reasonable before surgery in all ACHD patients >40 years of age (Class IIa; Level of Evidence C).
3. Sixty-four–detector-row and higher CTA can be useful in lieu of invasive coronary angiography to exclude important CAD when the pretest probability is low to intermediate (Class IIa; Level of Evidence C).

### Electrophysiological Testing

Electrophysiological testing in the older adult with CHD requires careful planning, with detailed knowledge of the anatomy and prior surgical procedures being key. Arrhythmia management is frequently an issue in this population, and consultation with an electrophysiologist with expertise in CHD is recommended as a critical part of care. Electrophysiological studies should be performed at centers with expertise in the management of such patients. Ablation is recommended for treatment of many of the arrhythmias identified in these patients and is addressed below.

## Treatment of the Older Adult

### Percutaneous Intervention

There is a broad scope of potential percutaneous interventions in the adult with CHD that range from percutaneous coronary interventions to transcatheter valve implantation. Coronary intervention should be undertaken by an experienced coronary interventionalist with high-volume procedure experience. Interventionalists trained in pediatric cardiology or adult congenital intervention and adult structural interventionalists will likely have more experience with congenital interventions, including ASD closure, VSD closure, stenting of coarctation of the aorta, pulmonic valvuloplasty, or transcatheter pulmonic (pediatric and adult congenital interventionalists) and transcatheter aortic (adult structural/congenital interventionalists) valve replacement. In every case, it is essential that the operator understand the path of physiology and natural history of the lesion to avoid procedures that are either unnecessary, as in stenting of minor pulmonary arterial stenosis, or contraindicated, as in closure of the ASD in an Eisenmenger patient. All CHD interventions should be performed in centers with experience, ideally with >1 operator, and should have a conference at which cases are discussed and the pros and cons of medical interventional and surgical approaches weighed and compared before a consensus is reached on management.

### Surgery in ACHD for Patients >40 Years of Age

Although many classification schemes exist for cataloguing the growing number of patients with ACHD, this section will subdivide older ACHD patients into those with primary or previously unrepaired lesions and those with residual lesions after initial surgical repair. Primary lesions covered include ASDs, aortic valve pathology secondary to BAV, partial anomalous pulmonary venous connection (including Scimitar syndrome), double-chambered RV, Ebstein anomaly, and pulmonary stenosis. Residual lesions covered are more extensive and include RVOT reconstruction, aortic

root pathology after repair of TOF or arterial switch operation, failing Fontan physiology, CCTGA, AV valve regurgitation after repair of AV canal defects, VSD, and coarctation of the aorta.

## Primary Lesions in ACHD

### Atrial Septal Defects

Class I indications for ASD closure include right atrial or RV enlargement,<sup>49</sup> but it is also reasonable to consider closure in the presence of a Qp:Qs ratio  $\geq 1.5:1$  or when paradoxical embolism or symptoms of dyspnea or orthopnea are present. The presence of a sinus venosus ASD with anomalous pulmonary venous return can increase the left-to-right shunt and accelerate the onset of pulmonary hypertension; therefore, it may be reasonable to pursue surgical closure in the presence of these ASDs regardless of other indications. Patients with specific risk factors for CAD or those with documented echocardiographic evidence of pulmonary hypertension should undergo cardiac catheterization to guide the feasibility, timing, and conduct of surgical closure. Although traditionally, patients with severe pulmonary hypertension were considered inoperable, there is increasing evidence that with the use of preoperative pulmonary vasodilator drugs or fenestrated patch closure, postoperative outcomes have improved.<sup>339,340,344</sup>

Over the past 3 decades, percutaneous closure has become the preferred mechanism in patients with amenable secundum ASD anatomy and right-sided heart enlargement. ASD closure is the most common percutaneous procedure performed in this population. For sinus venosus, with or without partial anomalous pulmonary venous return, and for primum ASDs, surgical closure is required. If a secundum ASD is too large for device closure, minimally invasive surgical approaches can be considered, including ministernotomy and a thoracoscopic approach. In addition, minimally invasive transthoracic device closure of the ASD at advanced age without CPB is feasible and safe in the short term, with longer-term results pending.<sup>345</sup>

Traditional operative strategies, such as pericardial or synthetic patch closure, have been well established, with a low complication rate and a mortality rate close to zero among patients without pulmonary hypertension.<sup>346–349</sup> Recently, there have been an increasing number of reports regarding results after surgical closure among elderly patients (>60 years of age) that demonstrate equivalent survival to younger patients, albeit with slightly higher complication rates.<sup>36,350,351</sup> In a study<sup>36</sup> of 68 patients between 68 and 86 years of age at a single institution undergoing either surgical (n=13) or device (n=54) closure, the incidence of major complications (including pneumothorax, heart failure, and pneumonia) was 23%, higher than that recently reported<sup>352</sup> using the Society of Thoracic Surgeons' Congenital Heart Surgery Database (20%) and in another recent single-institution review<sup>353</sup> (12%). Of note, however, there were no operative deaths among the elderly cohort. Moreover, after ASD closure, echocardiographic indices of RV size and function were significantly improved from preoperative values, and functional capacity, as measured by standardized survey instruments, was also significantly improved.

**Aortic Valve Pathology (Bicuspid Valve)**

BAV is one of the most common congenital lesions, and valvar dysfunction may present early or may be silent until the fifth to seventh decade of life. Ascending aortic aneurysm and dissections are associated with valve disease in those with BAV. Criteria for surgical replacement of the aortic root or ascending aorta have recently been liberalized in the presence of a BAV, given the propensity for dissection to occur at smaller aortic diameters (mean of 5.1 mm). There may also be an accelerated growth rate for aneurysm in BAV compared with those with trileaflet valves. After careful consideration of the surgeon's own expertise and the patient's condition, it would be reasonable to recommend surgical intervention when the ascending aortic diameter reaches 4.5 cm, especially at centers where the 30-day mortality approximates 2%.<sup>354</sup> Optimum surgical therapy for aortic aneurysm or dissection with BAV consists of composite valved-graft implantation (mechanical or bioprosthetic) or valve-sparing root replacement in cases without valvar dysfunction.

Aortic valve stenosis is the most prevalent complication of BAV and can coexist with aortic regurgitation of variable severity. Surgical indications do not differ from those for acquired aortic valve disease.<sup>355</sup> Because the median age at presentation is generally after the fifth decade, it is not possible to quantify the perioperative mortality risk in patients >40 years of age; however, extrapolation of data from aortic valve replacement in older patients (>70 years) suggests that mortality risk likely increases with age but may be related predominantly to other comorbidities rather than just chronological age itself.<sup>356,357</sup> Therefore, age-specific modification of the guidelines for surgical therapy is not warranted. Optimum surgical therapy for aortic valve stenosis in older patients consists of aortic valve replacement. Although the durability of bioprosthetic valves has historically been inferior to mechanical valves in adolescents and young adults, those >40 years of age should have equivalent freedom from structural valve deterioration with either type of prosthesis.<sup>357</sup> The Ross operation, although a reasonable choice for other types of aortic pathology, cannot be strongly recommended in patients with BAV.<sup>358–360</sup> Given the frequent need for reintervention after Ross procedure, the advantage over aortic valve replacement in the older adult has not been established.<sup>361</sup>

**Aortic Coarctation**

Aortic coarctation is rarely diagnosed in those >40 years of age because the unoperated survival averages 35 years of age, with 75% mortality by 46 years of age. Aortic coarctation may be associated with BAV or other left-sided obstructive lesions as noted previously. Indications for surgical repair of native aortic coarctation in an adult are controversial. Endovascular therapy has largely supplanted traditional surgery except in women of childbearing age and in those with associated aneurysm or transverse arch hypoplasia. It is reasonable to recommend surgical therapy, consisting of excision of the narrowed segment with interposition graft, in the presence of a peak-to-peak coarctation gradient  $\geq 20$  mm Hg.<sup>49</sup> Although excision with extended end-to-end anastomosis is optimal in neonates and infants, immobility of the thoracic aorta because of the presence of important intercostal or lumbar vessels and fixation to the posterior mediastinum makes such a repair more

difficult and less durable in terms of freedom from recoarctation. Calcification and atherosclerosis of the aorta may also complicate surgery in the older adult.

**Partial Anomalous Pulmonary Venous Connection**

Isolated partial anomalous pulmonary venous connection is rarely diagnosed in adults. A recent study documented that partial anomalous pulmonary venous connection was seen in 0.2% of adults on retrospective examination of 1825 chest CT scans.<sup>362</sup> In contrast to previous series focusing on children, the anomalous vein in adults was most commonly noted in women, was not associated with the presence of an ASD, and originated from the left upper lobe.<sup>362</sup> Pulmonary or other cardiovascular symptoms are common, occurring in  $\approx 70\%$  of patients. Although there are no specific guidelines for when to repair partial anomalous pulmonary venous connection, it is reasonable to apply those guidelines established for closure of ASDs in adults.<sup>49</sup> Surgical therapy for the most common form (anomalous left upper pulmonary vein drainage to the innominate vein) consists of ligation and division of the ascending vertical vein concomitant with anastomosis of the anomalous vein to the left atrium. Many repairs can be performed without CPB. In cases in which the anomalous veins drain to the right superior vena cava >2 cm above the cavoatrial orifice, or when the anomalous veins are associated with a sinus venosus ASD, a Warden procedure is optimum to avoid obstruction of either the pulmonary veins or the superior vena cava.<sup>363,364</sup>

**Double-Chambered RV**

Surgical resection of muscle bands in a double-chambered RV accompanied by closure of a VSD, if present, is recommended for significant obstruction (mean Doppler gradient >40 mm Hg) independent of symptoms. In the symptomatic patient without other discernable cause, the threshold for surgery is a mean gradient >30 mm Hg.<sup>49</sup> Surgery should also be performed when cardiac surgery is planned to address other pathology.<sup>365</sup> However, a review of recent literature disclosed only 8 previously published cases in those >30 years of age<sup>366</sup>; therefore, each case does need to be considered carefully on an individual basis.

**Isolated Pulmonary Valve Stenosis**

Isolated valvar pulmonary stenosis occurs in  $\approx 7\%$  to 12% of all CHD and can be associated with Noonan syndrome. Patients with pulmonary stenosis are generally treated with transcatheter valvotomy and usually require surgical intervention (if at all) only after balloon valvotomy complicated by important pulmonary regurgitation. Surgical therapy for the resultant pulmonary insufficiency involves insertion of a bioprosthetic valve. Mechanical valves are rarely used in the pulmonary position because of the propensity for thrombosis. In cases in which patients are receiving warfarin anticoagulation for other reasons, mechanical valve insertion could be considered, although data on their use are very limited. The advent of transcatheter valve implantation with either the Melody or the SAPIEN valve has dramatically changed the treatment paradigm, and possibly the threshold for pulmonary valve implantation, although current size limitations and the requirement at this time for a conduit or other fixed structure in the RVOT may limit use in the patient without prior surgery.



### ***Congenitally Corrected Transposition (L-TGA)***

Unoperated patients usually come to medical attention because of systemic ventricular failure and severe systemic AV valve regurgitation, although this may be in the fourth or fifth decade. A “double-switch” operation has been attempted, which consists of an atrial diversion such as the Mustard or Senning procedure and an arterial switch, to place the LV in the systemic circulation. However, high mortality with failure to complete LV retraining among adult patients undergoing the double switch coupled with the recent evidence of excellent survival (84%) at 40 years achieved in patients with nonanatomic repairs has underscored the need for further comparative studies.<sup>367–370</sup> Nonanatomic repair consists of simple VSD closure (when intraventricular tunnel [Senning-Rastelli] is prohibited) with relief of pulmonary stenosis with concomitant replacement of the systemic AV valve.

Surgical intervention in the older patient is usually directed at correcting systemic AV valve regurgitation as a means to improve morphological RV function. Although the accepted paradigm is to attempt valve repair in most other situations, it is recommended that valve replacement be performed before RV dysfunction ensues if it is planned for the RV to remain in the systemic circulation.<sup>371,372</sup> Placement of a PA band has been considered in those with either normal or mildly impaired RV function as treatment for systemic AV valve regurgitation. The mechanism is thought to relate to changes in septal shift that reduce effective systemic AV valve annular size. Unfortunately, 2 recent, relatively large studies of 39 and 20 patients, respectively, showed no improvement in the degree of systemic AV valve regurgitation compared with pre-PA band data. Furthermore, the development of dysfunction in the subpulmonary LV can reduce the efficacy of this approach.<sup>373–375</sup> Cardiac resynchronization therapy has been disappointing in the setting of L-TGA with RV dysfunction, although it could be considered when other options cannot be implemented.<sup>376,377</sup>

### ***Ebstein Malformation***

Ebstein malformation is a rare congenital malformation ( $\approx 1\%$  of all congenital defects) and really should be considered an anomaly of the RV rather than an anomaly of the tricuspid valve. ACHD patients in the current era most likely present with progressive heart failure, tachyarrhythmias, or paradoxical embolism, and presentation for unoperated patients commonly can occur after their third decade.

Surgery is indicated in the presence of arrhythmias not amenable to transcatheter techniques, severe tricuspid regurgitation with evidence of deteriorating exercise capacity or reduced RV systolic function, progressive cyanosis, or paradoxical embolism. Initial therapy should include an attempt at valve repair, closure of the ASD, and reduction of the atrialized component of the RV. Concomitant arrhythmia surgery with either a right atrial maze or biatrial maze should be performed when atrial flutter or AF is present. Limited external pulmonary vein isolation with excision of the left atrial appendage can be considered in lieu of a full biatrial maze to avoid prolonged cross-clamp time in selected patients. Methods for valve repair are numerous (including the Cone reconstruction, modified Cone reconstruction, and full or partial annuloplasty techniques) and mainly depend on surgeon experience, the morphology of the valve itself, and the

mechanism of regurgitation. Despite the improvements in valve reconstruction and the advent of the Cone reconstruction, valve replacement is still necessary in 35% to 65% of cases.<sup>378–382</sup> No clear data exist regarding the optimum prosthesis for tricuspid valve replacement.<sup>355</sup> Recent data reported equivalent 10-year event-free survival was 31% for patients undergoing tricuspid valve replacement, with no statistically significant difference between mechanical or bioprosthetic valves.<sup>383</sup> An approach that integrates patient preference in the absence of clear contraindications is likely to result in improved outcomes.

### ***Coronary Artery Anomalies***

An unroofing procedure, which avoids coronary reimplantation but allows for ostial widening and unobstructed egress of the artery, avoiding an interarterial course (by eliminating the intramural segment), has been proven successful if anatomy is favorable. This procedure creates a large neo-orifice in the appropriate sinus perpendicular to the aortic root.<sup>384</sup> Coronary artery bypass grafting may risk competitive flow and graft failure, and use of the left internal mammary artery (if chosen) at a young age would then remove its potential use in old age should ischemic disease ensue. Outcomes of surgical intervention have been favorable.<sup>385</sup> In the presence of concomitant atherosclerotic CAD, coronary artery bypass grafting may be appropriate as an alternative surgical approach.<sup>384</sup> Other studies have focused on patients who have undergone repair at a young age with good short- and medium-term results.

## **Residual Lesions in ACHD**

### **Right-Sided Cardiac Complications**

#### ***Pulmonary Valve Regurgitation***

Pulmonary valve regurgitation is most commonly encountered after repair of TOF and was the most common ACHD operation performed in a recent analysis of the Society of Thoracic Surgeons' Congenital Heart Surgery Database.<sup>352</sup> Current indications for PVR are listed in Table 3. Pulmonary valve regurgitation after repair of TOF is relatively well tolerated in the short term, in part because the hypertrophied RV usually adapts to altered hemodynamic load.<sup>389</sup> However, the detrimental effects of chronic pulmonary valve regurgitation are numerous, including progressive RV dilation and failure, tricuspid valve regurgitation, exercise intolerance, arrhythmia, and sudden death.<sup>57,130,389,392–395</sup> Mechano-electrical interaction, whereby a dilated RV provides the substrate for electrical instability, may underlie the propensity toward ventricular arrhythmia.<sup>394</sup>

PVR has been shown to improve pulmonary regurgitation and to be protective against the development of recurrent ventricular and atrial arrhythmias.<sup>134,396–398</sup> The salutary effects of PVR before clinical manifestations may be related to a reduction of the QRS duration<sup>399</sup> or stabilization of the QRS duration.<sup>134</sup> Correlations between smaller RV size and reduced arrhythmia vulnerability suggest that a measurable reduction in RV size may be an important precursor required for favorable QRS changes after PVR.

The reported reoperation rate for PVR after TOF varies depending on the morphological substrate included, the predominant repair type, and the duration of follow-up. Rates of 98% freedom from PVR at 10 years after initial repair likely

**Table 3. Published Indications for Pulmonary Valve Replacement**

Clinical symptoms <sup>386</sup>
Exercise intolerance
Exertional dyspnea
Arrhythmia
Echocardiographic criteria
RV hypokinesia <sup>387</sup>
Isolated severe pulmonary valve regurgitation <sup>388</sup>
Pulmonary valve regurgitation associated with tricuspid valve regurgitation, pulmonary artery stenosis, or residual VSD <sup>389</sup>
Preoperative RV ejection fraction $\geq 0.40$ <sup>386</sup>
Progressive RV dilation <sup>134</sup>
Severe RV dilation <sup>387</sup>
RV end-diastolic volume $>170$ mL/m <sup>2</sup>
RV end-systolic volume $>85$ mL/m <sup>2</sup>
Severe RV dilation and RV dysfunction <sup>389</sup>
Moderate to severe RVOT obstruction (peak Doppler gradient $>50$ mm Hg) <sup>134</sup>
Electrocardiographic criteria
QRS duration $\geq 180$ ms <sup>390</sup>
Increased QRS duration rate of change ( $>3.5$ ms/y) <sup>390</sup>
Recurrent or sustained arrhythmia <sup>388</sup>
Other
Elapsed time interval from repair $>2$ y <sup>391</sup>

RV indicates right ventricular; RVOT, right ventricular outflow tract; and VSD, ventricular septal defect.

underestimate the actual prevalence because they reflect the historically conservative approach to PVR.<sup>400</sup> Presently published indications for PVR are variable and subjective (Table 3). Patients are generally referred when they are symptomatic with exercise intolerance or clinical arrhythmia, or when they have severe RV dilation or dysfunction.<sup>134,387,397</sup> The literature suggests that the appearance of these clinical signs may compromise RV functional recovery and limit the benefits of restoring pulmonary competence.<sup>386,389</sup> To define more exact criteria for PVR, 1 study obtained indices of RV volumes in 17 patients by use of MRI.<sup>387</sup> No patients with an RV end-diastolic volume  $>170$  mL/m<sup>2</sup> or an RV end-systolic volume  $>85$  mL/m<sup>2</sup> achieved normalization of RV volume. Additional evidence for liberalization of the current indications for PVR comes from a recent study<sup>399</sup> that demonstrated a significant decrease in both RV end-diastolic volume and QRS duration after PVR. Other studies<sup>401</sup> have shown RV recovery independent of the duration between repair and PVR, but the patient population was significantly younger at the time of PVR (mean age, 14.6 years) than the prior study (mean age, 33.9 years).<sup>387</sup> The potential for RV mechanical and electrical remodeling after PVR may diminish over time, and earlier PVR may have real benefit in the postrepair TOF population.<sup>389</sup> Reasonable equipoise must be sought, however, between the potential benefits of early intervention and the inevitable failure rate of the implanted prosthetic valve, which leads to reoperation.

Surgical PVR has been the standard for RVOT pathology in patients with CHD.<sup>396,397,402–404</sup> Surgical PVR usually involves removal of the existing transannular patch or conduit and resection of any aneurysmal dilatation of the RVOT replacement with

either an in situ bioprosthetic valve or another conduit. There are no prospective data to guide selection of the preferred conduit among older adult patients. However, data from the prospective, multi-institutional Congenital Heart Surgeons' Society studies among children suggest that the bovine jugular-venous valved conduit has superior durability compared with allografts or other heterografts.<sup>405,406</sup> Despite the uniformly excellent outcomes with surgical PVR, there are potentially increased risks associated with reoperative cardiac surgery (especially catastrophic bleeding from re sternotomy and introduction of air in patients with patent intracardiac shunts).<sup>402–404</sup> Unfortunately, there are no data quantifying this risk, and it has also been shown that the risk of surgical procedures among patients with CHD varies substantially depending on both institutional and surgeon factors.<sup>407</sup> Given the recent introduction of the Melody valve and the upcoming introduction of the Edwards' SAPIEN valve, transcatheter therapy is being offered as an alternative to conventional surgical PVR.<sup>408,409</sup> Short- and medium-term outcomes after transcatheter PVR are studied in the expanded multicenter US Melody valve trial. Transcatheter therapy is purported to be superior to surgical PVR because of the perceived mitigation of surgical risk and improved patient satisfaction and perceived quality of life. However, current reports quantifying the risk of transcatheter PVR demonstrate an important prevalence of adverse events, including 6% (8/136) from the recently published Melody trial data.<sup>408–410</sup> Another study similarly reported a procedural complication rate of 4.2% that necessitated urgent surgical rescue and a morbidity rate of 5.8% in patients who had percutaneous valves.<sup>411</sup> Recent data, however, would suggest that refinements in implantation strategies have substantially decreased the risk of coronary artery compression and stent fracture among the transcatheterization group. Currently available transcatheter valves are only suitable for patients with non-native RVOTs, although transcatheter valves with broader applicability are in early trials. Although dynamic and evolving, the early complications associated with transcatheter therapy at least are known. In contradistinction, contemporary morbidity, mortality, and durability of surgical PVR are not known, and therefore, there is no contemporaneous benchmark against which to compare transcatheter valve implantation. Previous studies have used historical controls.<sup>411</sup>

#### **Recurrent/Residual RVOT Obstruction**

Residual gradients at the level of the RV infundibulum, pulmonary valve annulus, and peripheral PAs after repair of tetralogy-like double-outlet RV and TOF are well described. In infant surgery, there appears to be a risk of RVOT obstruction within the first decade.<sup>400,412</sup> However, in adults, the increased RV mass from RVOT obstruction over time may result in protection from significant dilation of the RV in the setting of severe pulmonary regurgitation. Patients with pulmonic stenosis are most likely to display this phenomenon. Whether this extrapolates to differences in outcome has yet to be clearly elucidated.

#### **Tricuspid Valve Regurgitation**

Tricuspid valve regurgitation often coexists with important pulmonary regurgitation in postrepair survivors. Strategies to prevent clinical deterioration from tricuspid regurgitation include frequent evaluation with echocardiography, MRI, or cine-MRI to identify patients with preclinical RV dysfunction

or dilation. Early PVR with or without tricuspid valve repair is recommended. Judicious use of tricuspid valve annuloplasty, valve repair, and right atrial reduction plasty is indicated when there is evidence of more than mild valvular incompetence to prevent further deterioration and perhaps the onset of atrial arrhythmia.<sup>130,389,413–417</sup> Some authors also recommend that prophylactic cryoablation be performed in patients with severe tricuspid valve regurgitation and right atrial enlargement to decrease the risk of late arrhythmia.<sup>389,397</sup>

## Left-Sided Cardiac Complications

### *Aortic Root Dilatation and Aortic Valve Regurgitation*

Aortic root dilatation is known to be a feature of conotruncal anomalies, especially in those patients undergoing repair at an older age.<sup>418</sup> The pathophysiological mechanisms are unproven but are thought to be related to increased flow through the aorta from overriding of the infundibular septum and right-to-left shunting before repair.<sup>418,419</sup> Progressive aortic root dilatation may result in aortic regurgitation in 15% to 18% of operative survivors, some of whom will require valve replacement.<sup>419</sup> Although thresholds for surgical intervention are well established for primary aortic aneurysm, it is not clear that these same thresholds apply in patients with neo-aortas (after arterial switch or patch aortoplasty). Recent data from the Mayo Clinic demonstrated that moderate ascending aortic enlargement is common among patients with conotruncal anomalies coming to operation, but aortic dissection is rare, as is subsequent need for aortic reoperation. Despite current enthusiasm for prophylactic operations on the ascending aorta in patients with acquired disease, these data suggest that the moderately dilated aorta in this setting may be observed.<sup>50</sup> Patients with autografts, however, may represent a different population. Autograft dilation and development of aortic regurgitation that requires reintervention are more common. A recent report from the Ross registry noted that 15-year freedom from autograft sinus or ascending aortic dilatation was 79% and that autograft reoperation was required in 11% of patients.<sup>359</sup> Fortunately, many patients with autograft dilation-induced aortic regurgitation can be treated successfully with a valve-sparing root replacement.

### *Failed Fontan Physiology*

Outcomes after neonatal repair of single-ventricle lesions are excellent in most large centers, exceeding 90%.<sup>420,421</sup> However, because of the relative youth of the current survivors, the population of patients >40 years of age is small. Among 5265 ACHD patients catalogued in the Society of Thoracic Surgeons' Congenital Heart Surgery Database, Fontan revisions accounted for <1% of all surgical procedures, and no patients were >33 years of age.<sup>352</sup> Patients with failed Fontan physiology may present with refractory cyanosis, arrhythmia, edema attributable to protein losing enteropathy, cirrhosis, outflow tract obstruction, or AV valve dysfunction. Complete discussion of all of these is beyond the scope of the present report and, as mentioned above, may be currently irrelevant to the present statement.

Surgery should be performed in an experienced, high-volume ACHD center by a surgeon trained in the treatment of CHD. Reoperations for failed Fontan physiology could include Fontan revision or the correction of residual shunts

or valve dysfunction. In-hospital mortality after Fontan revision approaches 15% in contemporary multi-institutional series,<sup>352,422</sup> representing the highest mortality among all ACHD operations.

## Recommendations for Residual Lesions in ACHD

- 1. Cardiac surgery for patients with ACHD should be performed in centers with proven experience and good success rates for a proposed surgery. Surgeons should be trained in the treatment of ACHD (Class I; Level of Evidence B).**
- 2. We recommend that the approach to correction of primary lesions and residual disease be multidisciplinary for consideration of the risks and benefits of surgery, percutaneous interventions, and hybrid approaches (Class I; Level of Evidence B).**
- 3. Reoperation in an older ACHD patient may be complicated by thoracic abnormalities, mediastinal adhesions, superimposed acquired heart disease, limited vascular access, and extracardiac disease, all of which should be carefully evaluated preoperatively (Class I; Level of Evidence B).**

## Conclusions

As the population of adults with CHD continues to expand, there are not only an increasing number of patients who need longitudinal care, but also a larger group of older adults who present with unique needs that may not have been recognized previously. The progression of natural history of disease and childhood repairs and superimposed acquired heart disease offer new challenges for management, as well as opportunities to understand the evolution of many CHD lesions.

This scientific statement addresses epidemiology, diagnoses, complications, diagnostic testing, and interventions in the population of patients with CHD who are now >40 years of age. Over the lifetimes of these patients, there has been a significant evolution in cardiac surgery and noncardiac surgical interventions; however, there are few large clinical trials on which to base recommendations, and therefore, most recommendations are still based on expert consensus opinion. It is essential that we continue to collect accurate data on the outcomes of our treatment that can guide future management of these patients. In this age group, an important consideration is the interaction between the CHD and acquired heart disease. Screening for and treatment of traditional risk factors for CAD, development of heart failure, and progression of valvular disease all require continued and further study to determine whether the guidelines we apply in patients with acquired heart disease may be applicable or to develop unique guidelines for the older adult with CHD.

We hope this statement serves as a foundation for the care of the older adult with CHD and that in the coming years, natural history studies through registries and carefully designed trials will inform future versions of this document. It is encouraging for the field of ACHD that the treatment of the older adult is an issue that is now upon us, and it is an exciting time as our management strategies must now evolve along with this population of patients.

## Disclosures

## Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Philip Chang	University of Southern California	None	None	None	None	None	None	None
David Gregg	Medical University of South Carolina	None	None	None	None	None	None	None
Carole Warnes	Mayo Clinic—Rochester	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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KEY WORDS: AHA Scientific Statements ■ congenital heart defect ■ cardiac surgical procedures ■ cardiac imaging techniques ■ cardiac arrhythmia ■ heart failure ■ cardiac valves



## Congenital Heart Disease in the Older Adult: A Scientific Statement From the American Heart Association

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*Circulation*. published online April 20, 2015;

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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