Target Audience
This educational activity is designed to meet the needs of cardiologists treating at-risk patients for cardiac risk factors.

Statement of Need/Program Overview
Evidence in the existing literature indicates most emerging risk factors are not independently related to the risk of recurrent cardiovascular disease. However, some of these risk factors may be associated with increased risk of cardiac disease in patients already at risk. Even so, it has not been proven that lowering levels is associated with a significant decrease in the incidence or mortality of heart disease. Many of the assays/tests used to determine these levels are not standardized; accuracy, sensitivity, specificity, and predictive values have not been firmly established in the medical literature. In general, when comparing predictive values of the emerging risk factors with traditional measurements, some of the emerging risk factors have predictive value that is considered comparable, although some are not as predictive. For several of these emerging risk factors there is no consensus among authors towards identifying targeted therapy and if targeted therapy reduces risk and improves clinical outcomes when compared with the traditional evaluation and therapy. As a result, there is little agreement among authors regarding recommendations for performing any of the emerging cardiac risk factors as part of the routine risk assessment for the general population or as part of advanced lipid testing for those who may be at increased risk. There remains a need for continued discussion and additional evidence regarding advanced lipid testing. This activity focuses on a review of a series of patient case studies to further support this dialogue in the cardiology community.

Educational Objectives
After completing this activity, the participant should be better able to:
- Identify patients with emerging cardiac risk factors who would benefit most from advanced lipid testing
- Review guidelines for the evaluation and treatment of patients with cardiac risk factors
- Explain the clinical utility of traditional evaluation as well as treatment with advanced testing and targeted therapy

Physician Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Global Education Group (Global) and MRCME. Global is accredited by the ACCME to provide continuing medical education for physicians.

*This CME/CE activity complies with all requirements of the federal Physician Payment Sunshine Act. If a reportable event is associated with this activity, the accredited provider managing the program will provide the appropriate physician data to the Open Payments database.

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PC	MAC
Microsoft Windows 2000 SE or above.	MAC OS 10.2.8
Flash Player Plugin (v7.0.1.9 or greater)	Flash Player Plugin (v7.0.1.9 or greater)
Internet Explorer (v5.5 or greater), or Firefox	Safari
Adobe Acrobat Reader*	Adobe Acrobat Reader*
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Name of Faculty or Presenter	Reported Financial Relationship
Karol E. Watson, MD, PhD, FACC, FAHA	**Consultant/Independent Contractor:** Merck, Daiichi-Sankyo, Quest **Honoraria:** Merck, Daiichi-Sankyo, Quest
Eric H. Stocker, MD, FACC	**Speaker's Bureau:** Quest, Merck, Boston Heart Diagnostics
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Peter A. McCullough, MD, MPH, FACC, FAHA, FCCP, FNKF, FNLA	Nothing to disclose

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Ashley Marostica, RN, MSN	Nothing to disclose
Amanda Glazar, PhD	Nothing to disclose
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Advanced Lipid Testing: When, Why, and In Whom?
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Advanced Lipid Testing: When, Why, and In Whom?

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Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality in developed countries. The management of blood cholesterol with the use of statin drugs in at-risk patients is a pillar of medical therapy for the primary and secondary prevention of cardiovascular disease. Although the standard lipid panel is adequate to accurately assess cardiovascular disease risk in most patients, there are some situations in which conventional cholesterol testing does not fully identify cardiovascular risk or reflect disease progression. A number of advanced lipid tests can assist the clinician when assessing a patient's cardiovascular disease risk, including measurement of low-density lipoprotein particle number.

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KEY WORDS

Atherosclerotic cardiovascular disease • Risk • Low-density lipoprotein cholesterol • Low-density lipoprotein particle number • Statin therapy

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality in developed countries.[1] The management of blood cholesterol with the use of statin drugs in at-risk patients is a pillar of medical therapy for the primary and secondary prevention of cardiovascular disease. The standard lipid panel, measuring total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides,[2] has helped clinicians accurately assess heart disease risk for years. Although the standard lipid panel is adequate to accurately assess cardiovascular disease risk in most patients, there are some situations in which conventional cholesterol testing does not fully identify cardiovascular risk or reflect disease progression.

Lipoproteins are complex particles containing proteins, cholesterol, and phospholipids.[3] The standard

lipid panel typically provides information on cholesterol content from all dissolved particles, but not information on the protein component, the total size, or the number of lipoprotein particles. Typically reported on standard lipid panels are levels of total cholesterol (from all dissolved particles), LDL-C, HDL-C (by precipitation), and triglycerides (from all dissolved particles). What some clinicians and many patients may not realize is that the LDL-C value reported on most standard lipid panels is a calculated LDL-C, and not directly measured. LDL-C is calculated using the Friedewald equation,[4] which subtracts the sum of HDL-C plus triglycerides from the total cholesterol value and divides the result by 5. The Friedewald equation is a reasonable estimate of LDL-C in many situations; however, in the presence of other complications, such as metabolic syndrome, hypertriglyceridemia, and renal failure, it can be inaccurate. If a clinician wants the actual measured quantity of LDL-C to be reported, a direct LDL-C measurement should be requested.

What some clinicians and many patients may not realize is that the LDL-C value reported on most standard lipid panels is a calculated LDL-C, and not directly measured.

Key lipoprotein parameters are also absent from the standard lipid profile report, such as information about the apoproteins; the total size and number of lipoprotein particles; measures of cell signaling; and other blood elements of cardiovascular risk demonstrated in the literature.

Case 1

The patient is a 52-year-old woman; she is 160.02 cm in height and weighs 120 pounds. Her body mass index (BMI) is 21.3 kg/m^2. She describes herself as very physically active and adheres to a diet that is low in saturated fat and cholesterol, although she admits to having a "sweet tooth." She exercises daily and denies use of tobacco products. Her father had a myocardial infarction (MI) at age 52 years. She indicated that her father was "the picture of health" and had no bad habits; therefore, the family was shocked at his sudden death. She expressed concern that she may be at risk of a heart attack, as well.

Her mother is alive and healthy. The patient is employed as a physical therapist; because of her concern of her father's premature death (at the age she is now), she is seeking an opinion with regard to cardiovascular risk prevention.

Her past medical history includes infertility, reactive hypoglycemia, and hypothyroidism; she is currently taking oral levothyroxine, 175 µg/d. Her physical examination revealed a blood pressure of 114/70 mm Hg, a pulse rate of 56 beats/min, a body temperature of 36.2°C, and a respiration rate of 16 breaths/min. A Grade 1/6 midsystolic murmur was heard at the base of the heart with little radiation. A fasting lipid panel revealed a total cholesterol level of 192 mg/dL, a calculated LDL-C of 104 mg/dL, an HDL-C of 77 mg/dL, a triglyceride level of 56 mg/dL, and a non–HDL-C value of 115 mg/dL.

In November 2013, the American College of Cardiology/American Heart Association (ACC/AHA) published guidelines on the treatment of blood cholesterol to reduce ASCVD risk in adults.[5] An important concept in the new guidelines is the absence of set LDL-C targets. Instead, the guidelines recommend that the four statin-benefit groups be treated with the recommended intensity of statin therapy. The four statin benefit groups are as follows:

1. Individuals with clinical ASCVD (acute coronary syndrome, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin)
2. Individuals with primary elevations of LDL-C ≥ 190 mg/dL
3. Individuals age 40 to 75 years with diabetes, LDL-C 70-189 mg/dL, but no clinical ASCVD
4. Individuals without clinical ASCVD or diabetes, age 40 to 75 years with LDL-C 70 to 189 mg/dL, and have an estimated 10-year ASCVD risk of 7.5% or higher

The new ASCVD pooled cohorts equation risk estimator recommended by the ACC/AHA guidelines is designed with the aim to better model populations likely to benefit from statin therapy for primary prevention.[6] With this estimator, the risk factors that are input include age, sex, African American ethnicity, total cholesterol, HDL-C, systolic blood pressure, use of antihypertensive therapy, diabetes, and current tobacco use. The estimator then calculates a 10-year risk of cardiovascular death, MI, and stroke. Individuals between the ages of 40 and 79 years with a 10-year risk of at least 7.5% for an ASCVD event are considered likely to benefit from statin therapy. For patients

Individuals between the ages of 40 and 79 years with a 10-year risk of at least 7.5% for an ASCVD event are considered likely to benefit from statin therapy.

with risk levels between 5.0% and 7.5%, consideration may be given to statin therapy.

Because our patient does not fall into the first three statin benefit groups, we progress to the fourth statin benefit group (the primary prevention group) and estimate her 10-year ASCVD risk using the 2013 ACC/AHA guidelines. Her 10-year risk is estimated to be 0.8%, and her lifetime ASCVD risk is estimated to be 27%.

When the patient returns for follow-up, she is told that her cardiovascular assessment revealed that she is in good cardiovascular health and it appears that all of her cardiovascular risk factors are well controlled. She, however, is not convinced. She states that her father also was considered to be in good health, and had seen his own doctor shortly before his death. Because it is clear that her father harbored some unseen and undetected cardiovascular risk, she asks what else can be examined.

A recent consensus statement from the American Diabetes Association (ADA)[7] and the ACC suggests that direct LDL-C measurements are better than calculated measures. The ADA statement further states that for risk assessment, measurement of LDL particle number (LDL-P) is better than only measuring LDL-C, as LDL-P is a better predictor of cardiovascular risk than LDL-C alone.

Many patients have concordant levels of LDL-C and LDL-P,[8] meaning that when one level is high, the other level is also high, and vice versa. Interesting research, however, has been performed evaluating individuals who have discordant levels of LDL-C and LDL-P; these are individuals who may have the exact same LDL-C level, but very different LDL-P numbers. For example, one patient could have an LDL-C level of 100 mg/dL and 100 large LDL particles. A different patient may also have an LDL-C level of 100 mg/dL, but this patient could have 1000 small LDL particles. Which patient is at greater risk? Evidence has shown that the patient with higher LDL-P is at greater risk. The relationship between LDL-C level and LDL-P number has been known for many years. In 1967, Fredrickson and colleagues said, "LDL particles are the causal agents in atherosclerosis…The more LDL particles a person has, the higher the risk of plaque buildup that causes heart attacks, regardless of how much cholesterol those particles carry."[9]

The ADA in a consensus statement relates that, "the mean concentration of LDL cholesterol in those [patients] with type 2 diabetes is not significantly different from that in those individuals who [do] not have diabetes. However, qualitative changes in LDL cholesterol may be present…Patients with diabetes tend to have higher proportions of smaller and denser LDL-P, which is more susceptible to oxidation and may, therefore, increase the risk of cardiovascular events in atherosclerosis."[7]

Analysis of data from the Framingham Heart Study demonstrated a discordant relationship between LDL-C and LDL-P in that patients with high LDL-C (and low LDL-P) had relatively less risk for a poor outcome (measured as event-free survival) when compared with patients with a low LDL-C but high LDL-P.[10]

Data from the Multi-Ethnic Study of Atherosclerosis (MESA), which evaluated carotid atherosclerosis, demonstrated that, although carotid atherosclerosis risk was lower in individuals whose LDL-C was normal ($<$ 100 mg/dL) when coincident with a low LDL-P number (first quartile [Q1]), as LDL-P numbers became progressively higher (Q2 through Q4) carotid atherosclerosis risk continued to climb in a statistically significant trend.[8]

There are a number of advanced lipid tests that can assist the clinician when assessing a patient's cardiovascular disease risk, in particular, measurement of LDL-P. These advanced lipid tests generally utilize one of four different technical methods. These methods are gradient gel electrophoresis, the vertical automated profile method, nuclear magnetic resonance (NMR) spectroscopy, and ion mobility shift.[11–14]

Gradient Gel Electrophoresis

Gradient gel electrophoresis separates different lipoprotein particles based on their electrophoretic sizes using polyacrylamide gradient gels. Unlike the conventional lipid profile, it does not destroy particles in order to measure cholesterol and triglyceride levels. This method gives a relative distribution of lipoprotein particles.[11]

Vertical Automated Profile

This method is also called density-gradient ultracentrifugation. It measures the relative distribution of cholesterol within various lipoprotein subfractions, quantifying the cholesterol content of very low-density lipoprotein (VLDL), intermediate-density lipoprotein, LDL-C, lipoprotein(a), and HDL-C subclasses.[12] As with gradient gel electrophoresis, the particles remain intact and the assay is run using serum or plasma.

NMR Spectroscopy

This technique relies on NMR phenomena. Particles and lipoproteins of different sizes emit different NMR signals. Lipoprotein particles can be separated based on these signals.[13]

Ion Mobility Analysis

Ion mobility analysis is a relatively new method that measures both the

size and concentrations of lipoprotein particle subclasses on the basis of differential electric mobility.[14]

Advanced Lipid Panel

This patient underwent advanced lipid testing; the results revealed an LDL-P of 2100 nmol/L, a calculated LDL-C level of 106 mg/dL, an HDL-C level of 64 mg/dL, a triglyceride level of 103 mg/dL, and a total cholesterol value of 191 mg/dL.

The patient has a very elevated LDL-P number (optimal is $<$ 1000 nmol/L), despite having what appears to be a near optimal LDL-C level. Many different studies have shown that LDL-P is as good as, if not better than, LDL-C in predicting cardiovascular disease risk. Although we will never know, it is likely that the patient's father had a similar lipid abnormality, which led to his premature death. Given her severely elevated LDL-P and her family history of premature coronary heart disease, the physician and the patient mutually agree to begin statin therapy. She is started on moderate-intensity statin therapy, and follow-up is arranged in 6 weeks. She is also counseled to continue her current exercise patterns and to reduce her intake of simple sugars. At her follow-up appointment, the following laboratory values were obtained: LDL-P count, 1100 nmol/L; calculated LDL-C level, 76 mg/dL; HDL-C level, 66 mg/dL; triglyceride level, 53 mg/dL; and total cholesterol count, 153 mg/dL. This patient illustrates an example of a hidden cardiovascular risk that was uncovered with advanced lipid testing.

Case 2

A 48-year-old white man presents to his primary care physician for his annual wellness examination. His goal for the visit is to discuss his risk of a heart attack, because multiple family members had heart attacks in their 50s. His family history of premature atherosclerosis worries him. His father had an MI at age 52, although his father did not exercise and smoked; his paternal uncle had a heart attack at age 55, and his older brother had a stent placed at age 51. There is no cardiovascular disease on his mother's side of the family.

On his last visit almost 1 year prior, a lipid panel revealed the following: total cholesterol, 234 mg/dL; LDL-C, 136 mg/dL; HDL-C, 34 mg/dL; triglycerides, 320 mg/dL; and glucose, 102 mg/dL. He did not have known coronary artery disease or diabetes. At that time, his ASCVD pooled cohorts equation estimated risk was 5.1% over the next 10 years, with a lifetime risk of 45.5%. The ACC/AHA guidelines were discussed with the patient, indicating that with an estimated risk of $<$ 7.5%, treatment was deemed optional and needed to be individualized (although the new guidelines do state that with an estimated risk of between 5% and 7.5%, treatment is reasonable). The patient was hesitant to begin medication at this time and preferred additional risk assessment to determine whether or not he would benefit from taking a statin. Consistent with the guidelines, a coronary artery calcium (CAC) score was obtained by computed coronary tomographic angiography. The CAC score was 173, which is greater than the 75th percentile of risk for his age, race, and sex, and clearly identifies the presence of mild coronary atherosclerosis. On the basis of these results, the patient was placed on aspirin, 81 mg/d, and atorvastatin, 40 mg/d.

Over the past year, he has done well, and reports no medication side effects. With respect to lifestyle, he exercises three times per week for 20 minutes using a treadmill or stationary bike at a health club. He does not monitor his heart rate, but does break a mild sweat with his workout. While exercising, he has no cardiovascular symptoms, and no chest pain or difficulty breathing. He watches his diet, though acknowledges room to improve. He has never smoked, and drinks approximately three glasses of wine per week.

On examination, his blood pressure is 128/78 mm Hg. His heart rate is 72 beats/min, and his BMI is 25 kg/m^2, which is stable from the previous year. His physical examination results are normal; he has clear lungs and a regular heart rhythm with no murmurs, rubs, or gallops. No edema is present.

Recent fasting laboratory values on oral atorvastatin, 40 mg/d, include a total cholesterol count of 139 mg/dL, an LDL-C of 73 mg/dL, an HDL-C of 36 mg/dL, and a triglyceride level of 130 mg/dL. The patient's brother recently had a second stent placed because of an acute coronary syndrome, which he developed while being treated with atorvastatin, 40 mg/d; thus the patient is still concerned about his own risk and whether or not it is being adequately treated. The decision was made, therefore, to order advanced lipid testing. The results reveal an LDL-P of 1730 nmol/L; on the basis of this elevated LDL-P count, his statin dose was intensified to 80 mg/d to further reduce residual risk.

This case illustrates another example in which the results of advanced lipid testing were used to tailor lipid-lowering therapy. The 2013 ACC/AHA guidelines do an excellent job identifying four groups of patients for which statin therapy is beneficial to reduce risk. However, it does not give guidance on when or how to intensify statin therapy based on advanced laboratory parameters. The guidelines leave significant responsibility to the individual clinician and patient with regard to primary prevention

treatment decisions. For patients whose estimated cardiovascular risk is < 7.5%, the guidelines suggest individualizing the decision based on a multitude of factors, especially patient preference.

Case 2 provides an example of the decisions many clinicians face. The patient clearly has high lifetime risk, and is very concerned about maximally reducing his risk. The pooled cohort equation estimates his risk at approximately 5%, but this is not reassuring given his high lifetime risk.

In men over age 40, and women over age 50, the CAC score is a very powerful independent risk factor because it detects coronary atherosclerosis.

The first decision the clinician needs to make with the patient is whether to treat the patient with a statin. The decision was made to obtain a CAC score in order detect underlying atherosclerosis and to further refine his ASCVD risk. The guidelines state that the following factors may be used to help refine risk in cases in which the risk is still unclear: (1) primary LDL-C > 160 mg/dL or other evidence of genetic hyperlipidemias; (2) family history of premature ASCVD with onset at age < 55 years in a first-degree male relative or age < 65 years in a first-degree female relative; (3) high-sensitivity C-reactive protein (hsCRP) ≥ 2 mg/L; (4) CAC score ≥ 300 Agatston units or ≥ 75th percentile for age, sex, and ethnicity, indicating the presences of coronary atherosclerosis; (5) ankle brachial index < 0.9, indicating peripheral arterial atherosclerosis; and (6) elevated lifetime risk of ASCVD.

In men over age 40, and women over age 50, the CAC score is a very powerful independent risk factor because it detects coronary atherosclerosis. An abnormal score is found in more than 15% of adult patients, even those without any traditional risk factors, and the score correlates strongly with risk of cardiovascular events, including mortality, because coronary atherosclerosis is the anatomic substrate. Once an elevated score is obtained, the patient should be managed in a similar manner to other patients on statin therapy. Although not listed in the guidelines, other reasonable tests to help guide this initial decision on whether to treat a patient with a lower estimated cardiovascular risk may include advanced laboratory values (including apolipoprotein B, LDL-P, lipoprotein (a), hsCRP, and lipoprotein phospholipase A2 (mass and activity). In addition, the detection of subclinical atherosclerosis using CAC and computed tomography, carotid ultrasound for intima-media thickness and atherosclerotic plaques, and ankle brachial-index for peripheral arterial disease is very useful in educating and guiding patients on risk and risk modification. In general, the detection of subclinical atherosclerosis is more powerful than any individual risk factor in determining the future risk of cardiovascular events.

Once a decision has been made to treat a patient with a statin, beyond monitoring basic lipid profiles, clinicians may use advanced laboratory parameters to further identify dynamic risk and progression of disease. The example given in Case 2 relies on LDL-P. LDL-C and LDL-P commonly are discordant in the setting of cardiometabolic syndrome and elevated triglycerides. Evidence suggests that when the two LDL measures are discordant, the LDL-P more accurately predicts a patient's future risk of a cardiovascular event than the more commonly monitored LDL-C.

Evidence suggests that when the two LDL measures are discordant, the LDL-P more accurately predicts a patient's future risk of a cardiovascular event than the more commonly monitored LDL-C.

Case 3

The patient is a 51-year-old Hispanic man with an unremarkable past medical history, with the exception of an anxiety disorder. He was referred for cardiac evaluation due to a markedly abnormal result of a cardiac coronary calcium scan, which was ordered by his family physician due to a strong family history of coronary artery disease. His CAC score was 698, which placed him at the 98th percentile for age and sex. As a general heuristic, CAC scores > 400 indicate a very high probability of at least one significant coronary lesion with provocable ischemia in the subtended myocardium. He reports no cardiac symptoms, and he exercises regularly and vigorously. His only cardiac risk factor is his age. Both his Framingham Risk Score and Reynolds Risk Score place his 10-year risk of having a MI or cardiovascular death at 3%.

He reports no other significant medical or surgical history other than cholelithiasis, for which he underwent cholecystectomy. His family history is notable for two sisters who underwent coronary artery bypass graft surgery, one at age 65, and the other at age 67. The patient reports high work and family stress, and consumes a low-fat diet. His review of symptoms is notable only for snoring and

anxiety. His current medications include over-the-counter fish oil, 1000 mg/d; escitalopram, 5 mg/d; a daily multivitamin; and ursodeoxycholic acid, 300 mg/d. He has no drug allergies. His physical examination reveals a resting pulse of 61 beats/min, a blood pressure of 140/72 mm Hg, and a BMI of 23.5 kg/m^2. His cardiovascular examination results are completely normal. His standard lipid panel reveals a total cholesterol level of 170 mg/dL, a triglyceride level of 74 mg/dL, an HDL-C of 60 mg/dL, a calculated LDL-C of 95 mg/dL, a calculated VLDL-C of 15 mg/dL, and a total cholesterol/HDL-C ratio of 2.8. His hsCRP level is $<$ 0.2 mg/L. His 10-year risk is estimated at 3.0%, and his lifetime ASCVD risk is estimated at 46%. The patient underwent stress echocardiography and there was no evidence of stress-induced ischemia at a high work rate ($>$ 10 metabolic equivalents).

Because of the presence of coronary atherosclerosis, despite the unremarkable standard lipid profile, advanced lipid testing is obtained and reveals an LDL-P number of 1267 nmol/L and an apolipoprotein B value of 116 mg/dL. The results of this patient's advanced lipid testing are concordant with the results of his standard lipid panel. In this case, the clinician and the patient jointly decide to initiate a lower-potency statin (oral pravastatin, 40 mg/d) given the presence of atherosclerosis and reasonable lipid values. His risk will be reassessed on a regular basis.

Conclusions

The three cases illustrate potential situations in which advanced lipid testing may prove useful. Lipoproteins are very complex molecules containing proteins, cholesterol, and phospholipids. Standard lipid panels provide important clinical information as a starting point, but they do not provide the complete picture. Additional information beyond the standard lipid panel is sometimes needed to adequately assess risk, and advanced lipid testing can provide additional information that may help the clinician to better define risk and understand the etiology of premature atherosclerosis, and may provide inferences on dynamic risk and disease progression over time. Advanced lipid testing can be useful in select patients.

Additional information beyond the standard lipid panel is sometimes needed to adequately assess risk, and advanced lipid testing can provide additional information that may help the clinician to better define risk and understand the etiology of premature atherosclerosis, and may provide inferences on dynamic risk and disease progression over time.

When: When additional risk assessment/stratification is needed.

Why: Lipid parameters available on advanced testing, but not standard testing—such as LDL-P—are better for risk stratification than LDL-C.

In Whom: In patients suspected of having hidden atherosclerosis risk, who have detected asymptomatic atherosclerosis despite acceptable standard profiles, and in those with

MAIN POINTS

- Management of blood cholesterol with the use of statin drugs in at-risk patients is a pillar of medical therapy for the primary and secondary prevention of cardiovascular disease. The standard lipid panel has helped clinicians accurately assess heart disease risk for years; however, there are some situations in which conventional cholesterol testing does not fully identify cardiovascular risk or reflect disease progression.
- Calculated low-density lipoprotein cholesterol (LDL-C) is sufficient in many situations; however, in the presence of other complications, such as metabolic syndrome, hypertriglyceridemia, and renal failure, it can be inaccurate.
- In 2013, new American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults were published. An important concept in the new guidelines is the absence of set LDL-C targets. Instead, the guidelines recommend that four statin-benefit groups be treated with the recommended intensity of statin therapy.
- The American Diabetes Association statement indicates that for risk assessment, measurement of LDL particle number (LDL-P) is better than only measuring LDL-C, as LDL-P is a better predictor of cardiovascular risk than LDL-C alone.

family histories of unexplained premature atherosclerosis. ■

Dr Watson is a Consultant/Independent Contractor for Merck, Daiichi-Sankyo, and Quest, and has received honoraria from Merck, Daiichi-Sankyo, and Quest. Dr Jacoby is a Consultant/Independent Contractor for Quest. Dr Stocker is on the Speaker's Bureau for Quest, Merck, and Boston Heart Diagnostics. Dr McCullough has no real or apparent conflicts of interest to disclose.

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Instructions to Receive Credit
In order to receive credit for this activity, the participant must complete the post-test available online at www.mrcme-online.com.

I am a: ☐MD ☐DO ☐PharmD ☐RN ☐NP ☐PA ☐Other _____

Upon completion of this activity, participants will be able to:	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**
• Identify patients with emerging cardiac risk factors who would benefit most from advanced lipid testing	1	2	3	4
• Review guidelines for the evaluation and treatment of patients with cardiac risk factors	1	2	3	4
• Explain the clinical utility of traditional evaluation as well as treatment with advanced testing and targeted therapy	1	2	3	4
Please indicate the extent of your agreement with the following statements:	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**
• This activity was effective	1	2	3	4

- Overall, was this activity free from bias?
  - Yes
  - No
- Of the patients you will see in the next week, about how many will benefit from the information you learned today?
  - More than 50
  - 26 to 50
  - 11 to 25
  - 1 to 10
  - Not applicable
- Based on what I learned in this activity, I will improve my practice by incorporating the following (check all that apply):
  - Improved diagnosis/patient assessment
  - Useful therapies and appropriate uses
  - Cutting-edge science in this therapeutic area
  - Best practices of my colleagues and leaders
  - I do not plan to make any changes to my practice at this time
  - Other (explain) _____
- Which ONE delivery method do you find the most effective for CME/CE learning?
  - Live symposia at national/regional conferences
  - Live local meetings
  - Live grand rounds
  - Internet webcasts
  - Internet/print monographs
  - Other (explain) _____
- Please rate the professional practice value of each of the following in terms of improving your practice:

	Least Valuable	**Somewhat Valuable**	**Valuable**	**Most Valuable**
This CME activity	1	2	3	4
Direct to consumer advertising	1	2	3	4
Sales representative visits	1	2	3	4
Promotional/other noncertified education	1	2	3	4

- Based on your experience, which of the following are the primary barriers to implementing changes in practice (check all that apply):
  - Lack of knowledge regarding evidence-based strategies
  - Lack of convincing evidence to warrant change
  - Lack of time/resources to consider change
  - Insurance, reimbursement, or legal issues
  - Other (explain)
- What motivated you to participate in this activity?
  - CME credits
  - Faculty
  - Topic or therapeutic area
  - Format type

SELF-ASSESSMENT POST-TEST

Advanced Lipid Testing: When, Why, and In Whom?

In order to receive credit, participants must complete the post-test electronically by visiting mrcme-online.com and entering code card005 to access the post-test.

1. The low-density lipoprotein cholesterol (LDL-C) value provided in a standard lipid panel report is almost always calculated, rather than directly measured.
- **a.** True
- **b.** False

2. A seminal component of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk (ASCVD) is
- **a.** the addition of four major statin benefit groups
- **b.** an estimator to calculate 10-year risk of ASCVD
- **c.** the absence of set LDL-C target values
- **d.** all of the above
- **e.** none of the above

3. A very physically active 52-year-old woman presents with concerns regarding her risk of a heart attack. She reveals that her father had a myocardial infarction (MI) at age 52 years, although he was described as being "the picture of health." A fasting lipid panel revealed a total cholesterol level of 192 mg/dL, a calculated LDL-C of 104 mg/dL, a high-density lipoprotein cholesterol (HDL-C) value of 77 mg/dL, a triglyceride level of 56 mg/dL, and a non–HDL-C value of 115 mg/dL. Her 10-year ASCVD risk is estimated to be 0.8%, using the 2013 ACC/AHA guidelines. Although the patient's risk is very low, her father likely harbored unseen and undetected cardiovascular risk. What is the next best course of treatment for this patient?
- **a.** Do nothing further
- **b.** Initiate low-intensity statin therapy immediately
- **c.** Order advance lipid testing, including measurement of LDL particle (LDL-P) number
- **d.** Recommend she reduce her intake of simple sugars

4. Research has been performed evaluating individuals who have discordant levels of LDL-C and LDL-P. Patient #1 has an LDL-C level of 100 mg/dL and 100 large LDL particles. Patient #2 also has an LDL-C level of 100 mg/dL, but this patient has 1000 small LDL particles. Which patient is at greater risk of ASCVD?
- **a.** Patient #1
- **b.** Patient #2
- **c.** Both patients have the same risk

5. A 48-year-old white man presented to his primary care physician to discuss his risk of a heart attack because multiple family members had heart attacks in their 50s. One year prior, his ASCVD pooled cohorts equation estimated risk was 5.1% over the next 10 years. According to the ACC/AHA guidelines, with an estimated risk of $< 7.5\%$, treatment is deemed optional and must be individualized. The patient was hesitant to begin medication at this time and requested additional risk assessment to determine whether he would benefit from statin therapy. His coronary artery calcium score was 173, and clearly identified the presence of mild coronary atherosclerosis; he was placed on aspirin, 81 mg/d, and atorvastatin, 40 mg/d. The patient's brother developed an acute coronary syndrome while on the same dosage of atorvastatin; therefore, the patient expressed concern that his own risk was not being adequately addressed. Advanced lipid testing revealed an LDL-P of 1730 nmol/L. What is the most appropriate course of treatment for this patient?
- **a.** Add niacin
- **b.** Evaluate the patient for stent placement
- **c.** Increase the atorvastatin regimen to 80 mg/d
- **d.** Decrease the atorvastatin regimen to 20 mg/d

6. Based on data from the Framingham Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Veterans Affairs High-Density Lipoprotein Intervention Trial, advanced lipid testing—notably measurement of LDL-P—has proven to be a less accurate indicator of cardiovascular disease/cardiometabolic risk for many patients than LDL-C alone.
- **a.** True
- **b.** False

7. What is considered an optimal LDL-P number by the American Diabetes Association guidelines?
- **a.** > 1000 nmol/L
- **b.** < 2000 nmol/L
- **c.** > 1200 nmol/L
- **d.** < 1000 nmol/L