Managing borderline levels of risk for coronary heart disease: two illustrative case presentations

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Much has been learned about preventing and treating coronary heart disease (CHD) since publication of the National Cholesterol Education Program (NCEP) Adult Treatment Panel II (ATP II) guidelines in 1993. Even with the recent release of the ATP III guidelines, clinical decision making has become increasingly complex as a result of the tremendous volume of new data, and because many common patient types do not fit precisely into the defined risk categories. The case studies presented here illustrate how data from recent trials and the clinician’s judgment should be weighed together in the decision to initiate cholesterol-lowering therapy in patients with borderline risk levels, as part of a strategy for primary and secondary prevention of CHD.

(Key words: acute coronary syndrome, atherosclerosis, coronary heart disease, diabetes mellitus, myocardial infarction, National Cholesterol Education Program guidelines, primary prevention, secondary prevention, statins)

Since publication of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II, or ATP II) guidelines in 1993,1 clinical evidence and molecular approaches with respect to risk factors for atherosclerosis and strategies for preventing and treating coronary heart disease (CHD) continue to expand. Even with the revised guidelines recently reported by the NCEP ATP III,2 patient care decisions can be challenging. Time is often limited for a thorough risk assessment and patient counseling, and many common patient types do not fit precisely into the NCEP ATP risk categories. The NCEP ATP II and III, recognizing these limitations, advise physicians to use their clinical judgment in deciding whether to initiate drug therapy in patients whose lipid levels suggest borderline risk.1,2

The following two case studies illustrate some of the principles of preventive care in patients with similar risk profiles. These presentations focus on how existing treatment guidelines and data from recent clinical studies should be used to estimate CHD risk and to design an effective treatment program for primary or secondary prevention of coronary events (including lipid lowering with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor [statin] therapy immediately after acute coronary syndromes).

Case presentation 1
Initial presentation
A 57-year-old woman is admitted to the emergency department after several hours of chest pain. Previous diagnoses include hypertension, asthma, and hypothyroidism. Her family history is positive based on her father’s death due to a myocardial infarction (MI) at age 69 years and her mother’s coronary artery bypass graft (CABG) at age 62 years. Her current medications include triamterene/hydrochlorothiazide, potassium chloride, hormone replacement therapy, levothyroxine, aspirin, and albuterol. She does not use either tobacco or alcohol.

At physical examination, the patient’s blood pressure is 134/80 mm Hg. Her weight is 155 pounds with a body mass index (BMI) of 26.2, which is higher than optimal. No goiter or bruits are observed, and other physical findings are within normal limits. The electrocardiogram shows nonspecific anterolateral changes, which resolve shortly after admission to the hospital. Laboratory tests show her serum troponin level to be modestly elevated (3.6 μg/L), as are her serum creatine phosphokinase (CPK) (329 U/L) and CPK-MB (13.5 ng/mL) values. With thyroid hormone supplementation, her thyrotropin level (3.6 μU/mL) is within the normal range. Her fasting blood glucose level (86 mg/dL) is also within normal limits.

The patient’s lipid profile shows no dramatic abnormalities, with a total cholesterol (TC) level of 202 mg/dL, a high-density lipoprotein cholesterol (HDL-C) level of 45 mg/dL, a low-density lipoprotein cholesterol (LDL-C) level of 128 mg/dL, and a triglyceride level of 138 mg/dL.

She is started on therapy with heparin, nitroglycerin, and a glycoprotein IIb/IIIa inhibitor all administered intravenously, and she continues on aspirin therapy. Her chest pain resolves after hospital admission. Together with an angiotensin-converting enzyme (ACE) inhibitor, this regimen constitutes appropriate care for unstable angina after a likely subendocardial MI. In addition, this patient pass-
es a low-level stress test administered during her hospitalization.

**Risk evaluation**

Before her first coronary event, this patient did not fit the classic picture of elevated CHD risk. She had no evidence of diabetes, was not markedly overweight, did not smoke, and her hypertension was well controlled. Although her family history was suggestive of premature CHD, her father’s cardiac death at age 69 years is not a risk factor for CHD according to either the NCEP ATP II or III guidelines. However, these age-based risk criteria should not be interpreted as absolutes; her father’s history is clinically relevant. Therefore, this patient should be considered as having a positive family history for premature CHD, especially in light of the fact that her mother underwent CABG at age 62 years.

Although the NCEP ATP II or III guidelines may not have clearly identified this patient as a candidate for lipid-lowering therapy before her recent coronary event based solely on her LDL-C level and risk assessment, data strongly suggest that she may have benefited from early and intensive lipid reduction. Clinical trial data published in recent years show that the statins safely reduce CHD-related morbidity and mortality, not just in patients with severely elevated LDL-C levels, but even in those with mildly to moderately elevated levels (that is, patients who would not have qualified for immediate lipid-lowering therapy based on a strict interpretation of the NCEP guidelines).

Most recently, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study randomly assigned more than 3000 patients to receive atorvastatin calcium, 80 mg/d, or placebo within 96 hours after an episode of unstable angina or a non-Q-wave MI. In the first 16 weeks after randomization, the rate of recurrent ischemic events, particularly recurrent symptomatic ischemia requiring hospitalization, was significantly decreased in the group receiving intensive atorvastatin therapy.

**Intervention and outcomes**

To minimize recurrence of a coronary ischemic event, atorvastatin calcium, 80 mg/d, is added to the patient’s other medications and she is advised to begin a program of moderate exercise. Six weeks later, she has lost 6 pounds and her lipid profile is clearly improved with a TC level of 138 mg/dL, an HDL-C level of 48 mg/dL, an LDL-C level of 62 mg/dL, and a triglyceride level of 99 mg/dL. At her 5-month follow-up visit, she remains asymptomatic and has lost an additional 3 pounds. She tolerates her medications well and continues with her lipid-lowering regimen. According to the NCEP ATP III guidelines, LDL-C levels below 100 mg/dL are considered optimal for patients in the highest-risk category (that is, those with established CHD or CHD risk equivalent).

This case is an excellent example of the value of aggressive care and multiple-risk-factor modification in the setting of acute coronary syndrome, in which the LDL-C level is viewed as one of several treatable risk factors, even when it is not profoundly elevated.

Significant progress has been made in identifying patients at risk and providing comprehensive treatment; however, much progress remains to be seen in both primary and secondary prevention of CHD. Certainly, lipid intervention for all patients with established CHD or the presence of risk factors for CHD should include a low-fat diet, exercise program, and a generally healthy lifestyle, in addition to antihyperlipidemic therapy when needed. A recent analysis of updated data from the National Health and Nutrition Examination Survey III (NHANES III) concludes:

...patients with a range of CHD risk profiles, including an LDL-C level that would be considered “average,” benefit from aggressive lipid-lowering therapy. The clinical trial evidence supports the extension of treatment to individuals who would not be treated with lipid-lowering drugs under a strict application of the [NCEP] ATP II cutpoints for drug therapy.

**Case presentation 2**

**Initial presentation**

During a complete physical examination, a 55-year-old Filipino man asks for advice about an episode of atypical chest pain that occurred while he was away from home. A thallium stress test at that time was negative, and the cardiologist whom he consulted recommended metoprolol, aspirin, and cerivastatin sodium, 0.4 mg/d. The patient reports that he currently takes aspirin and cerivastatin, but does not use the β-blocker because of concerns about side effects. In addition, he has started taking over-the-counter, sustained-release niacin, 250 mg/d, on his own initiative.

His previous diagnoses include gastroesophageal reflux disease and hypercholesterolemia. He reports no tobacco use or significant alcohol consumption. His family history includes two important risk factors: diabetes mellitus in his mother and hypertension in his brother. In addition, his brother underwent angioplasty at age 53 years, indicating the presence of premature CHD.

At presentation, the patient reports that he has not had recurrent chest pain.
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Figure 1. Association of patient age and sex with prescription of lipid-lowering medications at hospital discharge after acute myocardial infarction. (Source: Adapted with permission from Fonarow GC, French WJ, Parsons LS, Sun H, Malmgren JA, for the National Registry of Myocardial Infarction 3 Participants. Use of lipid-lowering medications at discharge in patients with acute myocardial infarction. Data from the National Registry of Myocardial Infarction 3. Circulation 2001;103:38-44.)

He shows no evidence of MI, diabetes mellitus, hypertension, or stroke. His blood pressure (130/78 mm Hg) is near the upper limit of the acceptable range, and he is considerably overweight (163 pounds with a BMI of 29), though not obese.7 Aside from a cholecystectomy scar, the findings of the physical examination are within normal limits. However, his lipid profile includes the following values: TC, 226 mg/dL; HDL-C, 29 mg/dL; LDL-C, 149 mg/dL; and triglycerides, 309 mg/dL. His liver function tests show slightly elevated levels of serum aspartate transaminase (AST), 48 U/L, and alanine transaminase (ALT), 67 U/L. Based on the most recent criteria for the diagnosis of diabetes mellitus, his fasting glucose level of 114 mg/dL would be classified as impaired fasting glucose.

Risk evaluation
This patient represents another case in which standard treatment guidelines do not clearly show whether lipid intervention is warranted. Viewed globally, the abnormalities in his lipid profile along with his positive family history suggest considerable cardiovascular risk. Yet, by strict interpretation of the NCEP ATP II guidelines, his LDL-C level of 149 mg/dL is below the cutpoint of 160 mg/dL for a patient without established CHD and having fewer than two risk factors.1 Nevertheless, each risk factor must be weighed within the entire clinical context. For example, this patient has a significant family history of diabetes mellitus and vascular disease. Asians are one of several ethnic groups that are particularly susceptible to type 2 diabetes mellitus.7 In addition, this patient’s recent history of chest pain suggests possible myocardial ischemia. His lipid profile, including average LDL-C, low HDL-C, and high triglyceride levels, suggests a high atherogenic potential. In addition, moderate hypertriglyceridemia and low HDL-C levels (as seen in this patient) are often associated with the presence of small, dense LDL-C particles that are highly atherogenic and predictive of cardiovascular disease.8 Together, these lipid abnormalities are a significant cause for concern.

It should also be noted that this type of lipid profile is commonly observed in patients with insulin resistance associated with the metabolic syndrome.7 Patients with this syndrome typically present with a constellation of major risk factors, including insulin resistance and atherogenic dyslipidemia that contribute independently to the risk of cardiovascular disease.7

As previously noted, this patient already has an impaired fasting glucose level; the patient’s hemoglobin A1c level is 5.9% (the upper limit of normal), confirming his tendency toward insulin resistance and eventually overt diabetes mellitus. Because hyperglycemia and insulin resistance increase cardiovascular risk,9 the American Heart Association (AHA) recommends aggressive intervention in patients who have both poor glycemic control and other risk factors—even in patients whose LDL-C levels are borderline high risk (130 mg/dL to 159 mg/dL), or whose lipid profile is typical of diabetes mellitus. Moreover, the AHA emphasizes that, “a genetic basis for risk, as revealed by a positive family history of CVD [cardiovascular disease] or diabetes, may point to the need for pharmacological control of risk factors.” This patient’s family history is positive for a first-degree relative with diabetes mellitus, and a first-degree male relative with cardiovascular disease before age 55 years.7

Intervention and outcomes
An important new feature of the recently released NCEP ATP III guidelines is the focus on primary prevention in patients with multiple risk factors, includ-
ing those with the metabolic syndrome and diabetic dyslipidemia, comparable to the patient described in case 2. A checklist of clinical considerations for the diagnosis and treatment of diabetic dyslipidemia and prevention of atherosclerosis is presented in Figure 2. The guidelines specify that patients with the metabolic syndrome should be identified as candidates for intensified therapeutic lifestyle changes, including weight reduction and increased physical activity. In addition, LDL-C reduction remains the primary target of therapy in patients with the metabolic syndrome. An important distinction between the NCEP ATP II and III guidelines is the classification of diabetes mellitus as a CHD risk equivalent with a corresponding recommendation to lower LDL-C to levels below 100 mg/dL in patients with this condition. Additional recommendations of the ATP III guidelines include lowering the triglyceride goal to approximately below 150 mg/dL and treatment beyond lowering LDL-C in patients whose triglyceride levels exceed 200 mg/dL.

Therefore, a rational first step in the long-term care of this patient is referral to a nutritionist for advice on a low-fat, low-carbohydrate diet to control his lipid levels. He is also advised to begin a program of regular exercise for improving his low HDL-C levels. In addition, he is switched from cerivastatin sodium, 0.4 mg/d, to atorvastatin calcium, 40 mg/d, to achieve greater reductions in LDL-C and triglyceride levels. His low-dose niacin therapy is discontinued.

As a result of concerns over this patient’s elevated AST and ALT levels and the potential for statin therapy to be associated with such abnormalities, he is referred for additional blood testing and an abdominal ultrasound study. The results reveal no hepatitis B or C but show fatty infiltration of the liver (non-alcoholic steatohepatitis), which is consistent with the clinical picture of many patients with obesity, insulin resistance, and hypertriglyceridemia. This finding is likely to (1) account for his abnormal values on liver function tests, (2) essentially rule out any relationship to the drug therapy, and (3) should not preclude initiation of more intensive lipid-lowering medication.

Three months after initiating his lifestyle modifications and switching statins, the patient shows marked improvement in his lipid profile, which includes TC level of 184 mg/dL, LDL-C level of 97 mg/dL, triglyceride level of 240 mg/dL, and HDL-C level of 32 mg/dL. Although these changes represent progress, his HDL-C level remains lower than optimal and his triglyceride level is still unacceptably high. To bring these values within the normal range, gemfibrozil, 600 mg twice daily, is added to his daily regimen.

After an additional 3-month interval, this change in medication produces a modest reduction in TC level, from 184 mg/dL to 177 mg/dL, but a dramatic decrease in the triglyceride level, from 240 mg/dL to 159 mg/dL. His HDL-C levels increase slightly to 35 mg/dL, but his LDL-C levels also increase by a small margin to 110 mg/dL, which is not uncommon when fibrate therapy is introduced. It is also important to note that the results of his liver function tests have normalized, most likely because his dyslipidemia and insulin resistance are better controlled.

At this point, several options are considered to further reduce his risk. These include adjusting the dose of atorvastatin to restore his LDL-C to below the target level of 100 mg/dL, switching to an ACE inhibitor, or adding a thiazolidinedione. His physician opts to raise the dose of atorvastatin calcium to 80 mg/d, which after 3 months further improves his lipid profile. His LDL-C levels decrease to 99 mg/dL, accompanied by further reductions in TC (165 mg/dL) and triglycerides (140 mg/dL), and his HDL-C level increases to 38 mg/dL. His liver function remains normal.

Figure 2. Clinical considerations for the diagnosis and treatment of diabetic dyslipidemia and prevention of atherosclerosis.

- Figure 2. Clinical considerations for the diagnosis and treatment of diabetic dyslipidemia and prevention of atherosclerosis.
**Long-term outcome**

After 1 year on atorvastatin and gemfibrozil combination therapy, the patient remains healthy, with a weight loss of 13 pounds and a decrease in blood pressure to 122/76 mm Hg. His lipid profile actually improved even further (TC, 151 mg/dL; HDL-C, 40 mg/dL; LDL-C, 86 mg/dL; and triglycerides, 122 mg/dL), a testament to the benefits of weight reduction in addition to intensive pharmacologic therapy. His fasting blood glucose levels are also normalized.

This case illustrates two important points in the care of dyslipidemic patients: first, a clustering of mild metabolic derangements can add up to significant global risk, warranting aggressive intervention. In this patient, the risk factors included transient chest pain, early signs of insulin resistance, and moderate dyslipidemia in addition to a family history suggestive of vascular disease. Second, a treatment plan designed for primary prevention of CHD may require not only targeted dietary restrictions and exercise to reduce body weight, but also combination lipid-lowering therapy to normalize hyperlipidemia.

Other preventive options include omega-3 fatty acid supplementation, thiazolidinediones to enhance insulin sensitization (and potentially to lower triglyceride levels), and ACE inhibitors to control blood pressure and slow the progression of diabetes. According to the AHA...

...in patients with insulin resistance, the “clock starts ticking” for acceleration of atherogenesis long before the onset of hyperglycemia. Thus, early detection of risk factors associated with the metabolic syndrome is needed for institution of appropriate primary prevention measures in patients at risk for diabetes.

**References**


