Coronary Disease and Modifying Cardiovascular Risk in Adult Congenital Heart Disease Patients: Should General Guidelines Apply?

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ABSTRACT

There are >1.4 million adult congenital heart disease (CHD; ACHD) patients living in the United States. Coronary artery disease (CAD) is at least as prevalent in ACHD patients as in the general population and has become a leading cause of their mortality. In the majority of cases, CAD in the ACHD population is driven by the presence of traditional cardiovascular disease (CVD) risk factors. 80% of ACHD patients have at least one CVD risk factor. Hypertension (HTN), obesity and physical inactivity are frequently seen in both pediatric and adult patients with CHD. Many ACHD patients demonstrate abnormal glucose metabolism and are at an increased risk for developing diabetes. Current guidelines for CVD risk assessment and prevention do not specifically mention patients with CHD but are likely applicable to most of these patients. Specific CHD populations have “high-risk” lesions that are associated with an increased risk of CVD complications and may warrant intensified screening and treatment. These include patients with a history of coarctation of the aorta or with prior coronary artery ostial manipulation (patients with a history of d-transposition of the great arteries or anomalous aortic origin of a coronary artery). The physiology of single ventricle patients is also poorly suited for the effects of superimposed CVD; these patients may benefit from intensified treatment of CVD risk factors, particularly HTN and obesity.

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Contents

CVD risk in the ACHD population ....................................................... 301
CVD risk factors in the ACHD population ........................................... 301
Hyperlipidemia ........................................................................ 302
Obesity and physical inactivity. ........................................................ 303
Smoking .................................................................................. 304
Diabetes mellitus. ....................................................................... 304
Congenital coronary anomalies and CVD risk ................................. 304
Summary ................................................................................ 306
Statement of conflict of interest ......................................................... 306
References ............................................................................. 306

Abbreviations: ACHD, adult congenital heart disease; ALCA-R, anomalous left coronary artery from right sinus of Valsalva; ARCA-L, anomalous right coronary artery from left sinus of Valsalva; ASCVD, atherosclerotic cardiovascular disease; ASD, atrial septal defect; BP, blood pressure; CAD, coronary artery disease; cCTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; CoA, coarctation of the aorta; CVD, cardiovascular disease; DM, diabetes mellitus; D-TGA, d-transposition of the great arteries; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SCD, sudden cardiac death; ToF, tetralogy of Fallot; US, United States; VSD, ventricular septal defect.

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Congenital heart disease (CHD) is the most common birth abnormality, occurring in nearly 1 in 100 newborns. Due to significant medical and surgical advances over recent decades, defects that were once fatal in childhood can now be successfully repaired or palliated. Owing to these successes, >90% of patients born with CHD are expected to live into adulthood, and adult CHD (ACHD) patients now outnumber the pediatric CHD population. There are currently >1.4 million ACHD patients living in the United States (US), with an additional 20,000 CHD patients reaching adolescence each year.1,2 The aging ACHD population now faces the usual risks of adult acquired cardiovascular disease (CVD) in addition to chronic issues stemming from their inherent congenital defects. It is often assumed that all ACHD patients face an increased risk of CVD, however, evidence suggests that few CHD lesions inherently increase a patient’s risk of coronary artery disease (CAD). Patients with CHD may also have abnormal cardiac physiology and myocardial substrate that would poorly tolerate the effects of any superimposed CVD.3 In older ACHD patients, the presence of CAD has been associated with a five-fold increase in all-cause mortality.4 Thus it is important to examine the scope of CVD as it pertains to the ACHD population and define an optimal approach for CVD screening in this unique patient population.

CVD risk in the ACHD population

CVD has been the leading cause of death in the US for the past century. The majority of these deaths are attributable to CAD.5 The burden of CAD in the ACHD population is already significant. In a retrospective review of coronary deaths in the US from 1979 to 2005, Pillutla et al.6 demonstrated that myocardial infarction surpassed arrhythmia as the leading cause of death for noncyanotic CHD patients after 1990 (Fig 1). However, this may simply indicate that the aging ACHD population is following national mortality trends. Several small, single-center studies have attempted to define the prevalence of CAD within the ACHD population. Giannakoulas et al.7 reported on coronary angiography from 250 ACHD patients who underwent cardiac catheterization for reasons other than suspected CAD. They found an overall CAD prevalence of 14% in their population, of which 9.2% of patients had significant lesions with ≥50% occlusion. This number exceeds the prevalence of the general US adult population which is estimated to be around 6.8%.7 The data on whether or not ACHD patients are at risk of premature CAD has been mixed. In the Giannakoulas study, the mean age of the study population was 51 years (range 18–90) and no patient under the age of 47 had significant CAD. In an analysis by Yalonetsky et al.8 of ACHD patients with known CAD, 14% of the study population with obstructive CAD was under the age of 40, the youngest being only 27 years old. The overall prevalence of early onset CAD is likely lower given this study specifically evaluated known CAD patients and not all CHD patients. All patients in the study with early CAD had at least one traditional CVD risk factor.

Interestingly CAD is rarely seen in cyanotic heart disease. None of the complex cyanotic CHD patients in the Giannakoulas study were found to have significant CAD, albeit this group was overall younger in age due to the more recent advent of surgical techniques for these lesions.7,8 It is thought that persistent cyanosis induces multiple antiatherosclerotic effects that protect against the development of CAD. These patients typically have low cholesterol levels, elevated bilirubin, lower platelet counts and an increased bioavailability of nitric oxide, all of which may help prevent atherogenesis.7,8 Conversely, there is emerging evidence that cyanotic patients may be subject to chronic endothelial dysfunction and that this may actually increase their risk of developing CAD.6,10 Although most studies have demonstrated a paucity of CAD in cyanotic patients, the Yalonetsky study included 7 Eisenmenger patients with obstructive CAD.8 It is also important to keep in mind that chronic cyanosis is associated with an increased risk of both stroke and peripheral vascular disease, owing to the significantly increased erythrocytosis in these patients.11

CVD risk factors in the ACHD population

Atherosclerotic disease begins early in life and progresses over the ensuing decades. Autopsy studies have demonstrated the appearance of fatty streaks and raised coronary atheromas starting in the teenage years (Fig 2). As children, the focus of cardiology care is often purely on the CHD and not on acquired heart disease. Providers may forgo discussions on healthy lifestyle modifications and assessment of CVD risk at this stage. Hypertension (HTN) is more prevalent in pediatric CHD patients over the general population, and dyslipidemias are also frequently seen.12,13 Much of what CHD patients and their parents experience as children may set them up later for obesity and physical inactivity. Many pediatric CHD patients struggle with weight gain

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**Fig 1.** Principle causes of mortality from 1979 to 2005 for cyanotic and noncyanotic CHD. Reprinted with permission from publisher.6
early in life and are placed on high caloric diets to mitigate their growth failure. As their clinical status improves, discussions of lessened caloric need may be overlooked in the setting of treating serious structural heart disease. Both pediatric and adult CHD patients may also face activity restrictions which often result in more sedentary lifestyles. Patients may become overly limited from physical activities, often due to patient or parental concerns about placing too much stress on the patient’s heart, combined with a lack of appropriate guidance, reinforcement and reassurance at clinic visits. Even the child with a structurally normal heart and a benign murmur may end up being restricted from sports when the topic is not specifically discussed. These factors coupled with societal dietary and physical activity (PA) trends have created a situation where excessive weight gain is more prevalent in the pediatric CHD population, with 25% of patients being overweight or obese.

Traditional modifiable CVD risk factors are present in the majority of ACHD patients in whom significant CAD is found. These risk factors include diabetes, tobacco use, obesity and physical inactivity. HTN and hyperlipidemia are also both frequently present in ACHD patients with known CAD. In a large Belgian cohort of ACHD patients, 80% of the population had at least one of these CVD risk factors present. This is especially alarming given that the median age of the study cohort was only 26 years old. Given these findings, CVD risk assessment should at a minimum follow the currently established guidelines for the general population. Those patients with increased CAD risk due to their underlying CHD may additionally benefit from intensified screening and treatments (Table 1).

Hypertension

HTN is a leading cause of morbidity and mortality throughout the world, with half of CVD and cerebrovascular deaths globally attributable to systemic HTN. The overall prevalence of HTN in the general US adult population is 34% but this varies substantially with age and increases to 67% among persons ≥60 years old. The prevalence of HTN in the general ACHD population has been reported at 19–35%, and has been found in as many as 55% of patients with known CAD. The true prevalence of HTN in this population is difficult to determine given that many CHD patients are treated with long-

![Progression of atherosclerotic disease of the right coronary artery over time. The proximal portion of the artery is on the left and distal portion on right. Prevalence of lesions represented by increasing color intensity. Reprinted with permission from publisher.](image-url)
term cardiac medications with anti-HTN properties. Current HTN guidelines should be applied to ACHD patients with recommendations for healthy lifestyle modifications made to all patients. Typical anti-HTN therapies should be utilized for patients with a blood pressure (BP) >140/90 mm Hg to achieve a goal BP of <130/80 mm Hg. Additionally, in the absence of a history of coarctation of the aorta, younger CHD patients (>30 years old) should be screened for the usual secondary causes of HTN based on pertinent exam and laboratory findings. Patients with a history of coarctation of the aorta are at a significantly increased risk of developing HTN over their lifetime. This risk is dependent on the age of initial coarctation repair with later repair carrying an increased risk. However, even those who undergo intervention in childhood face a 30% risk of developing HTN over the next decade. HTN is essentially universal in those repaired after their teenage years. Long-term survival in patients after repair of coarctation of the aorta has historically been poor. In one of the earliest longitudinal studies by McGoon and colleagues, the mean age of patient death was 38 years and the 30-year survival was only 72%. CAD is the primary cause of death in this population. It remains unknown whether the increased incidence of CAD seen in coarctation patients is primarily the result of long-standing HTN or if there is an underlying endothelial abnormality in these patients leading to accelerated atherosclerosis. There is evidence showing that CVD events in this population are abnormal in these patients leading to accelerated atherosclerosis. In the Giannakoulas study, 19% of patients had hyperlipidemia and this prevalence decreased with increasing complexity of cardiac lesions. In the Yalonetsky study of ACHD patients with known CAD, the prevalence of hyperlipidemia was 47%. Data from the Quebec Congenital Heart Disease Database demonstrated a prevalence of hyperlipidemia of 27% in their population of ACHD patients >65 years old. Thus it is likely that the overall prevalence of hyperlipidemia in ACHD patients is similar to that of the general adult population.

Hyperlipidemia

It is well-established that elevated low-density lipoprotein cholesterol (LDL-C) levels play a causal role in the formation of CAD. Limited data exists on the prevalence of hyperlipidemia in the ACHD population. In the Giannakoulas study, 19% of patients had hyperlipidemia and this prevalence decreased with increasing complexity of cardiac lesions. In the Yalonetsky study of ACHD patients with known CAD, the prevalence of hyperlipidemia was 47%. Data from the Quebec Congenital Heart Disease Database demonstrated a prevalence of hyperlipidemia of 27% in their population of ACHD patients >65 years old. Thus it is likely that the overall prevalence of hyperlipidemia in ACHD patients is similar to that of the general adult population.

As per American College of Cardiology and American Heart Association guidelines, ACHD patients with an elevated LDL-C ≥190 mg/dL, patients with DM, and those with an elevated 10-year atherosclerotic CVD (ASCVD) risk should be initiated on statin therapy. As previously discussed, traditional CVD risk factors are typically seen in ACHD patients with CAD and thus using 10-year ASCVD risk prediction is likely appropriate to guide statin initiation in most patients. However, the guidelines become less applicable to ACHD patients <40 years old and those without traditional CVD risk factors but whose underlying anatomy has been associated with increased CVD risk. This includes patients with a history of coarctation, as well as patients with prior surgical coronary artery manipulation (discussed below). In all CHD patients, it may be reasonable to obtain a baseline lipid screening once they reach adulthood and at standard intervals thereafter. Consideration should be given to treating patients with prior coarctation or surgical coronary manipulation as a high-risk group with initiation of statin therapy at an LDL-C <70 mg/dL.1,24,25

Obesity and physical inactivity

Obesity rates in the US have risen to epidemic proportions. Today one third of children and nearly 70% of US adults are overweight or obese.26,27 Obesity is frequently seen in ACHD patients as well although it is unclear if its prevalence equals that of the general population. In a
study of the Dutch CHD registry 40% of adults were found to be overweight or obese compared to 49% of the general Dutch population. The study also found that obesity rates declined with increasing CHD lesion complexity (45% of patients with mild CHD versus 30% of severe lesions). 30% of ACHD patients in a Belgian study were overweight or obese. This was similar to the study's control group though the obesity rate was slightly higher in ACHD patients (8.8 vs 5.8%, respectively). While the Dutch cohort demonstrated an inverse relationship between obesity and CHD complexity, several additional studies have raised concern that the opposite may be true. Rates of obesity are seen to triple within 5 years of patients undergoing Fontan operation. 29 Zaidi et al. found that 50% of young adults with moderate or complex CHD undergoing cardiac surgery were either overweight or obese. Obesity in single ventricle patients has especially deleterious effects given the associated risks of hypertension which may lead to diastolic dysfunction and obesity hypoventilation syndrome that can result in pulmonary HTN. Minimal elevations in pulmonary vascular resistance are poorly tolerated in the Fontan circulation and can directly lead to significantly reduced cardiac output.

People in general are also leading increasingly sedentary lifestyles, which goes hand-in-hand with the increase in obesity rates. The majority of adults fail to meet recommended PA guidelines. Only half of ACHD patients self-report participating in any regular PA and most ACHD patients lack knowledge regarding exercise guidelines. Although CHD-specific exercise guidelines do exist, these primarily relate to competitive sports and are difficult to apply to individual exercise routines. It is important to recognize that all ACHD patients, even those with a history of simple shunting lesions, experience some limitation in exercise capacity. The greatest limitations are seen in complex CHD, including those patients with Fontan circulation or Eisenmenger syndrome (Fig 3). Outside of the intrinsic limitations of their underlying CHD, most patients should be able to be as physically active as they desire without restrictions. Certain populations, including those with aortopathies, pacemakers, or on systemic anticoagulation may need to avoid PA with a high static component (i.e. power weight lifting) and sports with a high collision risk.

**Smoking**

Smoking is the largest preventable cause of premature death in the US. The association between smoking and CAD has been established since the 1950s. Smoking rates among ACHD patients vary globally, but are overall less than the general population. The prevalence of cigarette use among ACHD patients in European studies has been between 14 and 18%. Like other CVD risk factors, smoking rates are significantly higher among patients with known CAD.

**Diabetes mellitus**

Over 400 million people globally are diagnosed with DM. The prevalence of type 2 DM in persons <20 years old has increased by 30% in recent decades. CAD is the leading cause of mortality in patients with DM, accounting for 75% of deaths. Atherosclerotic build-up begins well before the onset of clinical DM symptoms, and cardiac outcomes are significantly worsened in the presence of DM.

The prevalence of DM among the ACHD population is 3 to 4%. This estimate is based on studies from Canada and European countries, where the overall prevalence of DM is less than in the US. Overall the prevalence appears to be similar to the general population. However, there is evidence that ACHD patients may be at an increased risk of developing DM. Patients with complex CHD have been found to have abnormal glucose metabolism despite a normal fasting glucose level. A study by Madsen et al. found that ACHD patients were at substantially greater risk for developing DM compared to the general population. Interestingly, this risk was more significant for patients with cyanotic heart disease (double the rate of acyanotic patients). Impaired glucose metabolism has been associated with impairments in liver and kidney function, increased diuretic use and elevated plasma renin activity. As complex CHD patients often have many of these exposures, this may explain their higher DM risk. Low high-density lipoprotein cholesterol and elevated triglyceride levels are also more frequently seen in ACHD patients, and the overall risk of metabolic syndrome is at least two-fold greater in the ACHD population compared to healthy controls. The American Diabetes Association recommends routine DM screening of all adults over age 45 years, and in younger adults with a body mass index body >25 kg/m² and at least one additional risk factor for DM. Screening should take place at least every 3 years. Given the increased propensity toward abnormal glucose metabolism in ACHD patients, it would be reasonable to consider CHD as a risk factor for DM and screen all adult patients with CHD at least once with a hemoglobin A1C test or oral glucose tolerance test. Routine screening should then be continued for all ACHD patients with a body mass index >25 kg/m² and those with traditional risk factors for DM.

**Congenital coronary anomalies and CVD risk**

Isolated congenital coronary anomalies are rare, representing <1% of all congenital cardiac lesions. Variations in coronary anatomy are more common in association with CHD, where they are seen in 5–10% of cases. Most are benign variants of normal anatomy but are important to understand predominantly for surgical planning. For example, 5% of patients with tetralogy of Fallot have an anomalous origin of the left anterior descending artery from their right coronary. It often courses anterior to the right ventricular outflow tract and is subject to unintentional injury during surgical intervention in that area. Patients with d-transposition of the great arteries (d-TGA) undergo coronary artery manipulation as part of their definitive repair. The standard repair for d-TGA is now the arterial switch operation, which was first successfully performed by Jatene in 1975 and became the standard for neonatal repair over the following decade. The procedure is performed by translocating the discordant pulmonary artery and aorta to their anatomically correct ventricles. The coronary arteries are moved by removing them along with buttons of surrounding tissue and anastomosing them to the neoartoria root. Long-term survival following this procedure is excellent, with the earliest cohorts of patients now reaching their fourth decade of life. Most deaths occur within the first 5 years after undergoing arterial switch and are primarily due coronary artery obstruction. This obstruction may be caused by abnormal kinking or twisting that results from translocation of the coronary vessels. Coronary artery manipulation also carries an increased long-term risk of CVD events. There is sympathetic denervation of the artery, resulting in abnormal vasoreactivity and increased intimal thickness over time. This derangement may also lead to a diminished pain response to ischemia. Given these findings, it has been postulated that d-TGA patients may represent a higher risk group for CAD after arterial switch and warrant more aggressive risk factor modification. These patients should also undergo baseline imaging as an adult to document coronary artery patency, as well as provocative physiologic or pharmacologic stress testing to look for inducible ischemia every 3–5 years.

The most pertinent isolated congenital coronary abnormalities include anomalous aortic origins of the right or left coronary artery from the opposite sinus of Valsalva. These have been associated with an increased risk of sudden cardiac death (SCD). This is most commonly seen when the vessel takes an interarterial course between the aorta and pulmonary artery and is subject to compression and ischemia during exercise. However this explanation is incomplete. Anomalous right coronary artery from the left sinus of Valsalva (ARCA-L) is far more common than an anomalous left coronary artery (ALCA-R) and almost always takes an interarterial course. Despite this, ALCA-R is associated with a four to fivefold higher risk of SCD over ARCA-L. Additional potential mechanisms of ischemia include an
acute take-off of the vessel creating a slit-like orifice, an intramural course of the proximal portion of the vessel that is subject to narrowing and aortic compression, vessel spasm and intussusception of the vessel.\textsuperscript{39}

There is currently no formal approach to stratify these patients by risk of SCD and therefore management remains controversial.\textsuperscript{43,47} Current guidelines recommend surgery for all patients with an interarterial ALCA-R, and symptomatic patients with an interarterial ARCA-L.\textsuperscript{39} Surgery is also recommended for any patient with an anomalous coronary and sequelae of ischemia (ischemic chest pain, syncope presumed due to ventricular arrhythmia, and aborted SCD). Although surgical mortality is low, it has not yet demonstrated a clear long-term survival benefit over medical management.\textsuperscript{47} Multiple corrective surgical techniques have been employed, including coronary unroofing (currently the preferred approach for patients with an interarterial and intramural course), coronary reimplantation, ostioplasty and bypass grafting. As with d-TGA patients who have undergone the arterial switch procedure, coronary reimplantation here will result in sympathetic denervation and the same increased long-term risks of CAD. Bypass grafting has a historically poor success rate, owing to competitive flow through the native anomalous artery resulting in frequent early graft failure. Therefore, areas of obstruction in the anomalous vessel are not necessarily relieved after bypass surgery. Some patients with ARCA-L and ALCA-R who are medically managed will have clinically silent areas of coronary narrowing such as within intramural segments. The combined effect of this along with superimposed CAD creating further downstream obstruction is unknown. Follow-up in patients who have undergone surgical repair should include provocative physiologic or pharmacologic stress testing to look for inducible ischemia every 1–3 years (depending on their activity level).\textsuperscript{39} Given the potential associated CVD risk in those patients who are medically managed, undergo coronary reimplantation or undergo bypass grafting, more aggressive CVD risk management is warranted in these high risk groups.
Summary

CVD is becoming increasingly common in the aging ACHD population. The development of CAD and subsequent CVD events is predominantly driven by traditional CVD risk factors. Current CVD guidelines provide a good framework to determine screening and treatment strategies in the ACHD population. Patients with a history of coarctation of the aorta or who have had surgical coronary manipulation represent specific high-risk groups for future CVD events. Single ventricle patients may also benefit from intensified risk factor treatment, as the effects of superimposed CVD would be poorly tolerated. Further studies are needed to define the optimal treatment thresholds and goals in this diverse population of ACHD patients.

Statement of conflict of interest

There is no conflict of interest of any of the listed authors.

References


