

# PREVENTION, DETECTION AND MANAGEMENT OF CORONARY ARTERY DISEASE IN MINORITY FEMALES

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**Background and Significance:** Heart disease is the leading cause of death for women living in the United States; this disease claims more female lives than all cancers combined. Additionally, according to the Centers of Disease Control data between the years 1979 and 2006, while cardiac-related mortality among men decreased significantly, only a modest decline was found among women. This disparity is greatest among minority females including Blacks and Hispanics who have an even greater prevalence of CVD and its risk factors

**Prevention:** There are several risk factors for coronary artery disease (CAD). Modifiable risk factors include: tobacco smoking, hypertension, diabetes, hyperlipidemia, obesity and physical inactivity. The prevention of CAD is grounded in decreasing or removing these modifiable risk factors.

**Detection:** Accurately diagnosing CAD is dependent on an accurate assessment of the patient's pre-test probability to determine the best diagnostic approach to pursue. The patient's functional status, resting EKG and cardiac risk factors also assist in determining the best non-invasive cardiac test to pursue.

**Management:** The goals and mainstay in the management of minority females with stable CAD includes surveillance for CAD symptoms, management of hypertension, diabetes mellitus and hyperlipidemia, as well as encouraging healthy habits.

**Conclusion:** Heart disease remains the leading cause of death in minority females. Providers must be diligent to aggressively decrease patients' cardiovascular risk and, when patients do present with cardiovascular symptoms, providers must be aggressive in accurately diagnosing and treating these patients to decrease cardiac morbidity and mortality. *Ethn Dis.* 2015;25(4):499-506; doi:10.18865/ed.25.4.499

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## BACKGROUND AND SIGNIFICANCE

Heart disease is the leading cause of death for women living in the United States; this disease claims more female lives than all cancers combined.<sup>1</sup> Despite this daunting fact, the general perception of female health threats is far different from reality. Many believe that breast cancer poses a greater threat to female mortality; in fact, twice as many females in the United States will die from heart disease than females dying from cancer.<sup>1,2</sup> Each year, for females aged > 84 years, approximately 225,000 will die from heart disease compared with approximately 50,000 deaths from cancer.<sup>3</sup>

Additionally according to the Centers of Disease Control data between the years 1979 and 2006, while cardiac-related mortality among men decreased significantly, only a mod-

est decline was found among women over this 27-year period.<sup>4</sup> Cardiovascular disease (CVD) also creates a great financial burden to the United States economy, costing more than \$300 billion in health care costs and lost economic productivity.<sup>5</sup>

The reasons for this great disparity between men and women in cardiovascular outcomes are multifactorial from two perspectives. First, women generally have an under-appreciation of cardiovascular symptoms, which may be due to the failure of the medical community to educate women on symptoms and risk factors for cardiovascular disease. Second, providers may under-recognize and under-treat cardiovascular disease and its risk factors among female patients. Another contributor may be the failure to identify at-risk females and the understudy of women in large research studies or registries. This sex disparity is greatest among minority females including Blacks and Hispanics who have an even greater prevalence of CVD and its risk factors. In fact, CVD age-adjusted deaths rates are 34% greater among Blacks when compared with the general US population.<sup>6</sup> American Indians and Alaskan Natives also die much earlier from heart disease; at least 36% of these patients are aged >65 years when compared with only 17% for the US population

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overall.<sup>7</sup> This disparity in outcomes is due to several health care and socioeconomic barriers. Ethnic minorities often face barriers to medical care in terms of diagnosing and treating CVD disease; which contribute to more severe CVD when compared their White counterparts.<sup>6</sup>

To raise awareness of this disease in the minority female population, the purpose of this ISHIB 2015 lecture and this subsequent article was to provide a review of the important factors in the prevention, detection and management of coronary artery disease (CAD) in the female minority patient.

## PREVENTION OF CORONARY ARTERY DISEASE

### Risk Factors for Coronary Artery Disease (CAD)

Risk factors for CAD are best divided into two groups: modifiable and non-modifiable risk factors.

Modifiable risk factors include: tobacco smoking, hypertension, diabetes, hyperlipidemia, obesity and physical inactivity. Non-modifiable risk factors include: family history of premature CAD, defined as a first-degree relative diagnosed with CAD before aged 55 years for males and before aged 65 years for females. Non-modifiable risk factors also include age and sex.

The prevalence of modifiable risk factors among females is significant, with at least 45%-54% of the US minority female population being overweight or obese and >40% of the US minority female population having elevated cholesterol levels.<sup>8</sup>

Many of the risk factors for CAD are modifiable. The prevention of CAD is grounded in decreasing or removing these modifiable risk factors. The single most dramatic decrease in risk for CAD results from smoking cessation.

### *Smoking*

According to statistics from the Centers for Disease Control and Prevention (CDC), tobacco use remains the single largest preventable cause of death and disease in the United States. Cigarette smoking kills >480,000 Americans each year.<sup>9</sup> In addition, smoking-related illness in the United States costs >\$300 billion a year, including nearly \$170 billion in direct medical care for adults and \$156 billion in lost productivity.<sup>10</sup> In 2013, an estimated 17.8% (42.1 million) US adults were current cigarette smokers. Of these, 76.9% (32.4 million) smoked every day, and 23.1% (9.7 million) smoked some days. Of these smokers, 18.3% were Blacks and 12.1% were Hispanics.<sup>11</sup>

Smoking cessation is a very important factor in decreasing risk for coronary artery disease. Counseling by physicians and other providers is vital and has a great impact.<sup>11</sup> Other aides that may be used for tobacco cessation include: nicotine replacement (patches or gum), Bupropion and Varenicline.

### *Hypertension*

Hypertension is common and poorly controlled in various ethnic minority groups (Blacks Hispanics, Pacific Islanders and Asians). Detection and awareness are also poor in these populations.

Target organ damage from hypertension is very prevalent among Blacks, resulting in a greater degree of left ventricular hypertrophy and diastolic left ventricular dysfunction among Blacks compared with Whites.<sup>12</sup> Compared with Whites, Blacks have a higher degree of target organ damage resulting in greater morbidity and mortality from hypertension; are more likely to develop hypertension at a younger age; are more often develop stage 2 hypertension; have a greater prevalence of chronic kidney disease and end stage renal failure from hypertension; are more likely to have thrombotic or hemorrhagic strokes related to intracerebral vascular disease; have more salt-sensitive, renin-independent hypertension; and, have a higher vascular resistance possibly due to lower levels of vasodilatory hormones.<sup>13</sup>

According to the latest JNC-8 Guidelines,<sup>14</sup> lifestyle interventions (eg, diet, increasing physical activity) are still a vital component in the management of hypertension. Pharmacologic therapy is the next tier in treatment and is based on patient's age, ethnicity, and the presence of diabetes mellitus (DM) or chronic kidney disease (CKD). Blood pressure targets have become more lenient with a target blood pressure goal of <150/90 mm Hg for patients aged >60 years and a target blood pressure goal of <140/90 mm Hg for all other patients including those with DM and CKD. Thiazide type diuretic and calcium channel blockers are still the recommended class of medications for treating hypertension in most patients, with a preference for angiotensin convert-

ing enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARB) in patients with DM and with CKD.<sup>14</sup>

### *Diabetes*

Diabetes mellitus is a far more powerful coronary risk factor for women than men, negating much of the protective effects of the female sex. According to the Nurses' Health Study, patients with type 2 diabetes have a 3- to 7-fold increased risk of having a cardiovascular event.<sup>15</sup> Diabetic women with myocardial infarction (MI) have twice the risk of another heart attack and a 4-fold likelihood of developing heart failure.<sup>15</sup> Among those with diabetes, 65% die from heart disease or stroke. Among women, 4.2 million American women have diabetes and the statistics are particularly high among African American women.<sup>16</sup>

The majority of people with type 2 (adult-onset) diabetes have additional risk factors for heart disease. Two out of three people with diabetes die of some type of CVD. Therefore, aggressive therapy for diabetes and high blood pressure is usually needed and can reduce the risk of heart disease and its associated complications.<sup>17-18</sup>

### *Hyperlipidemia*

Hyperlipidemia is another important risk factor for CAD and is very prevalent in the US female population. Approximately 40%-50% of US females have elevated total cholesterol levels >200 mg/dL.<sup>19</sup>

Several clinical trials have studied the use of statin therapy in the management of hyperlipidemia. Recently, at least 20 clinical trials have been conducted and pub-

lished, with at least nine focused on effects of sex. An analysis of 11 trials that included >15,000 females showed that statin therapy decreases cardiovascular mortality by 26%, nonfatal MI by 36%, and major cardiovascular events by 21%.<sup>20</sup>

In 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) published guidelines on the management of hyperlipidemia. The guidelines include a very useful asymptomatic cardiovascular disease risk calculator for providers to use in assessing risk for their patient and to help in decision-making on initial pharmacologic therapy.<sup>21</sup> This calculator is based on age, sex, ethnicity, cholesterol levels, and the presence of DM, hypertension, and tobacco smoking.<sup>21</sup>

### *Obesity and Physical Inactivity*

Obesity rates have increased in the US population among all ages and ethnicities in both male and females since 1980.<sup>13</sup> Ethnic disparities exist, with the prevalence of obesity being greater in Black and Hispanic females when compared with Whites.<sup>13</sup> The relative risk for CVD in females increases proportionately with increase in body mass index (BMI).<sup>22</sup> Additionally, the prevalence of angiographically significant CAD increases among patients with dysmetabolic features.<sup>23</sup>

Although challenging, providers must be persistent in their encouragement of patients to maintain a healthy weight and to become physically active. Patients' dietary habits and physical activity should be treated as the other set of "vital signs" at every clinic visit and should

be asked about during every clinic encounter. Dietary guidelines are also very important; it may be helpful to have printed patient education materials to distribute at the clinic visit to emphasize the importance of a heart healthy diet. Other tools that may be used to encourage physical activity include a physical activity log as well as the use of pedometers to track the number of steps walked each day (AHA recommends a goal of >10,000 steps/day).

It is also important to set goals for patients. Patients should be encouraged to find ways to fit activity into their daily routine. Examples include taking the stairs instead of the elevator, parking further away, or walking to another bus stop. Patients should aim for at least 150 minutes/week of moderate aerobic exercise. This can be broken down into multiple periods of activity each day. For patients just beginning an exercise routine, they should be advised to start with only 5 or 10 minutes of moderate aerobic activity, three times per day and build from there.

For weight loss, patients should limit calorie intake to <1800 calories for most females and should engage in physical activity per the following guidelines of the American College of Sports Medicine (ACSM). To maintain weight, one must do between 150-250 minutes of moderate intensity physical activity per week. This translates to between two and a half and about four hours per week. If the goal is to lose significant weight, the ACSM states that >250 minutes (four hours plus) per week of moderate intensity physical activity is necessary. To prevent regaining

any weight that has been lost, the ACSM states that evidence suggests that as much exercise as needed for weight loss - more than four hours a week (more than 250 minutes) is necessary to achieve this goal.<sup>24</sup>

Other factors that assist with weight loss and management include the simplification of the diet by avoiding processed foods, such as replacing sugary sodas with water and fresh fruit, eating whole grains, nuts and vegetables/ fruit, and avoiding foods containing high fructose corn syrup. Patient should also be encouraged to decrease the quantity of their meals while improving the quality of their meals. Additionally, patients should ideally eat their heaviest meal in the morning and their meals should get smaller as the day progresses and their activity level decreases.

## DIAGNOSING CORONARY ARTERY DISEASE

The diagnosis of CAD in the female population is of great importance. Unfortunately, according to the National Health and Nutrition Examination Survey (NHANES) data from 1992-2002, CAD is prevalent in more than half of the female population aged >55 years.<sup>25</sup> Despite this fact, when compared with men, fewer women (78% vs 73%, respectively) are referred for exercise treadmill stress testing and despite a higher angina class, even fewer women (48% vs 31%, respectively) are referred for diagnostic coronary angiogram.<sup>26</sup> Differences between men and women also exist with regard to presentation and

manifestation of CAD. In fact, 58% of women who die suddenly from an acute MI had no classic warning symptoms.<sup>27</sup> Additionally, 38% women vs 25% of men will die within one year of having their first MI.<sup>27</sup> Therefore, early detection of symptoms and accurate and timely diagnosis of CAD is important to decrease CAD-related mortality.

### Definition of Angina

Three features of chest pain that are typically thought to be anginal include exertional exacerbation, a substernal location and relief with rest or with nitroglycerin within 10 minutes. Chest pain is classified as being typical angina if all three of these features are present; if two out of the three features are present it is classified as atypical angina; and, if one or none of the three features are present, it is classified as non-anginal.

However, many women may not present with classic symptoms of obstructive CAD, such as angina but may present with symptoms that could be anginal equivalents. These symptoms include exertional dyspnea or fatigue resulting in reduced exercise capacity. The presence of these symptoms should alert the physician to rule out the presence of coronary artery disease. This is particularly true for diabetic females who may not have the classic anginal symptoms.

### Ischemic Cascade

As coronary artery disease progresses over time, there are various stages that occur during the disease process. The first stage usually is subclinical and begins with the deposition of cholesterol plaque along the

intima of the coronary vessels resulting in fatty streaks. These plaques are usually non-obstructive and therefore non-ischemia and can usually be detected by coronary CT angiogram. As CAD progresses to further layering of plaque and the development of intermediate obstructive disease, this can usually begin to be detected by perfusion abnormalities on nuclear myocardial perfusion imaging suggesting the presence of myocardial ischemia. The further stages of this disease process usually results in significant obstruction of coronary blood flow resulting in a greater degree of ischemia that then causes myocardial wall motion abnormalities that can be detected by stress echocardiography or cardiac stress magnetic resonance imaging. At the extreme ends of this disease spectrum as the severity of the obstruction progress to near occlusion of blood flow mire, severe ischemia develops resulting in ST-T segment changes on electrocardiography (EKG), which can be detected on exercise stress EKG. At the extreme end of the progression, the patient may develop angina at rest. The progression of CAD along these stages is known as the "ischemic cascade," which should be considered when determining the best diagnostic strategy for patients who may present at different stages of this disease spectrum.

### Assessment of Pre-test Probability and Bayes' Theorem

The assessment of a patient's pre-test probability for having obstructive CAD is crucial in determining the best diagnostic path to take. The

clinically assessed pre-test probability of CAD determines the type of test that should be ordered for the patient to determine the presence of obstructive CAD in the patient presenting with angina or anginal equivalent. The pretest probability is based on sex, age and symptoms.<sup>28</sup> For example, a 39-year-old female presenting with atypical angina would have a very low (<10%) pre-test probability of having obstructive CAD. However, a female aged >50 years presenting with similar atypical angina will have an intermediate (10%-90%) pre-test probability of having obstructive CAD. Females aged >60 years presenting with atypical angina or non-anginal chest pain will have an intermediate pre-test probability of having obstructive CAD; those presenting with typical angina will have a high (>90%) pre-test probability of having obstructive CAD.

The Bayesian theory studies the relation between pre- and post-test probability. Diagnostic accuracy improves with a test with a higher sensitivity and specificity. Bayesian theory has shown that the value of non-invasive testing for CAD is greatest in patients with an intermediate pre-test probability (10%-90%) of having CAD. In this group of patients who undergo non-invasive testing, a negative (normal) result of a non-invasive test with a high sensitivity (Sn) and specificity (Sp) will reclassify that patient's posttest probability to low probability of having obstructive CAD. In this group of patients, a positive (abnormal) result will reclassify the patient's posttest probability to a high probability of having obstructive CAD and therefore

this patient would be recommended to have further conclusive diagnostic testing (eg, invasive coronary angiogram) for obstructive CAD.

### Cardiac Stress Testing

There are several types of cardiac stress testing available to diagnose the presence of CAD. This includes: exercise treadmill electrocardiogram (EKG) stress test (Sn of 61%, Sp of 70%); exercise treadmill stress echocardiography (Sn 81-89%, Sp 86%); exercise stress myocardial perfusion single photon emission computed tomography (SPECT) (Sn 87%, Sp 91%); pharmacological (dobutamine) exercise stress echo (Sn 80%, Sp 84%); and pharmacological stress myocardial perfusion SPECT (Sn 91%, Sp 86%).<sup>29</sup>

The type of test ordered to diagnose obstructive CAD is determined by the patient's functional status, EKG and risk factors. Functional status is an important clinical assessment that determines not only the type of test ordered but also patient cardiovascular outcomes. The National Institute of Health (NIH) sponsored the Women's Ischemia Syndrome Evaluation (WISE) study, which showed that female patients with poorer functional status as determined by the Duke Activity Status Index (DASI) had a shorter time to death or MI than did women with greater functional status and higher DASI score.<sup>30</sup>

Patients with good functional status, DASI score >5 metabolic equivalents (METs) and a normal EKG with no baseline ST-T segment abnormalities and no left bundle branch block (LBBB) may proceed

to have an exercise treadmill stress EKG. Patients with poor function capacity, particularly if their DASI score is <5 metabolic equivalents (METs), should be referred for pharmacological stress echo or SPECT imaging. Patients who are on digoxin or who have abnormal uninterpretable EKG (pre-excitation [Wolff-Parkinson-White] syndrome or >1 mm of resting ST depression) and have good functional status would be referred for exercise stress echo or exercise stress SPECT. Patients with complete left bundle-branch block (LBBB) or any interventricular conduction defect with QRS duration >120 msec or electronically paced ventricular rhythm, are best referred for vasodilatory pharmacological stress nuclear SPECT imaging for diagnosing CAD.<sup>31</sup> When compared with stress SPECT, stress echo and exercise stress EKG have the added value of not exposing the patient to any ionizing radiation. Therefore, these modalities should be strongly considered for young female patients to minimize radiation exposure. In obese females, however, echocardiography may be technically challenging even with the use of endocardial enhancing contrast agents; in these situations, stress SPECT may be the better imaging modality.

There are various features of the exercise stress test that are useful in determining the patient probability of having obstructive CAD; this is best summarized in the Duke Treadmill score (DTS). This score is determined by the exercise time, the degree of ST-T depressions and the presence or absence of limiting or non-limiting angina.<sup>31-33</sup> A

DTS score of > 5 suggests a low probability of obstructive CAD, a score of +4 to -10 suggests a moderate probability of obstructive CAD and a score < -11 suggests a high probability of obstructive CAD.

### **Coronary Computed Tomography Angiogram**

Coronary CT angiogram is another useful non-invasive cardiac imaging study to diagnose obstructive CAD. Its strength is its high negative predictive value of 93%. Sensitivity is 93% and specificity is 79%.<sup>34</sup> This study is considered appropriate for patients with low likelihood of having obstructive CAD but uninterpretable EKG or are unable to exercise. It is also considered appropriate for a patient with intermediate probability of having obstructive CAD and is useful for patients who have had an equivocal stress test.<sup>35</sup> It is important to note that patients with high probability of having obstructive CAD or have had prior coronary angioplasty with stent placement or prior coronary bypass graft surgery are generally best referred for invasive coronary angiogram due to the decreased specificity of this test in these patients.

### **Diagnosing Subclinical Coronary Artery Disease**

Diagnosing the presence of subclinical CAD in the asymptomatic female can be particularly useful in patients with a strong family history of premature disease. In fact non-contrast cardiac CT for coronary calcium scoring has a class IIa indication and is reasonable in asymptomatic adults with intermediate risk for CAD and asymptomatic

DM adults aged >40 years.<sup>35</sup> Stress SPECT has a Class II b indication in asymptomatic patients with DM or asymptomatic adults with previous risk assessment suggesting a high risk of CAD such as CAC score >400.<sup>36</sup>

### **MANAGEMENT OF STABLE ISCHEMIC HEART DISEASE IN MINORITY FEMALES**

Sex and ethnic disparity exists in the management of patients with stable ischemic heart disease. Compared with men, women are less likely to be placed on appropriate statin therapy and antiplatelet therapy both initially and after being diagnosed with CAD and up to 1 year after their diagnosis. Females are also less likely to be referred for coronary angiography than men (13% vs 29%, respectively).<sup>26</sup> In the national registry of MI between the years 1994 and 2002, more than 500,000 patients who were considered ideal candidates for treatment of CAD were studied. There was significant disparity in the management of CAD in minority females, and this correlated with greater mortality in this group of patients.<sup>37</sup> For example, Black females were less likely to be referred for coronary angiography and reperfusion, which correlated with an increase in mortality. The greatest disparity was seen between Black females and White males, with no indication that this gap has decreased in recent years.<sup>37</sup> It is therefore imperative that providers ensure that minority female patients with CAD are appropriately managed and treated with guideline-directed therapy.

The ACC/AHA 2012 guidelines on the management of patients with stable ischemic heart disease was updated in 2014. The management approach for these patients includes, "Guideline-directed medical therapy," along with ongoing patient education to include lifestyle modification (eg, a heart healthy diet, weight loss and management and physical activity). Patients should all be on a daily enteric-coated aspirin (81 mg daily), unless there is a serious adverse effect or contraindication. In that case, aspirin may be substituted with 75 mg of clopidogrel or aspirin desensitization could be considered. Smoking cessation should be encouraged in all patients who are smokers. Patients should be on moderate-to-high intensity statin. Patient's blood pressure should be controlled to <140/90 mm Hg, with the ACE-I/ARB in patients with left ventricular systolic dysfunction, diabetes or chronic kidney disease. Patients who are diabetic should be appropriately managed to achieve good glycemic control. For patients with stable angina, they may be managed with sublingual nitroglycerin, as needed, and with beta blockers, calcium channel blockers and/or long-term nitrates. Ranolazine is also another medication that may be added for control of angina. If medical management of angina is unsuccessful, coronary revascularization should be considered. It is also important to remember that cardiac rehabilitation is very useful for patients who have completed their coronary reperfusion performed via angioplasty or bypass graft surgery as this helps to promote a healthy

lifestyle of increased physical activity and weight management.<sup>38</sup>

The goals and mainstay in the management of minority females with stable CAD includes surveillance for CAD symptoms at each visit, as well as management of hypertension, DM and hyperlipidemia, and encouraging healthy habits (eg, minimizing alcohol intake, smoking cessation, heart healthy diet, being physically active and weight management). The ultimate goal in managing these patients is prevention of premature cardiovascular death, decreasing the risk of complication of stable ischemic heart disease, completely or near complete elimination of ischemic symptoms, restoring functional capacity and sense of well-being and minimizing health care costs by decreasing risk of adverse cardiac events and avoiding unnecessary testing and treatments.

## CONCLUSION

Heart disease remains the leading cause of death in minority females. Providers must be diligent to aggressively decrease patients' cardiovascular risks. When patients do present with cardiovascular symptoms, providers must be aggressive in accurately diagnosing these patients in a timely manner to decrease cardiac morbidity and mortality. For minority females with established CAD, providers must appropriately manage these patients to avoid premature cardiovascular death and decrease complications of ischemic heart disease and must encourage heart healthy habits that can lead to a sense of well-being.

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