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Management of Cardiovascular Risk Factors in Adults With Congenital Heart Disease

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Advances in surgical and clinical management of congenital heart disease (CHD) have allowed patients to survive into adulthood. The number of adult congenital heart disease (ACHD) patients continues to increase by 5% per year with >1 million individuals in the United States.[1,2] There is a misperception that ACHD patients are cured; residual hemodynamic and electrophysiologic abnormalities are increasingly prevalent and have increased the need for health care utilization and hospitalizations in this population.[3–6] Residual issues include ventricular dysfunction, valvular disease, shunts, and arrhythmias that have contributed to the increasing numbers of patients with and at risk for heart failure.[7,8] Significant morbidity and mortality are associated with heart failure–related hospitalizations.[9–11] Adult comorbidities like systemic hypertension (HTN), diabetes, and coronary artery disease (CAD) will further contribute to the problem of heart failure in ACHD patients. Evidence suggests that physical inactivity, obesity, diabetes, and acquired cardiovascular disease (CVD) may be at least as prevalent in patients with CHD as in the general population.[12] Furthermore, some types of CHD may place patients at increased risk for developing CVD.[13] Therefore, this review will discuss the evaluation and management of cardiovascular risk factors in adults with CHD so that providers may screen and possibly lower their risk of acquired CVD over the long term.

Acquired CVD remains the leading cause of death in the United States.[14] Manifestations of CVD include myocardial infarction (MI), stroke, transient ischemic attacks (TIA), aortic aneurysms, and peripheral vascular disease (PVD). More than 80% of adults with CHD have been identified to have ≥1 cardiovascular risk factors.[12] Preventive measures such as smoking cessation, diet and exercise, screening and treatment for HTN, diabetes, and hyperlipidemia may lower their cardiovascular risk over the long term. This review will discuss the epidemiology and pathophysiology of CVD as it relates to adults with CHD. A review of specific CHD lesions that are at highest risk for the development of CVD will be discussed in detail (Table 1).

Epidemiology

The death rate from CVD has decreased by 31% from 2000 to 2010.[15] However, 15.4 million individuals in the United States have coronary heart disease based on the 2014 Heart Disease and Stroke Statistics by the American Heart Association.[15] The prevalence of coronary heart disease in adults with CHD has been variably reported in the literature depending on the study cohort. Afilalo et al documented a 7% prevalence of MI in older adults with CHD that is higher than that of the general population.[16] A single center demonstrated that 1% of their adults with CHD had obstructive atherosclerotic CAD.[17] The majority of these patients had ≥1 cardiovascular risk factors, with HTN and hyperlipidemia being the most predominant. In a cohort of individuals with CHD who underwent catheterization, 9% had evidence of coronary atherosclerosis.[18] Patients with CAD were older with greater CHD complexity, as well as HTN and hyperlipidemia.[18] Additionally, many of these patients with CAD did not have symptoms and were diagnosed on preoperative angiography. CHD patients with pulmonary HTN are also at increased risk for CAD, with a prevalence of 6.5% for those who underwent catheterization.[19] Stulak et al demonstrated a trend toward reduced survival in patients who underwent repeat CHD surgery with concomitant coronary artery bypass graft surgery.[20] Acute MI was a risk factor for mortality during heart failure related hospital admission.[11] These findings illustrate the importance of identifying early modifiable cardiovascular risk factors for coronary heart disease in adults with CHD.

The risk of cerebrovascular disease in adults with CHD is estimated to be higher than the general population.[21] Additionally, this risk of stroke occurs in a younger mean age of 30 to 40 years compared with the general population.[21] Causes of cerebrovascular accident (CVA)

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Table 1. Risks of Cardiovascular Disease by Type of Congenital Heart Disease

	Coronary Artery Disease	Cerebrovascular Disease	Peripheral Vascular Disease
Repaired ASD/VSD	Not known to have increased risk	Increased risk if residual shunt	Not known to have increased risk
Bicuspid aortic valve	Potential risk after Ross procedure with reimplantation of coronary arteries	Not known to have increased risk	Increased risk related to aortic aneurysm
Coarctation of aorta	Increased risk may be related to accelerated atherosclerosis versus late HTN	Increased risk related to residual HTN and/or intracranial aneurysms	Increased risk related to residual coarctation and/or aortic aneurysm
Ebstein's anomaly	Not known to have increased risk	Increased risk if interatrial shunt	Not known to have increased risk
Tetralogy of Fallot	Increased risk may be related to coronary anomalies	Increased risk if residual intracardiac shunt	Increased risk related to aortic dilation
TGA atrial switch	Increased risk may be related to coronary anomalies	Increased risk if residual baffle leak	Increased risk may be related to prior catheterizations
TGA arterial switch	Increased risk related to reduced coronary flow reserve, proximal intimal thickening, and coronary anomalies	Not known to have increased risk	Increased risk related to neoaortic dilation
Fontan	Increased risk may be related to coronary anomalies	Increased risk if Fontan fenestration	Increased risk related to Fontan venous pressures and prior catheterizations
Cyanotic CHD	Potential decreased risk	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome
Eisenmenger syndrome	Potential decreased risk	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome	Increased risk related to secondary erythrocytosis and hyperviscosity syndrome

ASD indicates atrial septal defect; VSD, ventricular septal defect; TGA, transposition of the great arteries; CHD, congenital heart disease.

may be related to paradoxical emboli from residual shunts or hyperviscosity related to secondary erythrocytosis in cyanotic CHD. However, a higher prevalence of atrial arrhythmias and vascular abnormalities is also seen in CHD patients, which can contribute to the risk of CVA.[21] Additionally, as the CHD population ages, risk factors for the development of stroke will add to the burden of their disease including smoking, diabetes, and HTN. The prevalence of stroke has ranged from 4% to 14% in ACHD patients where cyanotic patients tended to be at highest risk.[22,23] Before the era of screening for atherosclerotic risk factors and antihypertensive therapy, stroke in addition to CAD was one of the leading causes of death in aortic coarctation (COA) patients.[24] Neurologic complications in COA may be related to a higher prevalence of intracranial aneurysms.[25,26] Other CHD populations at risk of CVA include those with atrial septal defect, transposition of the great arteries (TGA) after atrial switch procedure with residual baffle leak, Fontan, and mechanical prostheses.[21] Thromboembolic disease is the leading cause of death in Fontan patients.[27] CHD patients with an intracardiac pacemaker or implanted cardioverter-defibrillator and a residual shunt are also at increased risk of stroke despite aspirin and warfarin use.[28] CVA is a major morbidity for CHD patients and may increase as this population ages.

Peripheral vascular disease (PVD) in CHD patients is not uncommon. Certain types of CHD and CHD repairs are associated with thoracic and abdominal aortic aneurysms including bicuspid aortic valves, COA, TGA after arterial switch operation (ASO), hypoplastic left heart syndrome after Norwood repair, and prior Ross procedures.[29] Nearly a third of adults with repaired tetralogy of Fallot have a dilated aortic root.[30] Patients post COA repair have an increased risk of aortic aneurysm and dissection.[31] Recoarctation after repair may lead to symptoms of claudication and exercise intolerance requiring further intervention. Abnormalities of the great arterial medial architecture were found in several types of CHD, which may be associated with the predisposition for dilation and aneurysm formation in the aorta.[32] Catheterizations in childhood have placed the ACHD patient at risk for peripheral venous and arterial disease. There is a high prevalence of chronic venous insufficiency in Fontan patients, which is thought to be a result of the unique Fontan physiology and frequent catheterizations as a child.[33] The addition of acquired PVD may add to this burden in the CHD patient.

Pathophysiology of CHD and CVD

CHD patients represent a group that is at risk of premature CVD.[13] The pathophysiology of CVD in CHD patients is

multifactorial (Figure). These mechanisms may be directly related to the type of CHD or indirectly by association with increased atherosclerotic risk factors.[34,35] Surgical repair of CHD may result in the development of coronary heart disease and PVD. Finally, patients with CHD may possess a genetic syndrome that increases their risk for CVD.[36–40]

Congenital coronary anomalies may result in myocardial ischemia and sudden death, as in the cases of anomalous coronary arteries or coronary cameral fistulas. CAD has also been implicated as a leading cause of death after repaired COA.[24,41–43] Autopsy studies have demonstrated severe atheroma in the coronary arteries of patients with COA.[44] Roifman et al demonstrated higher rates of HTN, heart failure, and stroke in COA patients.[45] It is less clear whether COA alone versus the groups' increased prevalence of HTN or hyperlipidemia is associated with premature CVD. There have been suggestions of persistent endothelial dysfunction and impaired arterial reactivity, suggesting a primary vascular abnormality in COA.[46,47] Whether this might contribute to premature coronary heart disease independent of traditional cardiovascular risk factors requires further investigation.

Patients with moderate to complex CHD have been subjected to cyanosis, volume loading, ischemia, and reperfusion during early and late surgery.[48] This early insult may play a role in the development of atherosclerosis and heart failure in CHD patients.[8,49] Furthermore, the general inflammatory state of heart failure has been associated with worse exercise capacity, hospitalization, and decreased survival.[50] Coronary artery intimal hyperplasia was more often seen in patients after surgically repaired CHD than in those with nonrepaired CHD.[51] Residual hemodynamic abnormalities may lead to abnormalities in ventricular size, which have been associated with late atherosclerosis.[18] This is further corroborated with evidence of myocardial perfusion defects in moderate to complex CHD including TGA after atrial switch repair.[52–54] Several reports of the need for coronary artery bypass grafting after repair of tetralogy of Fallot have been reported.[55–57] Furthermore, the surgical repair of CHD may result in abnormalities of the coronary arteries early in life. These include the ASO for complete TGA, Ross procedure with reimplantation of the coronary arteries during aortic root replacement, and repair of anomalous coronary arteries. Coronary lesions have been seen in 5% of late survivors of TGA ASO.[58] Complex preoperative coronary anatomy including intramural segments and single coronary ostia has been implicated as risk factors for coronary stenosis after ASO.[58–62] Abnormalities in coronary flow reserve and proximal intimal thickening have been seen in the coronary arteries of patients after ASO.[63,64] Coronary stenoses in TGA ASO are often asymptomatic, and some have advocated routine screening with coronary angiography or computed tomography coronary angiography.[61,65] Despite these findings, long-term outcome has been good in this population with few adverse coronary events.[64,66,67] However, this population remains quite young and the impact of acquired coronary heart disease is unknown.

Genetic syndromes such as Marfan, Turner, and Williams are associated with an inherent arterial vasculopathy.[35] HTN is prevalent in patients with Turner and Williams syndrome.[36–40] Cardiovascular risk factors such as obesity and sleep

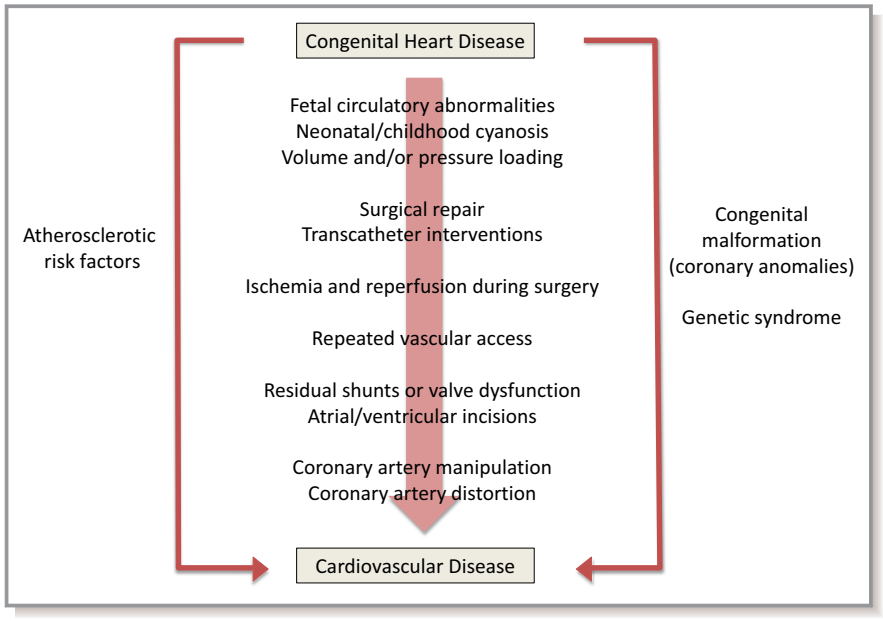

Figure. Potential mechanism of cardiovascular disease in adults with congenital heart disease.

apnea are seen in patients with Down syndrome and support the role of early screening and behavior modification in these patients.

Finally, adults with CHD are at increased risk for extracardiac comorbidities.[68] Hepatic complications of heart failure have been well documented in congestive heart failure patients; especially those with right heart failure.[69] In Fontan patients, the venous HTN, low cardiac output of single ventricular physiology, and prior operative insults may lead to liver injury and cirrhosis.[68,70] Renal impairment is prevalent at 9% of ACHD patients, with the highest risk in cyanotic and Eisenmenger patients.[71] Prior cardiac surgical repair and spinal abnormalities have resulted in an increased prevalence of restrictive lung disease.[68,72] The presence of these comorbidities may impact the survival of ACHD patients who remain relatively young with an average age of 35 to 40 years.[70,72,73] As this population ages with an increasing prevalence of complex CHD, it remains unknown how acquired CVD in combination with these extracardiac comorbidities will further affect their long-term outcome.

Cardiovascular Risk Factor Profile in Adults With CHD

Risk factors for the development of CVD are increasingly prevalent in the general population and ACHD patients (Table 2).[12,16,74] The modifiable risk factors for CVD include obesity, physical activity, HTN, diabetes, dyslipidemia, and smoking. The presence of these risk factors correlates with atherosclerosis; even in children and young adults.[75–77] In a study from Belgium, 1976 individuals with CHD were more often obese and hypertensive compared with the general population.[12] Obesity was present in 30% of adult patients with moderate and complex CHD requiring additional surgery.[78] Nearly one-third of patients with a history of TGA after ASO are obese.[79] While some studies have demonstrated lower rates of obesity in patients with single ventricles, obesity was present in 11% of pediatric and 17% of adult Fontan patients.[74,80–82] Obesity's association with diastolic dysfunction and ventricular hypertrophy may complicate the management of ACHD patients who are already at risk for ventricular dysfunction, arrhythmias, and heart failure.[83,84]

Table 2. Prevalence of Cardiovascular Risk Factors in Adults With Congenital Heart Disease

	Adults With Congenital Heart Disease Compared With General Population
Obesity	Higher prevalence in general ACHD population/Lower prevalence in Fontan
Physical inactivity	Insufficient evidence
Hypertension	Higher prevalence in coarctation, Turner or Williams syndrome
Diabetes	Higher prevalence of abnormal glucose metabolism
Dyslipidemia	Insufficient evidence
Smoking	Lower prevalence

Physical inactivity is one contributor to the rates of obesity in the United States. Stefan et al suggested that activity restriction was associated with higher rates of obesity in children with heart disease.[85] Swan et al found that exercise advice was more often prohibitive rather than reassuring and encouraging.[86] Some patients are limited by residual hemodynamic and electrophysiologic abnormalities. A few studies have demonstrated that the presence of CHD has an important and negative impact on physical activity.[87,88] Both the actual and perceived physical restrictions can lead to a sedentary lifestyle and deconditioning.

Systemic HTN is another important cardiovascular risk factor that can lead to premature coronary heart disease, stroke, arrhythmia, and PVD. In the Belgium study, 13% of adults with CHD were hypertensive.[12] In an older population of CHD patients (age >65 years), 47% were found to be hypertensive.[16] However, much of this population included simpler CHD lesions. Generally, HTN in this population is "essential" HTN. There are patients with moderate or complex CHD who are at increased risk of HTN including COA. While HTN was seen in 4% of the CHD group as a whole, it was as high as 46% in patients after COA repair.[22] HTN may increase the risk of aortic dilation in prior COA repair, bicuspid aortic valve, tetralogy of Fallot, and TGA after ASO. The long-term effects of longstanding HTN on the congenitally abnormal heart are not clear.

The prevalence of diabetes continues to rise in the United States with increasing rates of obesity.[89] In a comparison of 1496 patients with CHD in the Netherlands and a healthy control group, there was a significant difference in the prevalence of diabetes in the CHD group (3.4%) compared with the control group (2.3%).[90] Ohuchi et al also demonstrated a high prevalence of abnormal glucose metabolism in ACHD patients compared with a group of healthy controls.[91] The ACHD cohort had lower HDL levels compared with controls, suggesting a problem with dyslipidemia.[91] ACHD patients with an abnormal glucose regulation had associated morbidity and mortality.[92] Like diabetes, abnormal glucose response has been associated with CVD.[93,94] The development of diabetes in the adult with CHD may have long-term implications for CVD but also other associated comorbidities such as infection, PVD, and CAD.

Finally, cigarette smoking is an important reversible risk factor for coronary heart disease. The incidence of MI is several times higher in an individual who smokes versus

someone who has never smoked.[95,96] Smoking was found to be less common in ACHD patients compared with the general population, but 18% of individuals with CHD smoked.[12] Reid et al showed a similar 13% to 20% smoking in adolescents and young adults with CHD.[97] There is still an opportunity to make a difference in the cardiovascular health by encouraging smoking cessation.

Other nonmodifiable risk factors including premature family history of coronary heart disease, age, and sex are important in the assessment of cardiovascular risk in CHD patients. There are also novel inflammatory markers that can be associated with an increased risk of CVD including high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor.[98] The role of these markers in the management of CHD patients has not been defined but can help direct more aggressive or preventive therapies in a patient with intermediate risks for CVD.

Management of Cardiovascular Risk Factors in Adults With CHD

The development of atherosclerotic disease may affect the long-term outcome of individuals with CHD. This risk supports the recommendation for guideline-based screening and management of cardiovascular risk factors in this population. Unfortunately, the awareness of and management of the risk factors for premature atherosclerosis often take a back seat in the setting of CHD, especially in patients with more complex lesions. The limited longevity of this complex population may make some providers believe that it is unnecessary to screen or manage these risk factors. However, patients with tetralogy of Fallot are approaching their sixth and seventh decade of life, when CVD is prevalent in the general population. It is important that providers caring for adults with CHD discuss dietary patterns, physical activity, blood pressure screening, obesity, dyslipidemia, tobacco, and diabetes (Table 3).[99–104]

While supportive data regarding the benefits of intervention and modification of atherosclerotic risk factors remain limited, the ACHD patient population is at risk for CVD and therefore should undergo at least guideline-based screening, if not possibly more intense screening than the general population. The United States Preventive Services Task Force, American Heart Association, and American College of Cardiology have written guidelines regarding the management of cardiovascular risk factors in the general population.[99,101,102,104–107] These guidelines emphasize discussing a dietary pattern that includes reducing calories in saturated and trans fatty acids and lower sodium intake. The diet should include "intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar sweetened beverages, and red meats."[99] There is evidence that this dietary pattern can lower blood pressure and cholesterol.[99] Physical activity can have the same benefits. However, 25% of individuals with CHD did not engage in regular physical activity.[86] More than 50% of ACHD patients have impaired exercise capacity.[108] However, several studies have demonstrated that regular exercise can be safe and even improve exercise capacity in patients with CHD.[87,109] There is increasing evidence that physical activity has long term beneficial effects.[110] There may also be a role for cardiac rehabilitation program in patients with CHD.[111]

An assessment of the patient's diet, physical activity, and history of cigarette smoking should be obtained at every visit. Exercise testing may offer clinicians the ability to determine a safe level of exercise and therefore allow providers to offer ACHD patients an exercise prescription to promote physical activity. Providers should consider counseling on appropriate activities when there is ventricular dysfunction, aortic dilation, syncope, hypoxia, anticoagulation, and an implantable car-

Table 3. Screening for Cardiovascular Risk Factors in Adults With Congenital Heart Disease

	Testing	Frequency
Diet and physical activity	N/A	Yearly[99]
Tobacco	N/A	Yearly[99]
Hypertension	Office blood pressure measurement and/or ambulatory/home blood pressure monitor	Yearly[100]
Obesity	Weight, height, and body mass index	Yearly[101]
Dyslipidemia	Fasting lipid panel	Every 5 years[102]
Diabetes	Fasting plasma glucose, 75 g oral glucose tolerance test, or hemoglobin A1c	Every 3 years[103]
Peripheral arterial disease	Ankle-brachial index	Insufficient evidence but can consider in patients with diabetes and/or an additional cardiovascular risk factor[104]

dioverter defibrillator.[110] An exercise prescription that is realistic and appropriate for the individual patient can be built on over time so that they reach a goal of 30 minutes of moderate activity most days of the week. Even if patients require restriction because of residual abnormalities, providers should still promote physical activity and encourage types of low-intensity dynamic and static sports that are appropriate for the individual patient.[110] Tools like a pedometer or accelerometer may help motivate patients to achieve goals in physical activity.[110]

Dietary changes and increased physical activity will, it is hoped, have an impact on the development of obesity in adults with CHD. BMI should be performed annually, while waist circumference can be considered in overweight or obese adults.[101] If patients become overweight (BMI 25 to 29.9 kg/m^2) or obese, these individuals should be counseled about weight loss through lifestyle changes and nutrition consultation. Patients with a BMI ≥40 or BMI ≥35 with obesity-related comorbid conditions may be appropriate for bariatric surgery.[101] The risks and benefits of bariatric surgery will have to be weighed against any residual hemodynamic abnormalities in CHD individuals.

Dyslipidemia, HTN, and diabetes are important modifiable risk factors for CVD. It seems prudent to screen for these conditions in all CHD patients. Additionally, the presence of HTN or diabetes could complicate the management of a CHD patient during repeat CHD intervention or noncardiac surgery. Therefore, screening could be considered during the preoperative assessment of a CHD patient. The United States Preventive Services Task Force recommends beginning screening every 5 years in men between the ages of 20 and 35 years and women between ages 20 and 45 years for dyslipidemia.[102] The American Heart Association and American College of Cardiology guidelines highlight the following 4 main groups for initiation of treatment: "(1) individuals with clinical atherosclerotic CVD (ASCVD), (2) individuals with primary elevations of LDL-C ≥190 mg/dL, (3) individuals 40 to 75 years of age with diabetes with LDL-C 70 to 189 mg/dL, or (4) individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dL and estimated 10-year ASCVD risk 7.5% or higher."[106]

Standard blood pressure assessment is recommended during routine cardiovascular visits for CHD patients and should follow guidelines by the last Joint National Committee.[100] In Marfan syndrome, β-blockers and/or losartan has been suggested for antihypertensive therapy in the setting of aortic dilation.[35] β-Blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers have been advocated as first-line agents for residual HTN in patients with COA repair.[112] In the setting of ACHD and HTN during pregnancy, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers are contraindicated because of severe fetal toxicity. Therefore, α-methyldopa or β-blockers are the preferred agent, while calcium channel blockers are second line.[113]

Screening for diabetes is generally recommended in patients with a history of HTN or hyperlipidemia. Screening is recommended by the American Diabetes Association at 3-year intervals in adults aged >45 years or those aged <45 years with BMI ≥25 kg/m^2 and who have ≥1 of the following risk factors for the development of CVD: physical inactivity, family history, high-risk race/ethnicity, HTN, hyperlipidemia, CVD, or other condition associated with insulin resistance.[103] CHD is not considered in these guidelines. Based on the increased prevalence of diabetes and glucose intolerance, adults with CHD appear to be at risk for the development of diabetes and therefore one can consider regular screening at 3-year intervals (see Table 3).[90,91] By screening CHD individuals early, there is an opportunity for lifestyle modification and managing the multiple cardiovascular risks associated with diabetes.

Conclusion

Adult patients with CHD are at an increased risk for acquired CVD. The prevalence of cardiovascular risk factors in the CHD population appears to be increased compared with the general population. As these individuals survive into adulthood and reach their sixth and seventh decade of life, acquired comorbidities in addition to residual hemodynamic and electrophysiologic abnormalities may begin to define their outcome by increasing morbidity and health care utilization in the future. Screening for cardiovascular risk factors and modifying these risks earlier in life may improve their long-term outcome. The management of adults with CHD will require providers to be cognizant of their CHD as well as acquired medical conditions.

Disclosures

None.

References

1. Williams RG, Pearson GD, Barst RJ, Child JS, del Nido P, Gersony WM, Kuehl KS, Landzberg MJ, Myerson M, Neish SR, Sahn DJ, Verstappen A, Warnes CA, Webb CL. Report of the National Heart, Lung, and Blood Institute Working Group on research in adult congenital heart disease. *J Am Coll Cardiol*. 2006;47:701–707.
2. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*. 2001;37:1170–1175.
3. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health care resource utilization in adults with congenital heart disease. *Am J Cardiol*. 2007;99:839–843.
4. O'Leary JM, Siddiqi OK, de Ferranti S, Landzberg MJ, Opotowsky AR. The changing demographics of congenital heart disease hospitalizations in the United States, 1998 Through 2010. *JAMA*. 2013;309:984–986.
5. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis MA, Diller GP. Congenital heart disease

beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. *Eur Heart J*. 2014;35:725–732.

6. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol*. 2005;46:1–8.
7. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol*. 2007;50:1263–1271.
8. Fahed AC, Roberts AE, Mital S, Lakdawala NK. Heart failure in congenital heart disease: a confluence of acquired and congenital. *Heart Fail Clin*. 2014;10:219–227.
9. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; Investigators O-H and Coordinators. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *J Am Coll Cardiol*. 2008;52:347–356.
10. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol*. 2008;52:428–434.
11. Rodriguez FH III, Moodie DS, Parekh DR, Franklin WJ, Morales DL, Zafar F, Adams GJ, Friedman RA, Rossano JW. Outcomes of heart failure-related hospitalization in adults with congenital heart disease in the United States. *Congenit Heart Dis*. 2013;8:513–519.
12. Moons P, Van Deyk K, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2006;13:612–616.
13. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J; American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114:2710–2738.
14. Laslett LJ, Alagona P Jr, Clark BA III, Drozda JP Jr, Saldivar F, Wilson SR, Poe C, Hart M. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J Am Coll Cardiol*. 2012;60:S1–S49.
15. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129:399–410.
16. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease: burden of disease and predictors of mortality. *J Am Coll Cardiol*. 2011;58:1509–1515.
17. Yalonetsky S, Horlick EM, Osten MD, Benson LN, Oechslin EN, Silversides CK. Clinical characteristics of coronary artery disease in adults with congenital heart defects. *Int J Cardiol*. 2013;164:217–220.
18. Giannakoulas G, Dimopoulos K, Engel R, Goktekin O, Kucukdurmaz Z, Vatankulu MA, Bedard E, Diller GP, Papaphylactou M, Francis DP, Di Mario C, Gatzoulis MA. Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors. *Am J Cardiol*. 2009;103:1445–1450.
19. Shimony A, Eisenberg MJ, Rudski LG, Schlesinger R, Afilalo J, Joyal D, Dragatakis L, Hirsch A, Boutet K, Fox BD, Langleben D. Prevalence and impact of coronary artery disease in patients with pulmonary arterial hypertension. *Am J Cardiol*. 2011;108:460–464.
20. Stulak JM, Dearani JA, Burkhart HM, Ammash NM, Phillips SD, Schaff HV. Coronary artery disease in adult congenital heart disease: outcome after coronary artery bypass grafting. *Ann Thorac Surg*. 2012;93:116–122; discussion 122–3.
21. Hoffmann A, Chockalingam P, Balint OH, Dadashev A, Dimopoulos K, Engel R, Schmid M, Schwerzmann M, Gatzoulis MA, Mulder B, Oechslin E. Cerebrovascular accidents in adult patients with congenital heart disease. *Heart*. 2010;96:1223–1226.
22. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilen U, Kaemmerer H, Moons P, Meijboom F, Popelova J, Laforest V, Hirsch R, Daliento L, Thaulow E, Mulder B. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J*. 2005;26:2325–2333.
23. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J*. 1998;19:1845–1855.
24. Cohen M, Fuster V, Steele PM, Driscoll D, McGoon DC. Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. *Circulation*. 1989;80:840–845.
25. Connolly HM, Huston J III, Brown RD Jr, Warnes CA, Ammash NM, Tajik AJ. Intracranial aneurysms in patients with coarctation of the aorta: a prospective magnetic resonance angiographic study of 100 patients. *Mayo Clin Proc*. 2003;78:1491–1499.
26. Cook SC, Hickey J, Maul TM, Zumberge N, Krieger EV, Valente AM, Zaidi AN, Daniels CJ. Assessment of the cerebral circulation in adults with coarctation of the aorta. *Congenit Heart Dis*. 2013;8:289–295.
27. Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation*. 2008;117:85–92.
28. Khairy P, Landzberg MJ, Gatzoulis MA, Mercier LA, Fernandes SM, Cote JM, Lavoie JP, Fournier A, Guerra PG, Frogoudaki A, Walsh EP, Dore A; Epicardial Versus Ep and Thromboembolic events I. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. *Circulation*. 2006;113:2391–2397.
29. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med*. 2014;370:1920–1929.
30. Mongeon FP, Gurvitz MZ, Broberg CS, Aboulhosn J, Opotowsky AR, Kay JD, Valente AM, Earing MG, Lui GK, Fernandes SM, Gersony DR, Cook SC, Ting JG, Nickolaus MJ, Landzberg MJ, Khairy P; Alliance for Adult Research in Congenital C. Aortic root dilatation in adults with surgically repaired tetralogy of fallot: a multicenter cross-sectional study. *Circulation*. 2013;127:172–179.
31. Horlick EM, McLaughlin PR, Benson LN. The adult with repaired coarctation of the aorta. *Curr Cardiol Rep*. 2007;9:323–330.
32. Niwa K, Perloff JK, Bhuta SM, Laks H, Drinkwater DC, Child JS, Miner PD. Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. *Circulation*. 2001;103:393–400.
33. Valente AM, Bhatt AB, Cook S, Earing MG, Gersony DR, Aboulhosn J, Opotowsky AR, Lui G, Gurvitz M, Graham D, Fernandes SM, Khairy P, Webb G, Gerhard-Herman M, Landzberg MJ; Investigators A. The CALF (Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health in Fontan Patients) study. *J Am Coll Cardiol*. 2010;56:144–150.
34. Justino H, Khairy P. Congenital heart disease and coronary atherosclerosis: a looming concern? *Can J Cardiol*. 2013;29:757–758.
35. Roche SL, Silversides CK. Hypertension, obesity, and coronary artery disease in the survivors of congenital heart disease. *Can J Cardiol*. 2013;29:841–848.
36. Aligeti VR, Horn HR. Turner's syndrome and coronary artery disease. *Am J Cardiol*. 2007;99:741–742.
37. Daniels SR, Loggie JM, Schwartz DC, Strife JL, Kaplan S. Systemic hypertension secondary to peripheral vascular anomalies in patients with Williams syndrome. *J Pediatr*. 1985;106:249–251.
38. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol*. 1998;51:147–158.
39. Kozlowska-Wojciechowska M, Jez W, Zdrojewski T, Chwojnicki K. Are young women with Turner syndrome at greater risk of coronary artery disease? *Eur J Cardiovasc Prev Rehabil*. 2006;13:467–469.
40. Williams JC, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. *Circulation*. 1961;24:1311–1318.
41. Brouwer RM, Erasmus ME, Ebels T, Eijgelaar A. Influence of age on survival, late hypertension, and recoarctation in elective aortic coarctation repair. Including long-term results after elective aortic coarctation repair with a follow-up from 25 to 44 years. *J Thorac Cardiovasc Surg*. 1994;108:525–531.
42. Clarkson PM, Nicholson MR, Barratt-Boyes BG, Neutze JM, Whitlock RM. Results after repair of coarctation of the aorta beyond infancy: a 10 to 28 year follow-up with particular reference to late systemic hypertension. *Am J Cardiol*. 1983;51:1481–1488.
43. Toro-Salazar OH, Steinberger J, Thomas W, Rocchini AP, Carpenter B, Moller JH. Long-term follow-up of patients after coarctation of the aorta repair. *Am J Cardiol*. 2002;89:541–547.

44. Vlodaver Z, Neufeld HN. The coronary arteries in coarctation of the aorta. *Circulation*. 1968;37:449–454.
45. Roifman I, Therrien J, Ionescu-Ittu R, Pilote L, Guo L, Kotowycz MA, Martucci G, Marelli AJ. Coarctation of the aorta and coronary artery disease: fact or fiction? *Circulation*. 2012;126:16–21.
46. Beekman RH, Katz BP, Moorehead-Steffens C, Rocchini AP. Altered baroreceptor function in children with systolic hypertension after coarctation repair. *Am J Cardiol*. 1983;52:112–117.
47. Gidding SS, Rocchini AP, Moorehead C, Schork MA, Rosenthal A. Increased forearm vascular reactivity in patients with hypertension after repair of coarctation. *Circulation*. 1985;71:495–499.
48. Pemberton VL, McCrindle BW, Barkin S, Daniels SR, Barlow SE, Binns HJ, Cohen MS, Economos C, Faith MS, Gidding SS, Goldberg CS, Kavey RE, Longmuir P, Rocchini AP, Van Horn L, Kaltman JR. Report of the National Heart, Lung, and Blood Institute's Working Group on obesity and other cardiovascular risk factors in congenital heart disease. *Circulation*. 2010;121:1153–1159.
49. Bolger AP, Coats AJ, Gatzoulis MA. Congenital heart disease: the original heart failure syndrome. *Eur Heart J*. 2003;24:970–976.
50. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, Levy D, Wilson PW, D'Agostino RB; Framingham Heart S. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation*. 2003;107:1486–1491.
51. Guerri-Guttenberg RA, Castilla R, Francos GC, Muller A, Ambrosio G, Milei J. Transforming growth factor beta1 and coronary intimal hyperplasia in pediatric patients with congenital heart disease. *Can J Cardiol*. 2013;29:849–857.
52. Lubiszewska B, Gosiewska E, Hoffman P, Teresinska A, Rozanski J, Piotrowski W, Rydlewska-Sadowska W, Kubicka K, Ruzyllo W. Myocardial perfusion and function of the systemic right ventricle in patients after atrial switch procedure for complete transposition: long-term follow-up. *J Am Coll Cardiol*. 2000;36:1365–1370.
53. Millane T, Bernard EJ, Jaeggi E, Howman-Giles RB, Uren RF, Cartmill TB, Hawker RE, Celermajer DS. Role of ischemia and infarction in late right ventricular dysfunction after atrial repair of transposition of the great arteries. *J Am Coll Cardiol*. 2000;35:1661–1668.
54. Singh TP, Humes RA, Muzik O, Kottamasu S, Karpawich PP, Di Carli MF. Myocardial flow reserve in patients with a systemic right ventricle after atrial switch repair. *J Am Coll Cardiol*. 2001;37:2120–2125.
55. Bardy GH, Peter RH. Arteriosclerotic heart disease following correction of tetralogy of Fallot. *Chest*. 1983;83:279–280.
56. Coutu M, Poirier NC, Dore A, Carrier M, Perrault LP. Late myocardial revascularization in patients with tetralogy of Fallot. *Ann Thorac Surg*. 2004;77:1454–1455.
57. Cusimano RJ, Guest C. Coronary artery disease following repair of tetralogy of Fallot: implications and management. *Can J Cardiol*. 1996;12:172–174.
58. Raisky O, Bergoend E, Agnoletti G, Ou P, Bonnet D, Sidi D, Vouhe PR. Late coronary artery lesions after neonatal arterial switch operation: results of surgical coronary revascularization. *Eur J Cardiothoracic Surg*. 2007;31:894–898.
59. Ou P, Khraiche D, Celermajer DS, Agnoletti G, Le Quan Sang KH, Thalabard JC, Quintin M, Raisky O, Vouhe P, Sidi D, Bonnet D. Mechanisms of coronary complications after the arterial switch for transposition of the great arteries. *J Thorac Cardiovasc Surg*. 2013;145:1263–1269.
60. Pasquali SK, Hasselblad V, Li JS, Kong DF, Sanders SP. Coronary artery pattern and outcome of arterial switch operation for transposition of the great arteries: a meta-analysis. *Circulation*. 2002;106:2575–2580.
61. Raju V, Burkhart HM, Durham LA III, Eidem BW, Phillips SD, Li Z, Schaff HV, Dearani JA. Reoperation after arterial switch: a 27-year experience. *Ann Thorac Surg*. 2013;95:2105–2112; discussion 2112–3.
62. Jussli-Melchers J, Haneya A, Hoffmann G, Cremer J. Minimally invasive direct coronary artery bypass in a child with an occlusion of left main coronary artery after arterial switch operation. *Interact Cardiovasc Thorac Surg*. 2013;17:1040–1041.
63. Gagliardi MG, Adorisio R, Crea F, Versacci P, Di Donato R, Sanders SP. Abnormal vasomotor function of the epicardial coronary arteries in children five to eight years after arterial switch operation: an angiographic and intracoronary Doppler flow wire study. *J Am Coll Cardiol*. 2005;46:1565–1572.
64. Pedra SR, Pedra CA, Abizaid AA, Braga SL, Staico R, Arrieta R, Costa JR Jr, Vaz VD, Fontes VF, Sousa JE. Intracoronary ultrasound assessment late after the arterial switch operation for transposition of the great arteries. *J Am Coll Cardiol*. 2005;45:2061–2068.
65. Saini AP, Wolfe LT, Millington KA, Myers JL, Clark JB. Occult coronary ostial obstruction late after arterial switch operation. *J Card Surg*. 2013;28:308–311.
66. Legendre A, Losay J, Touchot-Kone A, Serraf A, Belli E, Piot JD, Lambert V, Capderou A, Planche C. Coronary events after arterial switch operation for transposition of the great arteries. *Circulation*. 2003;108(suppl 1):II186–II190.
67. Tobler D, Williams WG, Jegatheeswaran A, Van Arsdell GS, McCrindle BW, Greutmann M, Oechslin EN, Silversides CK. Cardiac outcomes in young adult survivors of the arterial switch operation for transposition of the great arteries. *J Am Coll Cardiol*. 2010;56:58–64.
68. Cohen SB, Ginde S, Bartz PJ, Earing MG. Extracardiac complications in adults with congenital heart disease. *Congenit Heart Dis*. 2013;8:370–380.
69. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. *Am Heart J*. 2000;140:111–120.
70. Assenza GE, Graham DA, Landzberg MJ, Valente AM, Singh MN, Bashir A, Fernandes S, Mortele KJ, Ukomadu C, Volpe M, Wu F. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. *Heart*. 2013;99:491–496.
71. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, Salukhe TV, Piepoli MF, Poole-Wilson PA, Best N, Francis DP, Gatzoulis MA. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. *Circulation*. 2008;117:2320–2328.
72. Ginde S, Bartz PJ, Hill GD, Danduran MJ, Biller J, Sowinski J, Tweddell JS, Earing MG. Restrictive lung disease is an independent predictor of exercise intolerance in the adult with congenital heart disease. *Congenit Heart Dis*. 2013;8:246–254.
73. Alonso-Gonzalez R, Borgia F, Diller GP, Inuzuka R, Kempny A, Martinez-Naharro A, Tutarel O, Marino P, Wustmann K, Charalambides M, Silva M, Swan L, Dimopoulos K, Gatzoulis MA. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. *Circulation*. 2013;127:882–890.
74. Pinto NM, Marino BS, Wernovsky G, de Ferranti SD, Walsh AZ, Laronde M, Hyland K, Dunn SO Jr, Cohen MS. Obesity is a common comorbidity in children with congenital and acquired heart disease. *Pediatrics*. 2007;120:e1157–e1164.
75. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650–1656.
76. Dawson JD, Sonka M, Blecha MB, Lin W, Davis PH. Risk factors associated with aortic and carotid intima-media thickness in adolescents and young adults: the Muscatine Offspring Study. *J Am Coll Cardiol*. 2009;53:2273–2279.
77. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnemaa T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277–2283.
78. Zaidi AN, Bauer JA, Michalsky MP, Olshove V, Boettner B, Phillips A, Cook SC. The impact of obesity on early postoperative outcomes in adults with congenital heart disease. *Congenit Heart Dis*. 2011;6:241–246.
79. Pasquali SK, Marino BS, Powell DJ, McBride MG, Paridon SM, Meyers KE, Mohler ER, Walker SA, Kren S, Cohen MS. Following the arterial switch operation, obese children have risk factors for early cardiovascular disease. *Congenit Heart Dis*. 2010;5:16–24.
80. Chung ST, Hong BJ, Patterson LW, Petit CJ, Ham JN. High overweight and obesity rates in Fontan patients: a twenty-year history. *Circulation*. 2012;126:A18917.
81. Shustak RJ, McGuire SB, October TW, Phoon CK, Chun AJ. Prevalence of obesity among patients with congenital and acquired heart disease. *Pediatr Cardiol*. 2012;33:8–14.
82. Vogt KN, Manlhiot C, Van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic growth in children with single ventricle physiology impact of physiologic state. *J Am Coll Cardiol*. 2007;50:1876–1883.
83. Daniels SR, Kimball TR, Morrison JA, Khoury P, Witt S, Meyer RA. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. *Circulation*. 1995;92:3249–3254.
84. Maser RE, Lenhard MJ. An overview of the effect of weight loss on cardiovascular autonomic function. *Curr Diabetes Rev*. 2007;3:204–211.
85. Stefan MA, Hopman WM, Smythe JF. Effect of activity restriction owing to heart disease on obesity. *Arch Pediatr Adolesc Med*. 2005;159:477–481.

86. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: a long way to go. *Heart*. 2000;83:685–687.

87. Dua JS, Cooper AR, Fox KR; Graham Stuart A. Physical activity levels in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2007;14:287–293.

88. Lunt D, Briffa T, Briffa NK, Ramsay J. Physical activity levels of adolescents with congenital heart disease. *Aust J Physiother*. 2003;49:43–50.

89. Li C, Balluz LS, Okoro CA, Strine TW, Lin JM, Town M, Garvin W, Murphy W, Bartoli W, Valluru B; Centers for Disease C and Prevention. Surveillance of certain health behaviors and conditions among states and selected local areas—Behavioral Risk Factor Surveillance System, United States, 2009. *MMWR Surveill Summ*. 2011;60:1–250.

90. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, Sieswerda GJ, Wajon EM, Plomp K, van Bergen PF, Verheugt CL, Krivka E, de Vries CJ, Lok DJ, Grobbee DE, Mulder BJ. Social burden and lifestyle in adults with congenital heart disease. *Am J Cardiol*. 2012;109:1657–1663.

91. Ohuchi H, Miyamoto Y, Yamamoto M, Ishihara H, Takata H, Miyazaki A, Yamada O, Yagihara T. High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease. *Am Heart J*. 2009;158:30–39.

92. Ohuchi H, Yasuda K, Ono S, Hayama Y, Negishi J, Noritake K, Mizuno M, Iwasa T, Miyazaki A, Yamada O. Low fasting plasma glucose level predicts morbidity and mortality in symptomatic adults with congenital heart disease. *Int J Cardiol*. 2014;174:306–312.

93. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J*. 2004;25:1990–1997.

94. Group AS, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC Jr, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH Jr, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*. 2011;364:818–828.

95. Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation*. 1996;93:450–456.

96. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998;316:1043–1047.

97. Reid GJ, Webb GD, McCrindle BW, Irvine MJ, Siu SC. Health behaviors among adolescents and young adults with congenital heart disease. *Congenit Heart Dis*. 2008;3:16–25.

98. Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J*. 2014;35:1782–1791.

99. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Miller NH, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TW, Yanovski SZ. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S76–S99.

100. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520.

101. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129:S102–S138.

102. US Preventive Services Task Force. Screening for Lipid Disorders in Adults. US Preventive Services Task Force; September 2014.

103. American Diabetes Association. Standards of medical care in diabetes–2014. *Diab Care*. 2014;37(suppl 1):S14–S80.

104. Moyer VA; Force USPST. Screening for peripheral artery disease and cardiovascular disease risk assessment with the ankle-brachial index in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;159:342–348.

105. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson J, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73.

106. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith SC Jr, Levy D, Watson K, Wilson PW. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2889–2934.

107. Force USPST. Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;148:846–854.

108. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828–835.

109. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. *Cardiol Young*. 2000;10:107–114.

110. Longmuir PE, Brothers JA, de Ferranti SD, Hayman LL, Van Hare GF, Matherne GP, Davis CK, Joy EA, McCrindle BW; American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Promotion of physical activity for children and adults with congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2013;127:2147–2159.

111. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005;116:1339–1345.

112. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation*. 2008;118:e714–e833.

113. European Society of G, Association for European Paediatric C, German Society for Gender M, Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L; Guidelines ESCCfP. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:3147–3197.

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