Management of Cardiovascular Risk Factors in Adults With Congenital Heart Disease

George K. Lui, MD; Susan Fernandes, LPD, PA-C; Doff B. McElhinney, MD

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

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

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. 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. 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. Neurologic complications in COA may be related to a higher prevalence of intracranial aneurysms.

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. Thromboembolic disease is the leading cause of death in Fontan patients. 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. 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. Nearly a third of adults with repaired tetralogy of Fallot have a dilated aortic root. Patients post COA repair have an increased risk of aortic aneurysm and dissection. 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. 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. 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. The pathophysiology of CVD in CHD patients is due to
multifactorial (Figure). These mechanisms may be directly related to the type of CHD or indirectly by association with increased atherosclerotic risk factors. 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.

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. Autopsy studies have demonstrated severe atheroma in the coronary arteries of patients with COA. Roifman et al demonstrated higher rates of HTN, heart failure, and stroke in COA patients. 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. 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. This early insult may play a role in the development of atherosclerosis and heart failure in CHD patients. Furthermore, the general inflammatory state of heart failure has been associated with worse exercise capacity, hospitalization, and decreased survival. Coronary artery intimal hyperplasia was more often seen in patients after surgically repaired CHD than in those with nonrepaired CHD. Residual hemodynamic abnormalities may lead to abnormalities in ventricular size, which have been associated with late atherosclerosis. This is further corroborated with evidence of myocardial perfusion defects in moderate to complex CHD including TGA after atrial switch repair. Several reports of the need for coronary artery bypass grafting after repair of tetralogy of Fallot have been reported. 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. Complex preoperative coronary anatomy including intramural segments and single coronary ostia has been implicated as risk factors for coronary stenosis after ASO. Abnormalities in coronary flow reserve and proximal intimal thickening have been seen in the coronary arteries of patients after ASO. Coronary stenoses in TGA ASO are often asymptomatic, and some have advocated routine screening with coronary angiography or computed tomography coronary angiography. Despite these findings, long-term outcome has been good in this population with few adverse coronary events. 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. HTN is prevalent in patients with Turner and Williams syndrome. Cardiovascular risk factors such as obesity and sleep...
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. Hepatic complications of heart failure have been well documented in congestive heart failure patients; especially those with right heart failure. In Fontan patients, the venous HTN, low cardiac output of single ventricular physiology, and prior operative insults may lead to liver injury and cirrhosis Renal impairment is prevalent at 9% of ACHD patients, with the highest risk in cyanotic and Eisenmenger patients. Prior cardiac surgical repair and spinal abnormalities have resulted in an increased prevalence of restrictive lung disease. 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. 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). 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. In a study from Belgium, 1976 individuals with CHD were more often obese and hypertensive compared with the general population. Obesity was present in 30% of adult patients with moderate and complex CHD requiring additional surgery. Nearly one-third of patients with a history of TGA after ASO are obese. 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. 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.

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. Swan et al found that exercise advice was more often prohibitive rather than reassuring and encouraging. 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. 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. In an older population of CHD patients (age >65 years), 47% were found to be hypertensive. 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. 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. 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%). Ohuchi et al also demonstrated a high prevalence of abnormal glucose metabolism in ACHD patients compared with a group of healthy controls. The ACHD cohort had lower HDL levels compared with controls, suggesting a problem with dyslipidemia. ACHD patients with an abnormal glucose regulation had associated morbidity and mortality. Like diabetes, abnormal glucose response has been associated with CVD. 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

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Comparison with General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Higher prevalence in general ACHD population/Lower prevalence in Fontan</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Higher prevalence in coarctation, Turner or Williams syndrome</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Higher prevalence of abnormal glucose metabolism</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Smoking</td>
<td>Lower prevalence</td>
</tr>
</tbody>
</table>

DOI: 10.1161/JAHA.114.001076
someone who has never smoked. Smoking was found to be less common in ACHD patients compared with the general population, but 18% of individuals with CHD smoked. Reid et al showed a similar 13% to 20% smoking in adolescents and young adults with CHD. 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. 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).

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. 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, non-tropical vegetable oils and nuts; and limits intake of sweets, sugar sweetened beverages, and red meats.” There is evidence that this dietary pattern can lower blood pressure and cholesterol. Physical activity can have the same benefits. However, 25% of individuals with CHD did not engage in regular physical activity. More than 50% of ACHD patients have impaired exercise capacity. However, several studies have demonstrated that regular exercise can be safe and even improve exercise capacity in patients with CHD. There is increasing evidence that physical activity has long term beneficial effects. There may also be a role for cardiac rehabilitation program in patients with CHD.

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>
<thead>
<tr>
<th>Table 3. Screening for Cardiovascular Risk Factors in Adults With Congenital Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
</tr>
<tr>
<td>Diet and physical activity</td>
</tr>
<tr>
<td>Tobacco</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
</tr>
</tbody>
</table>

DOI: 10.1161/JAHA.114.001076
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. 

Tools like a pedometer or accelerometer may help motivate patients to achieve goals in physical activity.

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. If patients become overweight (BMI 25 to 29.9 kg/m²) 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. 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. 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.

Standard blood pressure assessment is recommended during routine cardiovascular visits for CHD patients and should follow guidelines by the last Joint National Committee. In Marfan syndrome, β-blockers and/or losartan has been suggested for antihypertensive therapy in the setting of aortic dilation. 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. 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.

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/m² 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. 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). 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 electrophysiological 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


Management of Cardiovascular Risk Factors  

Lui et al


Management of Cardiovascular Risk Factors
Lui et al

Management of Cardiovascular Risk Factors Lui et al


Key Words: adult congenital heart disease • cardiovascular disease • risk factor

DOI: 10.1161/JAHA.114.001076
Management of Cardiovascular Risk Factors in Adults With Congenital Heart Disease
George K. Lui, Susan Fernandes and Doff B. McElhinney

*J Am Heart Assoc.* 2014;3:e001076; originally published October 30, 2014;
doi: 10.1161/JAHA.114.001076
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue,
Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://jaha.ahajournals.org/content/3/6/e001076