Achieving Treatment Goals in Low-Risk, Asymptomatic Patients

Keith C. Ferdinand, MD

Traditional risk factor assessments for coronary heart disease (CHD) often fail to take into account individual factors such as race and lipid profiles that may substantially elevate a patient’s risk for CHD or a cardiovascular event. Although numerous treatment guidelines have been issued on metabolic syndrome, discrepancies among the guidelines can create confusion. Cardiac biomarkers and imaging methods have emerged to help detect and quantify subclinical atherosclerosis, but many of these are not proven as cost-effective for use in clinical practice or for routine screening. As the present case-based activity demonstrates, determining appropriate diagnostic and management strategies according to CHD risk is a process that challenges physicians to consider myriad individual patient variables.

This article was developed in part from a CME-certified seminar held on Wednesday, November 4, 2009, during the American Osteopathic Association’s 114th Annual Osteopathic Medical Conference and Exposition in New Orleans, Louisiana. DIME staff have assisted faculty with content development.

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Dr Ferdinand reports that he received funding for research from Daiichi Sankyo, Inc; Forest Pharmaceuticals, Inc; Novartis Pharmaceuticals Corp, and Pfizer Inc. He has consulting agreements with AstraZeneca Pharmaceuticals LP; Daiichi Sankyo, Inc; Forest Pharmaceuticals, Inc; Merck & Co, Inc; and Novartis Pharmaceuticals Corp. In addition, he is on the speakers’ bureau or has honorarium agreements with AstraZeneca Pharmaceuticals LP; Daiichi Sankyo, Inc; Forest Pharmaceuticals, Inc; and Novartis Pharmaceuticals Corp. He also provides discussion of off-label, investigational, or experimental drug use for statins. Dr Ferdinand has no relevant financial interests or stock ownership.

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Appropriate patient evaluation for subclinical atherosclerosis is an important goal in primary care, considering that this condition manifests in 50% of first events as either myocardial infarction (MI) or sudden death.

Traditional scales such as the Framingham Risk Calculator can serve as useful starting points for evaluating cardiovascular risk. However, these methods of risk stratification fail to take into account individual factors that may substantially increase some patients’ chances of cardiovascular events.

The present report uses a case presentation to illustrate the various factors in examining, diagnosing, and treating a patient whose risk for metabolic syndrome and coronary heart disease (CHD) may not be evident based on the findings from traditional risk evaluation tools.

Case Presentation

The patient is a 51-year-old African American woman whose husband urged her to see a physician because of concerns related to her family history. The patient, a high school teacher, weighs 191 pounds and admits to a recent 25-pound weight gain. She has no history of surgery, no known history of diabetes, does not smoke tobacco, and does not drink alcohol. She currently takes atenolol, 25 mg daily, for hypertension. Family history is significant for cardiovascular disease (CVD)—the patient’s father died of an MI at age 51 years, and her brother had an MI at age 44 years.

Physical examination reveals a body mass index (BMI) of 30.82, which meets criteria for obesity, and a waist circumference of 35.4 inches with a waist-hip ratio of 0.88. Her blood pressure is elevated (148/96 mm Hg) despite antihypertensive therapy.

Does This Patient Have Metabolic Syndrome?

Metabolic syndrome is a constellation of interrelated clinical and biochemical disorders that includes dyslipidemia, hypertension, elevated fasting glucose, and central obesity. It represents increased risk for CVD and type 2 diabetes mel-

This supplement is supported by an independent educational grant from AstraZeneca Pharmaceuticals LP.
People with metabolic syndrome have double the risk of developing CVD within the next 5 to 10 years and a 5-fold increase in risk for developing T2DM.2,3

Various organizations have issued guidelines for the diagnosis and management of metabolic syndrome, including the National Cholesterol Education Program (NCEP),3 the World Health Organization (WHO),4 and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI).5 These organizations collaborated on a new statement in 2009 in an effort to unify these criteria, which are listed in (Figure 1).1

On the basis of her waist circumference, high blood pressure, and elevated fasting glucose (Table 1), this patient can be diagnosed as having metabolic syndrome. Although her cholesterol levels may not appear to fall within the high-risk ranges, these values may be less sensitive or misleading, particularly in African Americans with obesity. Several studies6-7 have shown that triglycerides and high-density lipoprotein cholesterol (HDL-C) may not appear abnormal in African Americans, leading to underdiagnosis of metabolic syndrome in this population.

Ford and colleagues8 used survey data from the third National Health and Nutrition Examination (NHANES III) to estimate the prevalence of metabolic syndrome among various US racial/ethnic groups. The prevalence of metabolic syndrome was shown to be highest among Mexican Americans, affecting 28% of men and 36% of women, followed by white men (25%) and white women (23%). African Americans may have high rates of metabolic syndrome; yet they appear to be underrepresented in these data, affecting 16% of men and 26% of women. A likely reason is that the prevalence of metabolic syndrome in this group could be misrepresented because of arbitrary cut points for triglycerides and HDL-C that do not apply well to this population.6,8

Risk for diabetes also may be difficult to assess when laboratory values are near the borderline. This patient does not have a known history of diabetes, but approximately 30% of people with diabetes remain unaware of their condition despite expanded educational efforts.9 Although the patient’s fasting glucose of 100 mg/dL is not high enough for a formal diagnosis of diabetes, it does indicate insulin resistance, which concerns a 7-fold increased risk for developing T2DM.7 Her glycated hemoglobin level of 5.9% suggests longstanding elevation of glucose.

A urinary albumin excretion (UAE) rate of 20 μg/min or higher is among the clinical criteria for metabolic syndrome issued in the WHO guidelines.4 The patient’s UAE of 45 μg/min indicates microalbuminuria, an early sign of diabetic nephropathy. In this case, UAE is an important variable because of the increased incidence of renal dysfunction in African Americans with diabetes10 and poorer cardiovascular prognosis associated with this finding.11 With the patient’s creatinine count of 1.1 (at the high end of normal for a woman), these findings warrant further exploration for signs of kidney disease.

Traditional Risk Scoring Systems

The NCEP III guideline12 is one of the most comprehensive available for the management of dyslipidemia in the primary and secondary prevention of CHD. Updated guidelines (NCEP IV) are expected in mid-2010. The NCEP III is an improvement over previous guidelines in that a broader group of people qualifies for pharmacotherapy.12 However, an increasing body of data suggests that the current guidelines do not go far enough in determining groups appropriate for therapy or therapeutic cholesterol targets.

The NCEP III guideline uses the Framingham Risk Scoring system13 to determine 10-year risk for developing CHD. A study by Akosah and colleagues14 evaluated the accuracy of the Framingham score in a retrospective

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**Table 1**

<table>
<thead>
<tr>
<th>Measure *</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measure</strong></td>
<td><strong>Categorical Cut Points</strong></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>mg/dL*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>186</td>
</tr>
<tr>
<td>HDL-C</td>
<td>108</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>49</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>118</td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
<td>%</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>normal</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.1</td>
</tr>
<tr>
<td>Urinary albumin excretion, μg/min</td>
<td>45</td>
</tr>
</tbody>
</table>

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**Figure 1. Criteria for clinical diagnosis of metabolic syndrome.** *Three of these five criteria must be present for a diagnosis of metabolic syndrome. †To meet these criteria, patients must meet the categorical cut point or be receiving pharmacologic treatment for the condition. ‡For elevated blood pressure, the patient must meet the criterion for systolic blood pressure, diastolic blood pressure, or both. Abbreviations: HDL-C, high-density lipoprotein cholesterol.

Source: Adapted from: Alberti KG et al. Circulation. 2009;120(16):1640-1645.2
review of clinical data from 449 adults (men aged ≤55 years; women aged ≤65 years) with no history of CHD or diabetes who were hospitalized for a first acute MI over a 6-year period. On the basis of their Framingham scores before the event, most would not have qualified for pharmacotherapy under the NCEP III guideline. As these authors argue, presentation with acute MI automatically suggests that the patients were high risk, but clearly the vast majority of them were misclassified according to this system.14

The NCEP III guideline was applied to population data in a study by Ford and colleagues15 using a large database of 13,769 participants from NHANES III, which was conducted from 1988 to 1994. These data can be extrapolated to represent more than 157 million US adults. Among participants who did not have self-reported CHD (MI history or angina), stroke, peripheral vascular disease, or diabetes, 81.7% (140 million adults) had a 10-year risk for CHD less than 10%. Only 2.9% (4 million adults) had a 10-year risk for CHD greater than 20%. This analysis shows how risk in women is underrepresented. More than 92% of diabetes-free women under age 70 years would be classified as low-risk for CHD. A mere 1.4% of women in the age bracket of 50 to 69 years would be categorized as intermediate risk, while 8% of those aged 60 to 69 years had a 10-year CHD risk in the 10% to 20% range.15 Thus, guideline-based risk assessments fail to identify a large proportion of Americans with a high burden of subclinical atherosclerosis.

The patient in the current case represents a person who would typically be placed in a low-risk category using the Framingham Risk Scoring system alone (Table 2). Her total points of 14 convert to a 10-year risk score of 2%—low risk—and are tallied mainly from her age and history of hypertension. However, the Framingham Risk Scoring system13 preceded the concept of metabolic syndrome, which is now recognized to greatly increase cardiovascular risk. In addition, it does not account for family history or clinical variables such as elevated C-reactive protein (CRP) or coronary calcium.

Because clinically significant overlap of low-density lipoprotein cholesterol (LDL-C) levels exists between people with and without CHD, LDL-C levels alone do not give a true picture of cardiovascular health. In an analysis based on the Framingham Heart Study 26-year follow-up data,16 80% of people who had an MI had cholesterol levels similar to those who did not. This is partly a reflection of higher LDL-C and total cholesterol levels seen population-wide in asymptomatic and symptomatic people.

The Reynolds Risk Score, introduced in 2007, is a newer risk-scoring algorithm developed especially for women.17 This system accounts for family history and elevated CRP in addition to standard risk factors such as age, smoking history, blood pressure, and cholesterol level. However, even with these variables, the Reynolds Risk Score places our patient at low risk, with a 10-year risk score of 3%.

### Coronary Artery Disease Risk Among African Americans

African Americans have the highest overall CAD mortality in the US, particularly among young adults.3 The major risk factors that occur at higher rates among African Americans include diabetes, hypertension, obesity, left ventricular hypertrophy (driven by hypertension and obesity), physical inactivity, and smoking.3

The 2002 NCEP guideline included a section that specifically addressed CAD in the African American population.3 This document describes some of the racial differences that tend to occur with respect to dyslipidemia. Typical lipid profiles for African Americans as compared with whites are shown in Figure 2.

The lipid-modifying effects of statin therapy in African Americans with dyslipidemia have not been well characterized. In the African American Rosuvastatin Investigation of Efficacy and Safety (ARIES) Trial,18 my colleagues and I compared the effects of two different atorvastatin doses (10 mg and 20 mg daily) with equivalent doses of rosvastatin in 774 African Americans with dyslipidemia over a 6-week period. A greater proportion of patients achieved LDL-C goals with rosvastatin vs atorvastatin in equivalent doses. The observed differences were most notable in high-risk patients with an LDL-C goal of less than 100 mg/dL.

The ARIES Trial also examined the effects of statin therapy on CRP using high-sensitivity testing. Median CRP was significantly reduced from baseline with the higher doses of both rosvastatin and atorvastatin. In the subgroup of patients with high baseline CRP (>2.0 mg/L), rosvastatin significantly reduced CRP at both doses, while atorvastatin significantly reduced CRP only at the 20 mg

### Table 2

Framingham Risk Score for Patient in the Illustrative Case

<table>
<thead>
<tr>
<th>Category</th>
<th>Patient Data</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>186</td>
<td>2</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td>Tobacco smoker</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148</td>
<td>3</td>
</tr>
<tr>
<td>Currently on blood pressure medication</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Total score</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>10-year risk</td>
<td>2% (low)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on Framingham Risk Assessment Tool for estimating 10-year risk of developing hard coronary heart disease (CHD) defined as myocardial infarction or coronary death. Tool is designed to estimate risk in adults aged 20 years or older who do not have heart disease or diabetes.

Abbreviation: HDL-C, high-density lipoprotein cholesterol.

Source: Adapted from National Cholesterol Education Program. Risk assessment tool for estimating 10-year risk of developing hard CHD (myocardial infarction and coronary death).

arterial disease and occlusion). How -
high-sensitivity CRP (a marker of vas-
atherosclerotic rupture) and coronary
artery calcification score (a marker of
validity for use as routine screening tools
for CVD in asymptomatic people.
Force recently evaluated several nontra-
such tests in asymptomatic patients must
precipitate an acute event. These include
very rare events of atheromatous plaque

dose. Our results showed that overall
lipid profiles in this group of African
Americans with dyslipidemia improved to
a greater extent with rosuvastatin than
with equivalent doses of atorvastatin.

Nontraditional Risk Factors and Imaging Methods
As the pathogenesis of atherosclerosis is
better understood, a number of measures
have emerged that can provide more
patient-specific information about car-
diovascular health and factors that may
precipitate an acute event. These include
high-sensitivity CRP (a marker of vas-
cular inflammation and potential for
atherosclerotic rupture) and coronary
artery calcification score (a marker of
arterial disease and occlusion).
However, the practical aspects of conducting
such tests in asymptomatic patients must
be taken into account, especially consid-
ering the need for cost containment.

The US Preventive Services Task
Force recently evaluated several nontra-
ditional risk factors to determine their
validity for use as routine screening tools
for CVD in asymptomatic people (Figure 3).
The task force determined that insufficient evidence exists to con-
sider any of these nontraditional mea-
sures as part of routine screening for CVD
among asymptomatic men and women
with no history of CVD. Therefore, the
“ultimate effect on CHD risk” of nontra-
ditional measures remains unclear.
Two of the tests, high-sensitivity CRP and
ankle-brachial index, met the criteria for reclassifying intermediate-risk patients
as either low risk or high risk.

Although they are not yet recom-
mended for routine screening of healthy
persons, many of these tests have clini-
cal value in evaluating individual
patients. Ankle-brachial index—the ratio
of blood pressure in the lower legs to
blood pressure in the arms—may be par-
ticularly useful in patients with symp-
toms of peripheral vascular disease such
as leg fatigue or claudication. High-sen-
titivity CRP is an indicator of vascular
inflammation that can predict cardio-
vascular risk in otherwise low-risk per-
sons. The JUPITER Trial showed the
powerful effects of reducing both LDL-C
and CRP with statin therapy in a group
of low-risk, asymptomatic patients. Orig-
inally a 5-year study, this large trial that
enrolled more than 17,000 subjects was
stopped after an average follow-up of
1.9 years when the treatment group
(20 mg rosuvastatin) had a 47% or lower
incidence in CHD outcomes such as MI,
stroke, hospitalization for revasculariz-
ation, and cardiovascular death.

In a subgroup analysis from JUPITER,
subjects with average LDL-C but elevated CRP (>2 mg/L) had sig-
nificantly lower total mortality when they
received statin therapy. This finding sug-
ests the benefits of evaluation and treat-
ment based on CRP even in people with
normal LDL-C, though this recommenda-
tion is not yet supported in US clinical
practice guidelines.

Although risk factor assessment pro-
vides only an estimate of atherosclerosis,
modern imaging methods can provide
direct evidence in terms of arterial wall
thickening, stenosis, and plaque compo-
sition and dynamics. Unlike coronary
angiography, noninvasive imaging
enables the evaluation of asymptomatic
people who have preclinical disease.
Some organizations have called for expanded use of noninvasive imaging to detect subclinical atherosclerosis and prevent CHD morbidity and mortality, much as screening is used to detect early colorectal and breast cancer.24

Intravascular ultrasonography remains mainly an investigational tool, used in clinical practice only for people who have stent placement. However, coronary artery calcification by electron beam computed tomography (EBCT) can provide direct evidence of subclinical atherosclerosis and the risk for events related to calcification of plaque.25 Although various methods are used to quantify coronary calcium scores, a score of 11 to 100 generally indicates mild risk, with 101 to 400 indicating moderate risk.26

Case Continuation
The physician orders a coronary calcium score via EBCT and high-sensitivity CRP level to better determine the degree of atherosclerosis and the patient’s risk for cardiac events, as requested by the patient after discussion of additional cost-risk considerations. Coronary calcium yields a result of 94, which indicates mild to moderate evidence of calcification. High-sensitivity CRP is also measured and yields a result of 4.2 mg/L, indicating an elevated level of vascular inflammation and risk for plaque instability.

Guideline-Based Treatment Recommendations
For primary prevention of CHD, the NCEP III guideline22 recommends a treatment approach based on lifestyle changes, including: (1) reduced intake of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control to lower cholesterol levels and reduce CHD risk. The aim of primary prevention is to reduce both long-term (>10-year) and short-term risk (Figure 4).

The higher the overall risk for CHD, the lower the goal for LDL-C should be. People with existing CHD should have an LDL-C goal lower than 100 mg/dL, those with 2 or more risk factors should have LDL-C less than 130 mg/dL, and those with 0 to 1 risk factors should have LDL-C less than 160 mg/dL.2 Because clinical data such as those from the JUPITER trial have demonstrated substantially better outcomes with much lower LDL-C levels, future guideline updates may suggest even lower LDL-C targets.

The guideline recommends assessing patients with elevated LDL-C or other hyperlipidemias for secondary causes of dyslipidemia before initiating a lipid-lowering therapy such as a statin, bile acid sequestrant, or nicotinic acid. These causes might include diabetes, hypothyroidism, obstructive liver disease or chronic renal failure, or use of drugs such as corticosteroids that could alter lipid profiles.3

After a statin or other lipid-lowering therapy has been initiated, it is important to monitor the patient’s response and adherence to therapy. Lifestyle modification should be maintained during lipid-lowering therapy. If the LDL-C goal is not achieved after a 6-week trial, the next step in the NCEP III guideline is to intensify therapy by increasing the statin dosage and rechecking in another 6 weeks. If this approach fails to achieve the target LDL-C, the physician may combine the statin with another agent, refer the patient to a lipid specialist, or explore the possibility of nonadherence as a cause of treatment failure.

Controlling LDL-C with pharmacologic therapy is a relatively straightforward approach to risk-factor management, but other risk factors must be addressed as well. Weight control and increased physical activity are key to reducing metabolic syndrome and should be stressed along with improved lipid profiles. Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome.2 Recommended approaches for reducing overweight and obesity can be found in the clinical guidelines of the NHLBI Obesity Education Initiative.27

The difficulty of maintaining adherence to pharmacologic therapy and lifestyle modifications cannot be overlooked. The NCEP III guideline2 includes suggestions for improving adherence that focus on both patient behavior and the approach to care employed in the physician’s practice (Figure 5).

Case Conclusion
At her 6-week follow-up visit, the patient has not managed to lose a clinically significant amount of weight and her lipid levels are approximately the same. Her CRP remains elevated at 4.2 mg/L. The physician prescribes rosuvastatin 10 mg daily with the goal of reducing LDL-C and CRP. At a subsequent follow-up visit 6 weeks after treatment began, the patient has lower total cholesterol (144 mg/dL) and substantially lower LDL-C (66 mg/dL). In addition, HDL-C is increased at 56 mg/dL and her triglycerides are 112 mg/dL.

With LDL-C goals achieved, the physician continues to monitor the patient’s weight-loss efforts and risk of diabetes and related complications. Additionally, atenolol, as monotherapy, is not optimal for antihypertensive control, especially in African Americans, and may worsen glucose intolerance and dyslipidemia. Initiation of blood pressure lowering with a thiazide diuretic or long-acting calcium channel blocker is an alternative. The patient was started on amiodipine 5 mg daily and instructed to get a home blood pressure monitor. Combination therapy, if needed, would potentially be one of these first-step alternatives added to an angiotensin enzyme inhibitor or angiotensin receptor blocker.

Conclusion
This present case-based report demonstrates that in many patients—especially women, African Americans, and some patients with metabolic syndrome—subclinical atherosclerosis may not be detected by conventional Framingham

Figure 4. Primary treatment goals for the patient in the illustrative case.
Interventions to Improve Patient Therapy Adherence

- Focus on the Patient
  - Simplify medication regimens
  - Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
  - Encourage the use of prompts to help patients remember treatment regimens
  - Use systems to reinforce adherence and maintain contact with the patient
  - Encourage the support of family and friends
  - Reinforce and reward adherence
  - Increase number of visits for patients unable to achieve treatment goals
  - Increase convenience and access to care
  - Involve patients in their care through self-monitoring

- Focus on the Physician and Medical Office
  - Teach physicians to implement lipid treatment guidelines
  - Use reminders to prompt physicians to attend to lipid management
  - Identify a patient advocate in the office to help deliver or prompt care
  - Enlist patients to prompt preventive care
  - Develop a standardized treatment plan to structure care
  - Use feedback from past performance to foster change in future care
  - Remind patients of appointments and follow up with them about missed appointments


risk scoring. Including high-sensitivity CRP in the laboratory workup or coronary calcium score via EBCT may provide increased information about CHD risk, though recent guidelines do not provide increased information about CHD. Lowering LDL-C is important, but weight management and other lifestyle factors must also be addressed, particularly in the context of metabolic syndrome.

References

(continued)


The American Osteopathic Association has been an active member of the Partnership to Fight Chronic Disease (PFCD) since 2007. The PFCD has been instrumental in raising awareness about rising chronic disease rates in the United States and ensuring that prevention and wellness measures were incorporated into the “Patient Protection and Affordable Care Act” (H.R. 3990), which was recently passed by Congress.

To learn more about the PFCD and how to take action, visit http://www.fightchronicdisease.org/index.cfm.