Clinical Feature:
Carotid IMT in Clinical Practice
—Thomas A. Barringer, MD, FNLA

In this issue
• Dietary Adjuncts in Dyslipidemia Management • Foundation of the NLA Grants
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Prevention in the Spotlight

At the end of September, two major statements on prevention were published in the Journal of the American College of Cardiology (and co-published in Circulation), the ACCF/AHA/ACP 2009 Competence and Training Statement: A Curriculum on Prevention of Cardiovascular Disease and the ACCF/AHA 2009 Performance Measures for Primary Prevention of Cardiovascular Disease in Adults.

Over the last few years, the American College of Cardiology Foundation in collaboration with the American Heart Association and many other organizations has published several training and competence statements related to the structure and content of formal subspecialty training and competence in the performance of various procedures ranging from ECG interpretation to invasive electrophysiology studies and cardiac interventional procedures. The current Competence and Training Statement for the first time tries to formulate clinical competency criteria for the cardiovascular preventive specialist. The writing group was chaired by Dr. Noel Bairey-Merz and included representatives from many organizations. Dr. Michael Davidson represented the NLA on the writing group and Janet Long and Peter Wilson, MD served as organizational reviewers for the NLA. The authors outline 17 topic areas (Table 1), and for each they provide a justification for its inclusion, the minimal knowledge to achieve competence, and, as available, avenues for formal training, alternate routes to achieve competence, and resources for education and to maintain competence. The document is extensively referenced and can thus be used as a study guide for individuals as well as a “prevention curriculum” for training programs. The authors acknowledge that the curriculum is vast and that, “similar to other subspecialty areas of medicine, cardiovascular preventive specialists will have varying areas of expertise and will not necessarily achieve all of the outlined areas of competencies.” Nevertheless, I think that all of us should strive to achieve competence in as many areas of cardiovascular disease prevention as we can and make sure that we assemble a clinical team that has expertise in all areas so that we can provide “optimal medical care” for this multi-factorial disease.

Nationally, quality of care is variable and implementation of guidelines often suboptimal. Performance measures are an attempt to define quality of care and to provide tools to measure quality of care which can be used for internal...
quality improvement. Increasingly, such measures are also used by payers for reimbursement purposes. The development of performance measures is complex because the measures must not only have a strong evidence base and be consistent with current clinical guidelines, but they also have to be implementable in vastly different care environments, documentation of data elements should not impose an undue burden on the practitioner, the data should be easily retrievable from the medical record (i.e., be auditable), and the measures have to be designed in such a way that patient complexity and severity of illness are taken into account when assessing achievement (or lack thereof) of treatment benchmarks. This is the first time that comprehensive performance measures for primary prevention have been defined. The writing group was chaired by Rita Redberg, MD, MSc, and included clinical content and methodology experts representing a variety of organizations. The authors propose 13 performance measures ranging from risk assessment to lifestyle counseling to pharmacologic therapy (Table 2). Some of the measures are recommended for use for internal quality improvement as well as for public reporting, while others are recommended for internal quality improvement only. Primary prevention for the purposes of this statement was defined as “prevention of the first occurrence of cardiovascular disease.” The statement thus applies to a broad spectrum of individuals ranging from those at very low risk to those who already have diabetes or asymptomatic “subclinical” atherosclerosis. It is important to note in this context that the performance

<table>
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<th>Table 1: Topic Areas Addressed in the Competence and Training Statement for CVD Prevention</th>
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<tr>
<td>• Cardiovascular and Vascular Biology</td>
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<tr>
<td>• Clinical Epidemiology and Biostatistics</td>
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<td>• Cardiovascular Pharmacology (Complex Multipharmacologic Understanding)</td>
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<td>• Genetics and Cardiovascular Disease in Individuals and Families</td>
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<td>• Behavioral and Psychosocial Programs (Financial and Socioeconomic Factors)</td>
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<td>• Advanced Risk Assessment (Renal, Inflammatory Diseases)</td>
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<td>• Subclinical Atherosclerosis Assessment (Imaging and Nonimaging)</td>
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<td>• Adherence and Disease Outcome Interdisciplinary Programs</td>
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<td>• Nutrition Management</td>
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<td>• Lipid Management (Management of Dyslipidemia)</td>
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<td>• Thrombosis Management</td>
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<td>• Hypertension Management</td>
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<td>• Smoking Cessation</td>
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<td>• Obesity Management (Behavioral Programs)</td>
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<td>• Exercise Physiology, Physical Activity Management, and Cardiac Rehabilitation (Secondary Prevention)</td>
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<td>• Prediabetes, Metabolic Syndrome, Insulin Resistance, and Diabetes Management</td>
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<td>• Chronic Disease Management</td>
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Rationale and endorsement for atherosclerosis imaging in risk assessment

Atherosclerosis is a systemic process that begins in childhood and progresses silently over many years before manifesting itself clinically, usually as a myocardial infarction, angina, sudden cardiac death, or stroke. This long latency period provides a great opportunity to utilize non-invasive imaging techniques to detect atherosclerosis at various stages, thereby identifying asymptomatic individuals at higher-than-average risk who would be candidates for more intensive prevention therapies. Currently, two imaging modalities are available to the practicing clinician: CT coronary calcium scoring and ultrasound measurement of carotid intima-media thickness (CIMT).

The imaging of arteries to identify and quantify the presence of subclinical vascular disease has been suggested in guidelines and by several expert consensus panels over the past decade. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) stated that CIMT “could be used as an adjunct in CHD (coronary heart disease) risk assessment… the finding of an elevated CIMT (eg ≥75th percentile for age and sex) could elevate a person with multiple risk factors to a higher risk category,” but noted that “expense, lack of availability, and difficulties with standardization preclude a current recommendation for its use in routine assessment.” The panel concluded that “if carried out under the proper conditions, CIMT could be used to identify persons at higher risk than that revealed by the major risk factors alone.”

Since that qualified endorsement seven years ago, two significant developments have enhanced the feasibility of using CIMT for assessing atherosclerosis in the individual patient in an office setting: 1) Advances in ultrasound technology and the associated quantitative software programs have vastly improved the accuracy and reproducibility of CIMT measurement; 2) the American Society of Echocardiography (ASE) has published a consensus statement with detailed recommendations for use of carotid IMT to assess subclinical vascular disease and cardiovascular disease (CVD) risk. This document addresses the critical issues of standardization and should be the guideline for any service wanting to provide high-quality CIMT studies.

Pathophysiology of intima-media thickening

The arterial wall has 3 layers—the intima, media, and adventitia. Aging alone is associated with carotid wall thickening, mainly in the intima layer. The anatomical and physiological changes that occur in the arterial wall with aging overlap with, but are not identical to, the changes observed with atherosclerosis. Their distinction is apparent on microscopy, but not by ultrasound. Hypertension also can produce smooth muscle hypertrophy in the media layer, but ultrasound imaging is unable to discriminate between the intima and media layers because of insufficient axial resolution. Therefore, an elevated carotid IMT may result from a thickened sub-intimal layer due to the early atherosclerotic process (deposition of atherogenic particles, macrophage infiltration, foam cell formation, etc.), increased smooth muscle hypertrophy (as seen in hypertension), in normal aging changes, or any combination of these processes. For this reason, some researchers have argued that...
an increased CIMT, in the absence of plaque intruding into the lumen, should be seen as a marker of early arterial wall damage, rather than as a true surrogate for atherosclerosis.\textsuperscript{10,11} Whatever the exact pathophysiology, multiple studies have shown that an elevated CIMT is associated with an increased risk for cardiovascular disease.\textsuperscript{12-20} One very recent study of hypertension patients, showed that increased CIMT and carotid plaques were both associated with worse cardiovascular outcomes independently of blood pressure and traditional risk factors.\textsuperscript{20}

**Clinical study evidence for using CIMT to evaluate CVD risk**

There are 9 published prospective studies with at least 1000 participants each that have assessed the association of CIMT with CVD outcomes and published the relative risk or hazard ratio after adjusting for traditional risk factors.\textsuperscript{12-20} All 9 studies demonstrated that CIMT was significantly associated with risk for myocardial infarction, stroke, CHD death, or a combination of these events; in most of the studies the adjusted relative risks, comparing the highest with the lowest group was 2.0 or more (Table 1). Although there was much heterogeneity among these studies, a recent meta-analysis, which included the 8 of them, calculated a 15% increased risk for myocardial infarction and an 18% increased risk for stroke per 0.1 mm increase in common carotid IMT.\textsuperscript{21} In two of the study cohorts (ARIC and CHS), CIMT values modestly increased the area under the receiving operator characteristic curve for predicting cardiovascular events.\textsuperscript{22,23} The majority of the participants in the major studies were between 42ñ74 years of age, however, in the one study (CAPS) that enrolled participants as young as age 19 (mean age 39 years), the relative risk associated with increased CIMT was higher among the younger than the older adults.\textsuperscript{15} For obvious reasons clinical outcome studies cannot be performed feasibly in young people, however numerous studies have established a strong association between CIMT and risk-factor burden in teenagers and younger adults.\textsuperscript{24-32}

There are also 6 large prospective studies that have assessed the predictive power of the presence of carotid plaque and published the adjusted relative risk,\textsuperscript{17,19,33-35} The relative risks were similar to or slightly higher than those observed with increased CIMT alone (Table 2). This is an important finding with clinical relevance because it is not unusual for an individual to have a normal CMT, specifically measured in the distal common carotid region, but to have obvious plaque in the bulb or internal carotid artery region. The distinction between excessive intima-media thickening and early plaque (i.e., luminal protrusion) is somewhat arbitrary, but it has been defined for the

### Table 1 Prospective studies of carotid IMT with relative risk (RR) for incident CVD

<table>
<thead>
<tr>
<th>Study (see ref.)</th>
<th>N (%F)</th>
<th>Age (yrs)</th>
<th>F/U (yrs)</th>
<th>Measurement and site</th>
<th>Event</th>
<th>CIMT cut-point RR (95% CI)*</th>
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<tr>
<td>ARIC\textsuperscript{12}</td>
<td>12,841 (57%)</td>
<td>45–64</td>
<td>5.2</td>
<td>mean of mean; CCA/bulb/ICA</td>
<td>MI, CHD death</td>
<td>Highest tertile: F: 2.53 (1.02–6.26) M: 2.02 (1.32–3.09)</td>
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<tr>
<td>ARIC\textsuperscript{14}</td>
<td>14,214 (55%)</td>
<td>45–64</td>
<td>7.2</td>
<td>mean; near + far wall CCA</td>
<td>Stroke</td>
<td>Highest tertile: F: 1.65 (0.85–3.19) M: 2.69 (1.49–4.87)</td>
</tr>
<tr>
<td>CAPS\textsuperscript{15}</td>
<td>5056 (50%)</td>
<td>19–90</td>
<td>4.2</td>
<td>mean; far wall CCA</td>
<td>MI Stroke Death, MI, Stroke</td>
<td>Highest quartile: 1.83 (0.97–3.45) Highest quartile: 1.82 (0.64–5.16) Highest quartile: 1.85 (1.09–3.15)</td>
</tr>
<tr>
<td>CHS\textsuperscript{13}</td>
<td>4476 (39%)</td>
<td>&gt;65</td>
<td>6.2</td>
<td>maximum; near + far CCA</td>
<td>MI Stroke</td>
<td>Highest quintile: 2.46 (1.51–4.01) Highest quintile: 2.13 (1.38–28)</td>
</tr>
<tr>
<td>KIH\textsuperscript{16}</td>
<td>1257 (0%)</td>
<td>42–60</td>
<td>3</td>
<td>maximum; far wall CCA</td>
<td>MI</td>
<td>&gt;1.0 mm (max): 2.1 (0.8–5.2)</td>
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<tr>
<td>Yao City\textsuperscript{17}</td>
<td>1289 (0%)</td>
<td>60–74</td>
<td>4.5</td>
<td>maximum; near + far CCA</td>
<td>Stroke</td>
<td>Highest quartile: 4.9 (1.9–12.0)</td>
</tr>
<tr>
<td>MDCS\textsuperscript{18}</td>
<td>5163 (60%)</td>
<td>46–68</td>
<td>7</td>
<td>maximum; far wall CCA</td>
<td>MI, CHD death</td>
<td>Highest tertile: 1.50 (0.81–2.59)</td>
</tr>
<tr>
<td>Rotterdam\textsuperscript{19}</td>
<td>6389 (62%)</td>
<td>&gt;55</td>
<td>7–10</td>
<td>maximum; near + far CCA</td>
<td>MI</td>
<td>Highest quartile: 1.95 (1.19–3.19)</td>
</tr>
<tr>
<td>ELSA\textsuperscript{20}</td>
<td>2334 (45%)</td>
<td>45–70</td>
<td>3.75</td>
<td>maximum; far wall CCA</td>
<td>MI, stroke, CV death</td>
<td>per 1mm increase 3.51 (1.88–6.56)</td>
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*adjusted for age, sex, and traditional risk factors
purpose of uniformity in research by both a US and a European consensus statement. The American Society of Echocardiography (ASE) defines non-obstructive plaque as the presence of focal thickening at least 50% greater than that of the surrounding vessel wall. The Mannheim CIMT Consensus Report similarly defines plaque as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness, or a thickness greater than or equal to 1.5 mm.

Who to screen with CIMT?

Measuring CIMT and identifying carotid plaque by ultrasound are most useful for refining the CVD risk estimate in patients who are deemed to be intermediate risk by traditional risk factor assessment (i.e., Framingham Risk Score of 6ñ20%). The ASE Consensus Statement adds that the following patient types might also be considered for CIMT measurement and carotid plaque detection:

1. Family history of premature CVD in a first-degree relative
2. Individuals younger than 60 with severe abnormalities in a single risk factor who otherwise would not be candidates for pharmacotherapy
3. Women younger than 60 with at least 2 other risk factors

In general, this test can be considered if the physician is uncertain about the appropriate level of intensiveness of the preventive therapeutic regimen, in which case the additional information about the burden of subclinical vascular disease and future CVD risk might alter the decision. Conversely, such imaging is not recommended in patients with established atherosclerotic vascular disease, as the results would not be expected to alter therapy.

In highly controlled research settings, serial carotid IMT has been used successfully to compare the effectiveness of various drug interventions. Determining effectiveness of treatment in the individual patient by using serial CIMT, however, is problematic. For one thing, the measurement variability intrinsic to the procedure is much larger than the expected annual rate of change, based on population data. In addition, any population-based expected rate of change, used to compare with the actual rate of change in a given individual for purposes of determining treatment efficacy, would come with a wide confidence interval, given all the determinants of this variable—innherent biological variability, drug effects, behavioral changes, age, etc. Therefore, performing serial studies of CIMT in order to assess the rate of progression is not recommended at this time for use in clinical practice.

Comparing CIMT to CT coronary calcium scanning

Both of these imaging modalities detect subclinical vascular disease but there are important differences. There is no radiation exposure with CIMT, which can vary substantially with CT coronary calcium scoring (CCS).
CIMT tends to be less expensive than CCS, although insurance coverage is beginning to occur in some states for CCS. CIMT can be used to stratify risk in anyone, whereas CCS has limited use in populations in which the prevalence of a zero score is high (e.g., men <45 and women <55). Although a zero coronary calcium score does indicate an excellent short-term prognosis, such individuals are a very heterogeneous group with regard to long-term prognosis. Therefore, in young people or in adults who are highly likely to have a zero coronary calcium score, a more accurate estimate of long-term risk can be obtained by using CIMT along with the FRS modified for “lifetime” or “30-year” risk.39-43 On the other hand, a positive coronary calcium score is more predictive of cardiovascular disease events in the short-term than CIMT.44 This is not surprising, since coronary calcification represents a more advanced stage of atherosclerosis than a thickened arterial wall.

CIMT for CVD risk prediction in clinical practice

Several clinical CVD risk assessment programs have published data showing that CIMT can identify patients with subclinical vascular disease and help reclassify patients at intermediate risk.45-48 As with most tests designed to improve accuracy of diagnosis or prognosis, there are no studies demonstrating that screening with CIMT improves clinical outcomes by reducing morbidity or mortality. The purpose of CIMT screening however, is to improve risk stratification in order to target treatment efforts more efficiently. To the degree that the specific therapy has been demonstrated to improve outcomes, and to the degree that the patient is adherent to the treatment regimen, improved outcomes should derive from the screening method which presumably led to the change in therapy. There are in fact a few small trials that have shown changes in physician or patient behavior that would be expected to lead to better outcomes.49-51 One study showed that physicians were more likely to prescribe aspirin and lipid-lowering therapy to patients who were found to have carotid plaque during CIMT screening in the office.49 In another small randomized trial, smokers who were shown images of their carotid plaques were more likely to stop smoking at 6 months.50 More studies of longer duration and greater numbers of participants are needed to confirm these preliminary findings.

Interpretation of CIMT results for CVD risk assessment

CIMT results are typically reported in two ways: 1) As a “vascular age,” which is the chronological age at which the reported value would be the 50th percentile. E.g., a 40-year-old white male has a mean common carotid IMT of 0.71 mm, which is the 50th percentile for a 56-year-old white male, therefore his “vascular age” is 56 years; or 2) As the actual percentile. E.g., a 40-year-old white male has a mean common carotid IMT of 0.71 mm, which represents the 83rd percentile. In addition to the CIMT percentile, the presence or absence of plaque is reported. High-grade carotid plaque indicates a very high short-term risk for stroke, as well as a high risk for significant coronary disease, and obviously warrants immediate further radiological evaluation and/or referral. The presence of plaque <50% stenosis is not associated with as much risk, however a carotid duplex scan may be useful for better delineation of the problem. The presence of any plaque is associated with risk equal to or greater than...
having abnormal IMT results. The NCEP ATP III and the 34th Bethesda Conference committee have recommended the 75th percentile as an appropriate threshold for elevating an individual to a higher risk category and considering more intensive risk-reduction therapies.\textsuperscript{2,52} Values in the 25th to 75th percentile are considered average and do not alter the pre-test probability as assessed by traditional risk factors. Values less than the 25th percentile are associated with lower risk, however it is not recommended at this time that the patient’s risk category and treatment goals be lowered. Therefore, all patients with values <75th percentile should be advised according to current national guidelines for cholesterol, blood pressure, diabetes, etc.

Integration of CIMT with other biomarkers in CVD risk assessment

Numerous non-traditional biomarkers have been studied in a prospective fashion to determine if their value is additive to the Framingham Risk Score (FRS), with variable results depending on the particular risk marker and population studied. Since CIMT also adds prognostic value to the FRS, combining CIMT with one or several of the other new biomarkers to improve risk assessment is a very attractive concept. To the author’s knowledge, this has been assessed in only one study. The Cardiovascular Health Study investigators evaluated the 12-year incidence of CVD events and total mortality in 5888 adults over the age of 64. The top tertile of carotid IMT values was more predictive for various endpoints than a CRP >3. However, when CRP was >3 among those with subclinical atherosclerosis, there was a 72% increase in risk for CVD death and a 52% increase in total mortality. Elevated CRP in the absence of atherosclerosis did not increase CVD or total mortality risk.\textsuperscript{53} Nambi and Ballantyne have published an algorithm that illustrates an approach to risk assessment that incorporates Framingham lifetime risk, newer biomarkers (e.g., CRP, genetic markers), and atherosclerosis imaging with CIMT and/or CCS.\textsuperscript{43} They also call for clinical trials to test such a strategy.

CIMT potential for risk assessment in adolescents and young adults

Current pediatric lipid guidelines recommend using traditional cardiovascular risk factors to identify youth in need of intensive prevention measures.\textsuperscript{54} However, except in the very high risk young person (e.g., familial hypercholesterolemia with family history of premature CVD), it is quite difficult to identify with confidence which individuals need to initiate early pharmacologic therapy or, more specifically, when to initiate drug therapy. Many experts, noting the widespread use of CIMT in pediatric research, have pointed out the great potential for clinical use of an accurate, non-invasive measure of early atherosclerotic disease.\textsuperscript{55,56} A very recent AHA Scientific Statement has reviewed the current literature on non-invasive assessment of atherosclerosis in children and adolescents, made recommendations for standardization of CIMT, and enumerated the current gaps in knowledge that need to be filled before it can be applied in the clinical setting.\textsuperscript{57} Fortunately, the research community is rising to the challenge to address the unresolved issues. The Muscatine Offspring Study, for example, recently found that aortic IMT in adolescents gives information beyond that obtained from CIMT alone, supporting an earlier study with similar findings.\textsuperscript{58,59} Morrison, et al., has shown that the strongest risk factors for an increased IMT in children and adolescents are age, family history of CHD, and dyslipidemia, as expressed by the TC/HDL ratio or apolipoproteins B and A1. Age, the strongest determinant, is probably a marker for cumulative exposure to CVD risk factors, but further research should clarify this and other issues.\textsuperscript{60}

Conclusions and personal experience

The paradigm for evaluation of cardiovascular disease risk is shifting from one based solely on risk-factor assessment to one that incorporates atherosclerosis imaging. The two modalities that are currently available to the practicing clinician, CT coronary calcium scoring (CCS) and carotid IMT (CIMT), are complementary, since they image different vascular territories and identify different stages of the atherosclerosis process. CIMT has an advantage for persons unlikely to have calcified plaque (most men <45 and women <55–60), having utility at any age. To use CIMT in the clinical setting, meticulous attention must be paid to all the variables that can reduce accuracy and reproducibility, from reader training to equipment to scanning protocol. The 2008 ASE Consensus Statement provides the necessary guidance.

While refinements in risk assessment will undoubtedly continue, CIMT has already become an indispensable tool in the author’s practice of cardiovascular disease prevention. We have had great success in identifying high risk individuals who would not have been recognized as such without the aid of imaging. Visual evidence of

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This article focuses on actual lipid disorders from actual patients, and how one clinical lipidologist evaluates the available clinical and laboratory data and then arrives at a therapeutic solution. Dr. Dayspring has been in practice 33 years and lectures extensively through the country on lipids and lipoprotein disorders.

Case One: A possibility of Familial Hyperlipidemia

I want to discuss the following case sent to me by a gynecologist because of the patient’s abnormal lipid profile, and I was asked about management. A 25-year-old asymptomatic married white female who has a father and paternal grandfather and grandmother as well as paternal aunt who require statins. None have had any cardiovascular events. She has had significant menstrual cycle trouble which has been corrected with the Orthro Evra patch (6.0 mg norelgestromin / 0.75 mg ethinyl estradiol). She is aware of the higher basal E2 levels and risk of stroke with this product. The patient weighs 114 pounds and has little to no body fat. Her hs-CRP was 3.6 (normal <2) and her homocysteine is 10.5 (normal <10.4). Her lipid profile is as follows:

Initial Profile:
- TC = 279 mg/dL
- HDL-C = 83 mg/dL
- LDL-C = 174 mg/dL
- TG = 110 mg/dL

4 Months Later:
- TC = 246 mg/dL
- HDL-C = 70 mg/dL
- LDL-C = 157 mg/dL
- TG = 96 mg/dL

DISCUSSION

Her elevated TC and LDL-C at age 25 suggests she is beginning to manifest the phenotype of heterozygous familial hyperlipidemia and indeed the NMR LipoProfile confirms what I believe is a better descriptive term, hyperbetalipoproteinemia.

Originally, lipoproteins were separated by ultracentrifugation and classified by their buoyancy or density. Later, electrophoresis separated lipoproteins by their migration pattern as judged against globulins: alpha (very mobile), beta (in-between mobility), or gamma (low mobility). The apolipoprotein B (apoB) particles separated with the beta-proteins and hence acquired the name betalipoproteins.

The HDLs migrated with alpha proteins and are termed alpha lipoproteins. If one uses the old Fredrickson’s Classification of Lipid Disorders, she would be classified as Type IIa (cholesterol elevations with normal TG). Her abnormal particle numbers as well as her cholesterol concentrations will likely continue to worsen with time. Since atherosclerosis is a lipoprotein-mediated disease (specifically apolipoprotein B containing lipoproteins), apoB or LDL particle (LDL-P) concentration is the primary determinant of atherogenesis and is now endorsed as the best predictor and goal of therapy by two major consensus statements.5,6

Because she does not have two major cardiovascular risk factors, she does not qualify for Framingham Risk Scoring (FRS), but if it is calculated she is in the low-risk category with a ten-year risk of <10%. Yet, the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial showed that many patients with low FRS, even younger patients with borderline lipid abnormalities, had significant subclinical atherosclerosis (on carotid ultrasound) and its progression was halted by use of rosuvastatin 40 mg daily.7 Using NCEP ATP-III she would not qualify for drug treatment as her ten-year risk of an event is low and her LDL-C is <190 mg/dL. She does not even qualify for FRS as she does not have two
major risk factors for CHD. So should we follow NCEP ATP-III recommendations and use therapeutic lifestyle advice to try and reduce the LDL-C, or based on the METEOR data should we just start her on rosuvastatin (Crestor) at 40 mg (the dose used in the study), or should we think about it a bit more? Note that the patient is at ideal weight, so I doubt additional lifestyle is going to do much.

LDLs are simply the by-product of lipoprotein and hepatic lipase-mediated lipolysis or hydrolysis of certain lipids (core TG and surface phospholipids from VLDL and IDL particles. Note that most VLDLs and IDLs (because they have not only apoB but multiple copies of apoE, which is also an LDLr ligand) are fairly quickly removed by hepatic LDLr. Only some VLDLs and IDLs are ultimately converted into LDL particles. LDLs (which have no apoE) have much longer half lives (1.5–3 days) during which time they traffic tocopherol (vitamin E) to various tissues, and also accept additional cholesteryl ester (CE) from HDLs via cholesteryl ester transfer protein (CETP). So if one asks, “where does the cholesterol in LDL particles originate?” the correct answer is from both VLDLs and HDLs. A significant part of cholesterol content in LDLs originates in HDL particles. Ultimately, most of the LDLs are internalized into tissues, predominantly the liver, by LDL receptors (LDLr). Hepatic internalization of LDL is a process termed indirect reverse cholesterol transport (RCT). Few of us were ever taught that a primary function of LDL particles is to perform RCT. Since all cells can synthesize most of their cholesterol needs, under physiologic conditions LDLs do not traffic large amounts of cholesterol or cholesteryl ester (CE) to peripheral tissues. Of course, if there are too many LDL particles in plasma (overproduction, impaired clearance or both), they accumulate (raising apoB and LDL-P) and unfortunately penetrate the arterial intima, where they are prone to oxidation and subsequent ingestion by macrophages creating foam cells, the histological hallmark of atherosclerosis.

What influences LDL-C, defined as the amount of cholesterol trafficked within all of the IDLs and LDLs that exist in a deciliter (or 100 cc) of plasma? Obviously it will be a product of the number of LDL particles, the volume of the LDL particles, and the core composition of the particles (TG/CE ratio). The volume of a round particle (sphere) is 4/3 πR³ (where R is the radius of the particle). Since the volume is related to the third power of the radius, even trivial particle size shifts can dramatically influence the volume. Thus, smaller particles or particles of any size carrying increased TG and necessarily less CE will be cholesterol-depleted particles that are often associated with high LDL-P. The little-known Ludwigshafen Risk and Cardiovascular Health Study nicely showed that high LDL-TG are related to coronary artery disease, systemic low-grade inflammation, and vasculopathy. High LDL-TGs are indicative of CE-depleted LDL, elevated IDL, and dense LDL. The conclusion was that LDL-TG may better reflect the atherogenic potential of LDL than LDL-C. Isn’t that amazing? In an insulin-resistant world, LDL-TG might be a far more informative lab test than the “beloved” LDL-C. In reality apoB or LDL-P is what we need to best adjudicate risk.

The patient at hand has very large LDL particles (22.5 nm) and we should start to ask why. She also has a significantly increased LDL particle count of almost 1700 nmol/L. This may explain why she has very high LDL-C concentrations, but in my experience, with 1700 nmols of very large particles the LDL-C should be much higher. It makes me wonder if her LDL particles, despite their very large size, were somewhat cholesterol-depleted, raising the possibility that they are TG-enriched and somewhat CE-poor despite the TG of 110 mg/dL. I also noted the very high HDL-C and increased large HDL-P. However, it is not unusual for FH patients to have increased HDL-C, as in such patients HDLs have many cholesterol-loaded tissues willing to lipidate them. It is interesting that the gynecologist advised the patient that the Ortho Evra is known to increase steady state estradiol levels and the package insert states that this may be associated with adversity. Estrogen is an inhibitor of hepatic lipase (HL), the enzyme that induces lipolysis of both LDL and HDL particles. Persons with hepatic lipase deficiency typically have very large LDLs and HDLs. Usually HDL-C is high, TG is elevated and LDL-C can be variable. Despite the high HDL-C, such patients may receive no cardioprotection from their HDLs. Based on the family...
CASE STUDIES

history of statin use, I believe this patient does have familial hypercholesterolemia (hyperbetalipoproteinemia), but she may also have an estrogen-induced reduction in hepatic lipase creating the very large LDL and HDL particles (perhaps with less function). However, I suspect her LDL core composition has increased TG and less CE than normal (usually a 4:1 ratio of CE to TG). This could explain why there is such a high concentration of very large LDL particles and an LDL-C <190 mg/dL. The elevated CRP of 3.6 is also of some concern as it is an independent predictor of risk. It should be repeated for validation but I would also run a PLAC test (lipoprotein associated phospholipase A2), which is a more lipoprotein specific marker of inflammation and one of our best predictors of stroke. Typically, transdermal estrogen products do not elevate CRP, but again Ortho Evra significantly elevates estradiol levels significantly more than menopausal transdermal estrogen products. Estrogen is not known to increase Lp-PLA2.

People with familial hypercholesterolemia (FH) typically have increased numbers of very large CE-rich LDL particles, explaining their high-risk LDL-C and LDL-P (apoB levels). So although we have classically been taught that LDL-C explains their risk, it is really LDL-P that is the true risk factor as it is particle number—not particle cholesterol content—that facilitates particle arterial wall entry. This same principal relates to HDL particles also. If one has high HDL-P concentrations, yet the HDLs were very small or they were TG-rich and CE-poor, the HDL-C would be lower than expected. Although it is desirable to have increased numbers of HDL particles or apoA-I, it is likely just as important that they be functional, i.e., be able to perform cardioprotective functions such as the ability to delipidate arterial wall macrophages or macrophage RCT, and the ability to traffic anti-atherogenic proteins on their surface. Total HDL-P = prebeta HDL-P plus large HDL-P plus medium HDL-P plus small HDL-P. NMR spectroscopy technology is not capable of measuring prebeta HDLs, which typically make up about 5% of total HDL-P. The more mature (lipidated) are termed alpha HDLs (small, medium, and large) and although all HDL species are important, many believe certain prebeta HDLs are among the most cardioprotective HDL species.

Why do the patients with FH have such high apoB and LDL-P concentrations? Liver cells upregulate LDLr when they need to replenish their cholesterol storage pools (the liver needs cholesterol for its cell membranes, to lipidate HDL particles, and to make bile acids). There is a nuclear transcription factor called sterol regulatory element binding protein (SREBP) that is activated when cellular cholesterol levels are low. One of its actions is to affect response elements on genes to initiate LDL receptor protein synthesis. The LDLr translocates to the hepatocyte surface and attaches to either apoB100 or apoE on lipoproteins causing their endocytosis. LDLr is a protein with specific surface charges that recognize opposing charges on the apoB on the surface of the lipoprotein. However, those charges and their specific locations depend on the specific configuration assumed by apoB. Clearly, very large and very small LDL particles will have different apoB configurations than normal-sized LDL particles. LDLr would be less efficient in recognizing and clearing very large or very small LDL particles. Thus impaired clearance, better termed ineffective indirect reverse cholesterol transport, would increase the plasma residence time (half life) and concentration of either very large or very small LDL particles. The FH patient with too many very large LDLs will have high levels of LDL-C; the diabetic with too many small LDL particles may or may not have a high LDL-C. In both patients, apoB and LDL-P and risk is high, but the LDL-C values and LDL size have no such relationship to the particle concentration or risk.

Genetic abnormalities causing defective LDLr or defective apoB are well known, classic causes of FH. Patients who have one abnormal copy (heterozygous) of the LDLr gene may have premature cardiovascular disease at the age of 30 to 40. Having two abnormal copies (homozygous) may cause severe cardiovascular disease in childhood. Heterozygous FH is a common genetic disorder, occurring in 1:500 or less people; homozygous FH is much rarer, occurring in 1 in a million births. However, there are other potential genetic defects beyond the scope of this discussion.
One emerging area of great interest is the proteolytic enzymes (peptidases) that catabolize LDL receptors. If one had too much of that enzyme, the LDLr would have very short lives, causing high LDL-C and LDL-P. On the other hand, if one had low levels of such a protease, LDLr half life would increase and such patients would have low levels of LDL-C and LDL-P (hypobetalipoproteinemia). The gene that controls this enzyme is undergoing intensive research as inhibition of such enzyme would help clinicians further lower LDL-C and LDL-P by extending the life of one’s LDLr. The gene is called PCSk9 or proprotein convertase subtilisin Kexin Type 9.10

Even though she is young, because of the high LDL-P, the elevated CRP, and the family history, I would screen for subclinical atherosclerosis with CIMT. If it is abnormal, her risk increases and LDL-lowering therapy would be indicated. One needs to upregulate LDLr as much and as safely as possible: this is best accomplished by the use of drugs that deplete the liver of its cholesterol stores, thereby forcing upregulation of as many LDLr as necessary to control apoB and LDL-P or their lipid surrogates (LDL-C, non-HDL-C). So we are looking at statins, ezetimibe (Zetia), bile acid sequestrant like colesevelam (Welchol), plant stanol (Benecol) or combination thereof. If hyperabsorption of cholesterol, which could be ascertained by doing sitosterol or campesterol levels, is a part of her problem we might be able to get away with low dose statin and ezetimibe. If not, we will need a higher dose of more potent statins. If one wished to use a nonsystemic medication, then Welchol would be the choice. However her LDL-P is quite high and a statin is going to be needed to get it to goal. Since she is on a contraceptive, there should be no reluctance to prescribe systemic lipid modulating drugs like statins that carry the Category X warning. If a statin is started many would likely begin with a generic like simvastatin, but again the LDL-P is very high and rosuvastatin or statin-ezetimibe or statin-colesevelam may be needed. Of course, if she ever wants to get pregnant, the statin can be stopped and Welchol used for the length of the pregnancy. Before starting a statin, despite the contraceptive, a pregnancy test might be wise and the patient must be educated (with documentation) that she cannot get pregnant on a statin. Also before proceeding with a pregnancy, it would be wise to have her husband screened because if he also has heterozygous familial hypercholesterolemia, their child has the risk of being a homozygote.

**Case 2: Assessment of risk presents a challenge**

I received the following case of a 65-year-old male with hypertension, type 2 diabetes (T2DM), metabolic syndrome, and increased LDL-P. His family history is positive for diabetes and premature CVD. He denies cardiac symptoms but has not had any evaluation for subclinical atherosclerosis, i.e., carotid IMT or coronary calcium scoring (CAC). A Cardiolite scan was negative a few years ago. The TSH is fine (0.86) and creatinine is normal at 1.0. He sees several physicians, which results in different and sometimes conflicting treatment plans. Current medications are simvastatin-ezetimibe (Vytorin 10/40 mg), aspirin 81 mg, metformin 500 mg twice a day, exanatide (Byetta) 5mcg bid, lisinopril 20 bid, amlodipline (Norvasc) 5mg daily, Terazosin 10 mg and Avodart .05 mg daily.

**Examination:** BP 120/82, Height = 6’1”, Weight = 258, BMI = 33, Waist size > 40 inches.

<table>
<thead>
<tr>
<th>Current Profile:</th>
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<tbody>
<tr>
<td>TC= 117 mg/dL</td>
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<tr>
<td>LDL-C = 62 mg/dL</td>
</tr>
<tr>
<td>HDL-C = 40 mg/dL</td>
</tr>
<tr>
<td>TG = 74 mg/dL</td>
</tr>
<tr>
<td>VLDL-C = 14 mg/dL</td>
</tr>
<tr>
<td>Non HDL-C = 77</td>
</tr>
<tr>
<td>ApoB = 55 mg/dL</td>
</tr>
<tr>
<td>(below 5th percentile cut-point)</td>
</tr>
<tr>
<td>ALT = 15 u</td>
</tr>
<tr>
<td>HgbA1c = 6.3%</td>
</tr>
<tr>
<td>Fasting glucose = 120 mg/dL</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Expanded Profile</th>
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</thead>
<tbody>
<tr>
<td>Total LDL-P = 1161 nmol/L (desirable &lt;1000 umol/L (~20th percentile cut-point)</td>
</tr>
<tr>
<td>Small LDL P = 1015 nmol/L (elevated)</td>
</tr>
<tr>
<td>LDL particle size = 19.9 nm (small or Phenotype B)</td>
</tr>
<tr>
<td>Large HDL-P = 2.6 umol/L (low)</td>
</tr>
<tr>
<td>Large VLDL-P = 0.4 nmol/L (normal)</td>
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I was not given any lipid data prior to initiation of a statin. Treatment has varied in the past couple of years with most debate centered on the question of statin-ezetimibe vs. statin plus fenofibrate. Apparently, he has made a lot of progress in controlling his diabetes over the past 2 years. The clinician is perplexed with the discordance between
apoB and LDL-P, which would suggest that there are still persistent atherogenic particles not being detected by apoB. He also asks if it is better to increase the statin dose to achieve lower non-HDL-C or LDL-P, or would this insulin-resistant patient be better served with a lower dose of statin with the addition of ezetimibe or perhaps fenofibrate that targets many of the problems encountered in patients with insulin resistance?

**DISCUSSION**

As discussed in the first case, atherosclerosis is a lipoprotein-mediated disease and the atherogenic lipoproteins (those capable of carrying cholesterol into the arterial wall) each contain a single molecule of apoB, the measurement of which serves as a concentration of potentially atherogenic particles. Because LDLs have a long half life, >90% of apoB particles are LDL particles (LDL-P). The determining factor on whether the particle stays in plasma or invades the artery is particle number or concentration. Lipid concentration surrogates of apoB are LDL-C or non-HDL-C (TC minus HDL-C). As indicated in the ADA/ACC consensus statement, there is moderate discordance between non-HDL-C and apoB or LDL-P.3,4 A few quotes from the Expert Panel of 30 Lipidologists representing 10 countries are:

> The lipid composition of the principal atherogenic lipoproteins differs substantially amongst individuals. Therefore, lipid levels do not automatically equal lipoprotein particle levels...Atherogenic particle number has been shown to be superior to LDL-C in judging the residual clinical risk on therapy in a number of the statin clinical trials such as AFCAPS/TexCAPS, the Leiden Heart Study and The Long Term Intervention with Pravastatin in Ischemic Disease (LIPID)...Because the amount of cholesterol per LDL particle varies substantially both between and within individuals, LDL cholesterol does not necessarily equal the most critical variable, the total number of LDL particles. This is the key point.11

One might assume the patient under discussion almost certainly has some degree of sub-clinical atherosclerosis. However, such screening is not necessarily indicated because his T2DM and age make him high risk. Whether plaque is present or not, our mission in such a patient is to prevent an atherothrombotic event. There is no data that plaque regression or simply stopping progression as determined by vascular imaging improves survival or is more indicative of reducing risk any better than is aggressive lipid-risk factor or BP management. If we normalize atherogenic lipoproteins, control glycemia, prescribe anti-platelet drugs and control BP, we would do all that is possible to maximize event reduction no matter what the arteries looked like. If we want to theorize outside of current evidence, perhaps if we reduced vascular wall inflammation and improved HDL functionality we could also improve outcome reduction. So I do not follow arterial images (CIMT or CAC) but rather concentrate on treatable risk factor goals.

In the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) study (an IVUS study), patients taking rosuvastatin 40 mg daily achieved a mean apoB of 85 and there was plaque regression in 2/3 and no plaque regression in 1/3.5 In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, atorvastatin (Lipitor) 80 mg achieved an apoB of 92 and there was no plaque progression, but also no regression. In the same study, pravastatin (Pravachol) 40 mg achieved an apoB of 112 and there was plaque progression.12 These studies suggest that the lower apoB is the better the arteries will look. However, these trials were too small and too short to follow event reduction. Interestingly, pravastatin has an excellent study record of reducing clinical events. Is what the statin does to HDL-C matter with respect to regression? A meta-analysis of several IVUS trials suggests that what a statin does to HDL-C is important and that “statin therapy is associated with regression of coronary atherosclerosis when LDL-C is substantially reduced and HDL-C is increased by more than 7.5%. These findings suggest that statin benefits are derived from both reductions in atherogenic lipoprotein levels and increases in HDL-C, although it remains to be determined whether the atherosclerotic regression associated with these changes in lipid levels will translate to meaningful reductions in clinical events and improved clinical outcomes.”13

The case at hand involves a high risk patient who does not qualify for the very-high-risk classification as he has no clinical atherosclerosis and has not had a CV event. I think an Lp-PLA2 and hs-CRP might help us better adjudicate risk. If they are high, there might be risk beyond that predicted by lipids and lipoproteins. However, his NCEP goals are an LDL-C of <100 and a non-HDL-C <130 mg/dL. Looking at the on-treatment lipids, NCEP would say for this patient: “mission accomplished.” The apoB of 55 would seem to agree...
with the perfect LDL-C and the non-HDL-C. Thus how do we explain the disconnect with the still slightly elevated LDL-P? It is not uncommon to see discrepancies between apoB and LDL-P, especially when LDLs are small or significant inflammation is present. Jayarajah, et al., offer a potential explanation. “Preliminary data from the authors’ investigations suggest that apo B, relative to LDL-P, “undervalues” small LDL particles compared with large LDL particles. A possible reason is that apo B adopts a substantially different conformation on small LDL than it does on large LDL, potentially causing differential exposure of the epitopes and differential antibody binding.” Others believe apoB epitopes can be affected by oxidative or other inflammatory forces and the protein immunoassay would not be less reliable in such cases. Note in the patient under discussion, the apoB/LDL-C ratio is less than one (55/62), which should not be if small particles are present. So the actual apoB may be higher and closer to 80, which would be more concordant with the LDL-P of 1100. So in this case the LDL-P is probably more believable than the apoB. If driving atherogenic particles down further is the mission, how can that be accomplished? Statin-ezetimibe is the current therapy. One option is to abandon the simvastatin-ezetimibe 40 mg and go to rosuvastatin 40 mg (the drug used in ASTEROID trial) and add ezetimibe to it. The EXamination of Potential Lipid modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone (EXPLORER) trial showed impressive apoB lowering with rosuvastatin-ezetimibe. There are other options: If, however, you want to drive apoB lower and perhaps improve macrophage RCT and many pleiotropic markers, one could also administer extended release niacin (Niaspan) and add it to the statin-ezetimibe combo. Fenofibric acid would add minimal (~5%) additional apoB lowering to the statin. However, many use fibrates in T2DM patients because of the microvascular benefits seen in the The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (retinal, albuminuria and distal amputations). Does it matter that the vast majority of the LDL particles are small? They are prone to oxidation by reactive oxygen species, adhere to intimal proteoglycans easily and are less likely to be cleared by LDLr. All of that is true, but all of the recent studies that measured both LDL-P and LDL size show that all LDLs are atherogenic if present in increased numbers, and the risk disappears as LDL-P becomes normal. So once total LDL-P is at desired goal, I do not think one has to drive the LDL-P down any further or increase particle size. Using drugs that shift LDL size (fibrates, niacin, N-3 FA) may help LDL receptors more easily clear the particles and help a statin further reduce the total LDL-P (apoB). So on simvastatin- ezetimibe 40 mg, the high-risk patient is at NCEP (and every other guideline) goal with respect to lipid levels. ApoB is excellent although for reasons discussed it may be a false negative. The LDL-P is almost at target: the AACC statement calls for an LDL-P goal of <1000 nmol/L. As discussed, adding Niaspan or fenofibrate (or fenofibric acid) may bring some microvascular benefits to T2DM patients, so if one wants to treat him very aggressively, either add-on makes sense. I’d also push the metformin to 2000 mg daily and try and further drop the HgbA1c.

References
Underutilization of Dietary Adjuncts in Dyslipidemia Management

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend a three-step approach to management of high blood cholesterol in adults: Step 1) Therapeutic Lifestyle Changes, including a diet low in saturated fat and cholesterol, regular physical activity, and weight loss where indicated; Step 2) use of dietary adjuncts, specifically, viscous dietary fibers (10–25 g/d), and plant sterols or stanols (2 g/d); and Step 3) prescription drug therapy if the first two steps are not sufficient to reach treatment goals.1,2

At our clinics we have queried more than 1000 individuals with dyslipidemia, many of whom were treated with lipid-altering medications, about their use of dietary adjuncts during screenings for participation in clinical trials or general health promotion. The results of this admittedly unscientific survey have led us to conclude that the ATP III recommendations regarding the use of dietary adjuncts are largely ignored in clinical practice, at least in the Midwest (our clinics are in the Chicago suburbs and central Indiana). Fewer than 10% of those screened were using the recommended dietary adjuncts, and most of those who were using viscous fiber reported that their use was for promoting bowel movement regularity rather than lipid management. Very few remembered hearing about viscous fibers or plant sterols/stanols from a healthcare provider as an option for cholesterol lowering. The apparent reluctance of clinicians to recommend dietary adjuncts may be due to concerns about the associated time required for patient education, the belief that they have minimal efficacy, or other factors. This is unfortunate since many clinical trials have shown that these dietary adjuncts are efficacious and would be expected to allow many patients to attain goal levels of low-density lipoprotein cholesterol (LDL-C) and/or non-high-density lipoprotein (HDL)-C without drug therapy, or with lower dosages of medications.1

Viscous fibers and plant sterol/stanol-containing products have been extensively studied and shown to reduce serum concentrations of LDL-C, non-HDL-C and the number of circulating atherogenic lipoprotein particles.1-6 Levels of triglycerides (TG) and HDL-C in subjects with hypercholesterolemia are generally unchanged by consumption of viscous fibers or plant sterols/stanols, although limited research suggests that TG levels may improve in patients with hypertriglyceridemia when consuming plant sterols and stanols.7-9

Viscous Fibers

Viscous fibers that have been studied in clinical trials include those from psyllium seeds, beta-glucan (from oats and barley), legumes, pectin (found in many fruits) as well as fibers used mostly as food ingredients or in laxative products such as guar gum, modified cellulose fibers and glucomannan. A meta-analysis of results from 55 clinical trials using viscous fibers including those from oats, psyllium, pectin and guar gum indicated that each gram of viscous fiber in the practical dose range of up to 10 g/d produced a mean change in LDL-C of -1.7 mg/dL (95% confidence interval -2.0 to -1.4 mg/dL).10 Based on the mean LDL-C level in the US population of 126 mg/dL,11 this translates into a reduction of ~1.3% per gram. Figure 1 shows LDL-C responses from a study in which subjects with hypercholesterolemia were randomly assigned to consume control, oatmeal or oat bran

[Discuss this article at www.lipid.org. Go to “Topics” and look for “Underutilization of Dietary Adjuncts in Dyslipidemia Management.”]
cereals, producing a range of daily beta-glucan intakes. In our experience, the absolute LDL-C response increases somewhat with higher baseline LDL-C concentrations, resulting in similar percent reductions across the range of usual baseline LDL-C levels. Thus, the addition of 3–10 g/d of viscous fiber to the diet would be expected to reduce LDL-C by roughly 4–13%. Larger reductions with intakes >10 g/d have been observed, but the practicality of such intakes over the long term is questionable and has not been studied extensively.

Results from studies ranging in length from several months to one year indicate that the LDL-C lowering effects of viscous fibers do not diminish over time. Viscous fibers lower cholesterol by forming a viscous solution in the gastrointestinal tract, thus creating a physical barrier that prevents or slows the translocation of micelles to the intestinal brush border. This results in reduced absorption of cholesterol and bile acids, increasing their excretion. As with bile acid sequestrants and cholesterol absorption inhibitors, the net effect is to reduce the quantity of cholesterol and bile acids returning to the liver, inducing hepatocytes to increase expression of LDL receptors, which enhances removal of LDL and other apolipoprotein B-containing lipoproteins from the circulation. An additional mechanism that may contribute to the cholesterol-lowering effects of viscous fibers is the slowing of glucose absorption, which blunts the postprandial insulin response. Lowering the day-long insulin level may contribute to cholesterol lowering by reducing the stimulatory effect of insulin on hepatic cholesterol synthesis.

**Plant Sterols and Stanols**

Meta-analyses of data from as many as 84 trials using plant sterols and stanols have shown that consumption of ~2 g/d of plant sterols or stanols (equivalent to ~3.3 g/d of sterol or stanol esters) is associated with a mean reduction in LDL-C of 13.1 mg/dL, representing a response of 10.3%, based on the mean LDL-C concentration in the US population. There is evidence of a dose-response relationship within the range of 1.0 g/d (~5.9% LDL-C reduction) to 3.0 g/d (~10.7% LDL-C reduction), but this flattens at higher doses, so there appears to be minimal additional benefit to consuming quantities beyond ~3.0 g/d (see Figure 2).

Figure 2. Weighted mean percent changes in low-density lipoprotein cholesterol (LDL-C) by daily dosage of plant sterol or stanol (calculated using the prediction equation published in reference 20). The response curves for sterols and stanols are indistinguishable, so they may be considered equivalent with regard to efficacy. As with viscous fibers, the absolute LDL-C reduction appears to increase with greater baseline LDL-C concentration, resulting in similar percent responses for a given dosage across the typical baseline LDL-C range. At an intake of ~2 g/d, the background diet (low or high fat/cholesterol) does not materially impact the response.

There appear to be at least two mechanisms that account for the effects of plant sterols and stanols on fasting lipids. One is that they have structural similarity to cholesterol and therefore compete with cholesterol for incorporation into micelles, a necessary step for delivery to cholesterol transporters (Nieman Pick C1 Like-1 transporters) in the upper small intestine. The second mechanism relates to up-regulation of the adenosine triphosphate binding cassette (ABC) G5 and G8 transporters. Plant sterols and stanols absorbed into the enterocytes trigger greater expression of these transporters that pump sterols (and stanols), including cholesterol, out of the enterocyte and back into the intestinal lumen. The net effect of these two mechanisms is to reduce cholesterol absorption, resulting in less availability of cholesterol to hepatic cells. In response to reduced hepatic cholesterol, hepatocytes increase expression of LDL receptors, which enhances removal of LDL and other apolipoprotein B-containing lipoproteins from the circulation.

**Dietary Adjuncts in Combination**

Limited data from studies in which viscous fibers and sterols or stanols have been used together suggest they have additive effects to lower LDL-C levels. For example, consumption of a cereal containing 5.0 g/d oat beta-glucan in combination with 1.5 g/d plant sterols lowered LDL-C significantly more (9.6%) than
consumption of a cereal containing 5.0 g/d oat beta-glucan and no plant sterols (5.0%). However, the LDL-C reduction with the combination cereal was less than predicted, suggesting that viscous fibers might partially interfere with the cholesterol-lowering effects of sterols/stanols. Therefore, if patients are going to take both viscous fibers and plant sterols or stanols, it may be prudent to advise them to consume these at separate meals. Our group recently demonstrated that the effects of consuming a ready-to-eat cereal containing oat beta-glucan on LDL-C and non-HDL-C were additive to those of weight loss.26

**Dietary Adjuncts Combined With Lipid-Altering Drug Therapy**

Results of studies assessing the lipid-altering effects of viscous fibers and sterol/stanol products when added to statin therapy have consistently shown that the LDL-C lowering effects are directly additive to those of statins.27-29 Dietary adjuncts may be particularly useful for patients who cannot tolerate high-dose statin therapy, or who have failed to achieve treatment targets for LDL-C and/or non-HDL-C at the maximal dose of a statin. Greater than 80% of the therapeutic effects of statin drugs are obtained at the typical starting doses with each subsequent doubling of the dosage adding only ~6% more LDL-C lowering.1 Accordingly, the effects of adding 10 g/d of viscous fiber or 2 g/d of sterols or stanols are approximately equivalent 1.5 to 2.0 doublings of the statin dosage. Additional research is needed to assess the effects of dietary adjuncts in combination with non-statin lipid-altering agents. There are theoretical reasons for concern that the effects of viscous fibers and plant sterol/stanol products might not be fully additive when added to drugs with intestinal modes of action (i.e., ezetimibe or bile acid sequestrants) and results from one study suggested that combining plant stanols and ezetimibe did not significantly enhance cholesterol lowering compared to ezetimibe alone.30

**Safety and Tolerability of Dietary Adjuncts**

The major concern with consumption of viscous fibers is the potential for gastrointestinal intolerance, particularly with fermentable fibers such as beta-glucan, guar and pectin. Anecdotal reports suggest that these symptoms lessen over time with continued use in many patients. Psyllium fiber (e.g., Metamucil®) and modified cellulose fibers (e.g., Citrucel®) have relatively low fermentability and may be tolerated by patients who experience symptoms with more fermentable fibers. There is also concern that consumption of viscous fibers may impair the absorption of minerals including calcium, phosphorous, and magnesium. A recent examination indicated that a diet rich in soluble fiber slightly reduced calcium and phosphorous balance in subjects with type 2 diabetes,31 but had no apparent effect on magnesium levels. However, these effects were minor and do not justify modifications of the NCEP ATP III dietary recommendations.

Results from meta-analyses indicate that vitamin A (retinol), vitamin D, and vitamin K-dependent clotting factors were generally unaffected by ≥1.5 g/d plant sterols and stanols.18 Statistically significant reductions were found for alpha carotene (9%), beta-carotene (28%), and lycopene (7%).18 However, after correction for the reduction in LDL, the lipoprotein carrier of carotenes, only the change in beta-carotene remained significant and this is of uncertain clinical significance. We generally advise such patients to include a rich source of carotenoids in their diet such as dark green leafy vegetables or vegetable juice (e.g., V-8®).

Of greater concern is that results from some observational studies have suggested that modest elevations in circulating levels of plant sterols may be independently associated with coronary heart disease risk, although data from other studies show no association.25 Also, statin use may increase sterol absorption (including plant sterols).33 While the relationship between circulating plant sterol levels and coronary heart disease risk in those without sitosterolemia (a condition in which ABCG5 and G8 activity are absent or impaired) remains theoretical, some clinicians favor products containing plant stanols over those with plant sterols because stanol absorption is much less than that of plant sterols (mean plant sterol absorption is <5%, plant stanol absorption is <0.5%, whereas cholesterol absorption is ~55%).34

**Conclusions**

Dietary adjuncts are underutilized in clinical practice. Results from meta-analyses indicate that consumption of 8 g/d of viscous fiber or 2 g/d of plant sterols or stanols will reduce LDL-C by ~10%,10,18,20 and that the

*continued on page 34*
The Accreditation Council for Clinical Lipidology

2009–2010 Certification Guide Available:

There are two pathways to recognition available through the ACCL:

**Core Certification**—Basic Competency in Clinical Lipidology (BCCL)
Open to anyone involved broadly in the field of lipidology and lipid management. Benchmark your professional competency in the field of clinical lipidology and sharpen your skills.

**Advanced Certification**—Clinical Lipid Specialist (CLS)
Open to licensed allied health professionals who provide specialized care to patients with dyslipidemia and related cardiometabolic conditions. Validate your training and expertise for patients, your employer, and professional colleagues.

**Why become certified?**
Achieving certification is an investment in one’s career, professional and personal development growth. The ACCL provides recognition and distinction in the field of Clinical Lipidology for those allied health and primary care professionals who successfully credential and complete a written examination.

**What are the differences between the two exams?**

The **BCCL program** offers a baseline competency assessment and certification pathway for any healthcare professional or paraprofessional involved in dyslipidemia management. This credential is appropriate for those who wish to demonstrate a core competency in clinical lipid management.

The BCCL exam was created at the intermediate level of difficulty and consists of between 50–75 multiple-choice questions. The two-hour BCCL examination is offered electronically at testing centers across the US and Canada year-round. Upon approval of your application, you will receive an e-mail providing instructions on selecting your exam date and location.

The **CLS program** is a recognition pathway open to licensed Allied Health Professionals who are pursuing advanced certification and provide specialized care to patients with dyslipidemia and related cardiometabolic conditions. Certification as a Clinical Lipid Specialist by the ACCL signifies that you have documented your commitment to continued professional development in Lipidology, and provides assurance to the public, your colleagues and the medical profession that you have successfully completed a course of education in lipid management.

The content of the CLS exam reflects the knowledge, skills, and attitudes deemed essential for the competent practice of Lipidology. The examination has been constructed at the upper level of difficulty and consists of approximately 200 multiple-choice questions. The 4-hour exam focuses on the approved Core Curriculum in Clinical Lipidology, and is offered three times during the year. Visit the website for locations, dates, and more details.

Learn more and register at: www.lipidspecialist.org.
“How-To” Customize Your Homepage in 6 Easy Steps

The National Lipid Association’s new community website has been available for a little over three months now, and the early adopters of our exciting new initiative are already reaping the benefits of participation. They experience increased interaction between NLA Leadership and the members, increased contact among members themselves, and easier communication between NLA members and NLA staff. This new web presence has been a long time in the making, but it has been worth the wait. Months of development and member feedback have yielded a site that is engaging, easy to use, and helping to reinforce a sense of community among the practitioners of our specialty. If you haven’t visited the new site yet, please give us a look at the same place we’ve always been: www.lipid.org.

We’d like to use this space to give you some ideas about how to use this new resource; and if you haven’t been to the website before, getting signed in is a good place to start. Depending on a variety of factors, what you actually see at the website may be slightly different from the illustrations below.

1. At the top right hand corner of every page, you will find a Login link.

Once you click this link, you’ll get a login prompt that looks like this:

2. The new community website takes the same username and password combination as the previous NLA website. If you do not remember this information or have difficulty accessing your account, send an email with your full name to webmaster@lipid.org or call Clark Morgan at the NLA office directly: 904-309-6202. He’ll be happy to get you started.

Once you’re logged in, you can freely browse all the many sections our website has to offer: for example, issues of our newsletter The Lipid Spin, members-only access to The Journal of Clinical Lipidology and a wealth of clinical articles and top-shelf educational programs like Lipid Insights.

The real action starts when you begin to interact with your peers. Read Blogs from your fellow members and comment on them, join Special Interest Groups such as Thomas Dayspring’s extraordinary Lipid Geeks, join active discussions in our Topics area or tie them all together with our Core Curriculum—a multidisciplinary approach to defining the science of lipidology.

With so much information to be found, how do you cut to the essential information you most need to know? The answer is the member portal page. This is what you see by default whenever you log in to your lipid.org account. At first, you’ll see a generic assortment of “widgets” featuring different content available on the site; now, take the opportunity to make lipid.org your own customized resource.

Start the customization process by clicking the “Account” link at the top right corner of the page.

3. The next page will have a sub-menu item for member home page customization:

4. From the following page, you can select the items you’d like to display on your member home page.

You can click the “Add It Now” button for any of these and the numerous other widgets listed to add that content your member home page. If you don’t read Blogs, don’t add them. If you’re more interested in seeing what the latest articles from the Journal of Clinical Lipidology are, then do add that widget. In this way, your first view of the site on any visit will highlight and emphasize the content you most enjoy using. There is a second level of customization available for the member home page as well. You can further customize most of widgets according to the subject matter. Each widget’s options are slightly different; but among other things,
From the NLA community

By Robert Wild, MD, Editor, Lipid Spin

[To discuss this article with Dr. Wild, please visit his blog at: www.lipid.org/community/blogs/entry/Progestin-in-OC-CVD-risk]

Progestin in OC CVD risk

NLA members should be alert to two recent reports that are important for clinical practice for women. These are particularly important from age 35 onward. Oral contraceptives (OCs) are being pushed to help with menopausal transition bleeding with a recent marketing to use 24-day active OCs with lower estrogen doses. Windows of opportunity seem to exist given recent reporting of a cohort and a case control study one from the Netherlands and one from Denmark comparing risk of venous thromboembolism (VTE) with the pill. Estimates of risk are remarkably similar and confirm past studies that progestin type in an OC is important. Risk is lowest for levonorgestrel and norethisterone, and the risk is 1.5–2.0 for gestodene, desogesterel, and norgestimate compared to levonorgestrel. OCs are being pushed to help women with perimenopause transition, given problems with menstrual bleeding, reduction of adenomyosis and—importantly—the need for contraception. The later is often forgotten and readers should be reminded that the most common time for unwanted pregnancy is prior to age 20 but the second most common time is after age 35!

OCs have 4–9 times more hormone content than does postmenopausal hormone therapy and with the extra steroid load side effects go up in terms of population frequency of events—importantly VTE. Readers should be aware, however, that the absolute risk difference in any of these agents is very small. Baseline risk is 5/10,000 and goes up to about 15–20/10,000. Personal VTE or family history is a contraindication (5% Caucasians have Factor V Leiden) and the studies did not deal adequately with this confounder. Smokers over 35 shouldn't take the pill but not because of VTE risk, it is because of arterial risk (e.g., stroke or MI). Obesity is not a contraindication, but we have limited data in obese patients regarding effectiveness. This is important because pregnancy carries a much greater risk than does the pill. Fortunately, alternatives are available and for sure one size does not fit all. So far there is no evidence that 35 ug is any riskier overall than a 20 ug estrogen pill. Many favor a lower dose estrogen OC yet lower doses may not be as effective in obese women (no real data as of yet). The differences between various OC preparations are small enough that individual choice or other side-effect profile may take preference. Remember that OCs have to be taken to be effective (typical use failure is 8% in the first year). IUD is more effective for contraception and carries less thrombotic risk, is very cost effective over 10 years (non medicated) and is often used for Gyn conditions (as progestin impregnated 5 years).
An independent physician certifying organization offering the highest benchmark of professional competency in clinical lipidology.

You are invited to become a . . .

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Why should you become a Certified Lipidologist?

- Validate knowledge essential to the practice of clinical lipidology.
- Enhance your professional stature and credibility in the field.
- Demonstrate your commitment to continued professional development and the highest standards of patient care.

Credentialing Requirements

The ABCL certification program is open to licensed physicians in the US or Canada. Applicants must meet credentialing requirements.

2010 EXAMINATIONS:
NEW IN 2010 - Exam to Be Offered Online in Testing Centers Across US and Canada

Spring Testing Window
March 15–April 15, 2010
(Application Deadline: February 22, 2010)

Summer Testing Window
June 14–July 14, 2010
(Application Deadline: May 17, 2010)

Fall Testing Window
September 20–October 20, 2010
(Application Deadline: August 30, 2010)

“Achieving Diplomate status from the American Board of Clinical Lipidology provided me a phenomenal education, and recognition as an expert. It has given me the opportunity to realize my dream of owning a comprehensive cardiometabolic risk reduction center, and the ability to establish myself as a thought leader within the lipidology community.”

Tara Lynn Dall, MD
President/Medical Director
Advanced Lipidology Early Detection Center for Heart Disease and Diabetes

For an application, handbook, eligibility requirements, and examination information, visit the ABCL website at:

www.lipidboard.org
or, contact us at: 904-674-0752
A New Therapeutic Option for Patients With Statin-Associated Myalgia

A significant barrier to effective low-density lipoprotein cholesterol (LDL-C) lowering is the fact that 5–10% of patients treated with statins develop myalgia, rendering ongoing treatment with that agent intolerable. Several strategies have been proposed to find a tolerable treatment with other statins or different LDL-C-lowering medications. In a novel approach, Becker, et al., report on the effectiveness of the dietary supplement red yeast rice, in achieving LDL-C reduction in subjects with statin-associated myalgia. Sixty-two hypercholesterolemic patients who had discontinued at least one statin because of myalgias with resolution of muscle pain, were randomized to either receive 3 600 mg capsules of red yeast rice or 3 placebo capsules twice daily for 24 weeks, together with a therapeutic lifestyle program. Their mean age was 61 years, 65% were women, 13–19% had coronary artery disease, the mean number of statins received before the trial was 1.7–2.0, and the mean LDL-C at baseline was 163–165 mg/dL. After 12 weeks of treatment, the mean LDL-C in the red yeast rice group was significantly lower at 120 mg/dL (-27%) than in the placebo group 154 mg/dL (-5.7%) (p<0.001). At 24 weeks these values were 128 mg/dL (-21%) and 150 mg/dL (-8.7%), respectively (p<0.011 for difference). There were no changes in high-density lipoprotein cholesterol (HDL-C) (mean baseline value was 52, 53 mg/dL) or triglycerides (mean baseline value was 146, 148), and no differences in weight or other standard biochemical tests between the two groups. Although there were no differences in pain inventory score (on a scale of 0–10, the mean score in the red years rice group was 1.4, while that in the placebo group was 2.0) or CPK levels, 2 of 29 patients in the red yeast rice group and 1 of the 30 subjects in the placebo group developed persistent intolerable myalgias. Two other patients discontinued red yeast rice because of dizziness in one and loose stools in another.

These results suggest that a regimen of red yeast rice and therapeutic lifestyle changes may offer a lipid-lowering option for patients with a history of intolerance to statin therapy. Because no definitive treatment for statin-associated myalgia exists, and as many as 57% of patients with statin-associated myalgia will develop muscle pain when rechallenged with a different statin, many patients adopt alternative therapies—including red yeast rice—to manage their hypercholesterolemia. Red yeast rice (the preparation consists of the fungus Monascus Purpureus layered on rice kernels and prepared as a capsule) contains naturally occurring fungal inhibitors of cholesterol synthesis known as monacolins. Monacolin K is in fact lovastatin. The obvious question is how did the red yeast rice lower LDL-C without causing myalgia? The authors suggest that the amount of monacolin K in the daily dose of the preparation is equivalent to 6 mg of lovastatin that may be too small an amount to cause myalgia, which is known to be dose-dependent. The ability to lower LDL-C when such a small dose of lovastatin-equivalent is used (in another study using twice as much monacolin K yielded a 42% reduction in LDL-C) may be due to the concomitant presence of other monacolins in the preparation which either lower LDL-C without provoking myalgia or potentiate the effect of monacolin K. Finally, a note of caution; red yeast rice has been reported to cause myopathy, rhabdomyolysis and hepatotoxicity, so the use of large doses of the preparation needs to be monitored as one would statin therapy.

Reference

The Accreditation Council for Clinical Lipidology (ACCL) is an independent certifying organization that has developed standards and an examination in the field of Clinical Lipidology for the growing number of allied health professionals who manage and treat patients with lipid and other related disorders.

The ACCL offers two unique pathways to certification and competency assessment in Clinical Lipidology:

- The Certified Lipid Specialist program is an advanced certification pathway open to licensed Allied Health Professionals specializing in lipid management.

- The Basic Competency in Clinical Lipidology program offers a competency assessment and credentialing pathway for any healthcare professional or paraprofessional with an interest or involvement in the area of dyslipidemia.

Each pathway offers a unique application process and examination that will assess and validate the specialized knowledge and training required to practice or work in the multifaceted and unique field of lipidology. Both exams are offered electronically at testing center locations around the country for maximum convenience and cost-effectiveness.

Certification and credentialing by the ACCL demonstrates your professional commitment to the prevention of cardiovascular disease and documents your expertise in lipid management for patients, referring professionals, employers and colleagues.

Need more information about ACCL exams?
Learn about the exams, the prerequisites, testing center locations, fees and topics covered in each exam. Apply online or download an application for both exams at www.lipidspecialist.org.

For additional information, please email tmackowiak@lipidspecialist.org or contact us at (904) 309-6250.

www.lipidspecialist.org
Paying Your 2010 Dues
Membership in the NLA is a tremendous value and is priced very low to make it easy for you to remain a member. By now or very soon, you’ll be receiving your dues statement for 2010. Once again, we’re offering the popular option of letting you renew for 3 years and save $50. New this year, your invoice has an option where you can make a tax-deductible contribution to the Foundation of the NLA and we hope you’ll participate. Do renew your dues and ensure that you retain full member access to www.lipid.org, and continue to receive the Journal of Clinical Lipidology and the Lipid Spin. We’re also sending out the Spring 2010 Education Catalog, which offers a full overview of our programs for next year. As you’ll see, membership in the NLA entitles you to deep discounts in the cost of our programs and meetings. We’re glad you’re a member and we hope you’ll renew by the deadline of January 15, 2010. For added convenience, you can renew directly at our website, www.lipid.org.

Call for Abstracts – NLA Annual Scientific Sessions
If you’re planning to submit a poster for the NLA Scientific Sessions to be held in Chicago, May 13–16, 2010, make a note that we will need your abstract fairly soon. The abstract submission deadline is February 15, 2010. Accepted abstracts will be published in the May/June 2010 issue of the Journal of Clinical Lipidology.

We are accepting three different poster categories: Young Investigators; Members in Practice; and Members in Industry.

Presenters who are Young Investigators (with accepted Abstracts) will receive a $300 travel voucher and free registration to the 2010 NLA Scientific Sessions. Submissions will also be eligible for the NLA Young Investigator Award. For more details on topics and to submit your abstract online, visit www.lipid.org/abstracts.

ACC Summit Conference Planning Underway
The NLA offers Masters Summit symposiums twice a year to provide members with cutting-edge information from the leaders in our field. If you missed the Masters Summit we held at AHA in November, keep an eye on lipid.org and at Medscape, where highlights from the Summit, “Overcoming Challenges in CVD Prevention,” will be posted soon.

Also, make sure you attend our next Summit, which is scheduled for March 13, 2010, to be held prior to American College of Cardiology Scientific Sessions in Atlanta, Georgia. This symposium will focus on the theme: “Progress in Prevention: Global Approaches to CVD Risk Assessment and Treatment.” Join an international panel of experts who will discuss and debate their approaches to prevention of CVD with an emphasis on the development of global guidelines, the influence of the healthcare system structure on guideline development and the impact of guideline implementation on patient outcomes. The conference will explore the accuracy of current risk prediction models in various ethnic populations and will present data around new models. These conferences are consistently popular with our members and others in the medical community, so save the date. We’ll have ads and registration forms available soon at lipid.org and keep an eye on your mail as well.

NLA PQRI Benefit Program Has Been Updated—Effective and Affordable Participation
For the second year running, the National Lipid Association has made it easier for physicians and other eligible professionals who wish to participate in PQRI (the Physicians Quality Reporting Initiative), a Centers for Medicare and Medicaid Services (CMS) program. Our Web-based reporting tool—PQRinet—facilitates claims-based reporting of individual quality measures for diabetic patients. Visit nla.pqrinet.com to sign up for this program. If you’re looking to participate, you may wish to review the PQRI instructions and frequently asked questions (FAQ) posted on the CMS PQRI website at www.cms.hhs.gov/pqri. Eligible participants can receive up to 2 percent of their Medicare billing for registered patient groups. More details are available at nla.pqrinet.com. You can also just follow the link from lipid.org on the news carousel. (There is a $299 fee for registration; but those who bill through CMS frequently should soon recoup the expense of this investment.)
FROM THE EDUCATION DEPARTMENT

**New Lipid Insights Programs Available**
Our Lipid Insights Virtual Journal Club are 60-minute CME/CE Webcasts that offer members and others the benefit of the NLA’s perspective on important new research and clinical trial updates. We now have two new programs available:

*Lipid Insights from the AHA—* Dr. Michael Davidson leads a discussion with Drs. Christie Ballantyne, Vera Bittner, and Roger Blumenthal providing interpretation and clinical application of important dyslipidemia research presented at this year’s AHA meeting.

*Lipid Insights Virtual Journal Club: Implications of the ARBITER-6 Trial—* Drs. Allen Taylor and Christie Ballantyne discuss the results and implications of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER-6 HALTS) study.

Both programs offer CME and can be viewed online at www.lipid.org/education/lipidinsights. Also, past Lipid Insights webcasts are archived and can be accessed at this URL as well.

Note that a ReachMD XM Radio podcast of Lipid Insights from the AHA is also available at www.reachmd.com and can be accessed from their homepage. CME credit is offered there as well.

**CLM SAPs Online**
You can now participate in four of our Complex Lipid Management Self-Assessment Programs (CLM SAPs) and self-study modules (NLA-SSMs) online. This is a convenient and expedited way to gain 5–6 educational credits and further sharpen your skills and assess areas needing improvement. The online modules are available at www.lipid.org/education.

Also, our newest CLM-SAP in the Series, Edition 13—Challenging Cases in Dyslipidemia—is being mailed together with the current edition of the Journal of Clinical Lipidology, so look for it in the mail. It will also be available online in January 2010.

**NEW: Patients Are Waiting at the Virtual Lipid Clinic**
If you haven’t visited the NLA vClinic™ yet, take a moment to see the future of online CME. In response to member requests, we’ve developed these case-based performance improvement modules. The NLA vClinic at lipid.org gives you the opportunity to work up and manage virtual patients over multiple visits with input from leading clinical experts, all while earning CME/CE credit. Be sure to use the vClinic CME Companion that accompanies these activities to assess your clinical mastery and compare your performance with other learners. Visit www.lipid.org/vclinic to participate. We are adding new patients frequently so come back if you haven’t visited lately. We are now discussing these cases at our Clinical Update Meetings so do investigate the vClinic and be prepared in advance.

**NEW: Fellows Training and Mentoring Programs**
The NLA Graduate Medical Education Committee is pursuing the development of a basic Clinical Lipidology fellowship curriculum and is collecting samples of curricula from any existing training programs. To expedite this lengthy process, the committee will enlist the services of an experienced consultant to assist in preparing the necessary application to secure approval by the ACGME. This process is essential to establishing Clinical Lipidology as a recognized specialty of medicine and will assist in obtaining recognition by the American Board of Medical Specialties.

Through the efforts of NLA President Dr. Vera Bittner, the NLA has completed a web-based in-service exam on lipid metabolism and dyslipidemia management to teach this aspect of the training guidelines for fellowship programs (COCATS), and to comply with the ACGME outcomes mandate. This online assessment exam is a derivative of the NLA Self-Assessment Program, with approximately 50 multiple-choice questions adapted from the NLA-SAP, Volume I. As an added feature of the module, Program Directors are able to track their Fellows’ performance on the exam and compare their program’s overall performance with their peers. The NLA-SAP, Fellows Edition will be made available to all Program Directors in December 2009, and first through the American College of Cardiology Training and Workforce Committee. Any members involved in Fellows training may contact the NLA office at fellows@lipid.org to apply for this program.

The NLA also plans to offer a 2010 Fellows Outreach Program in conjunction with the 3 scientific meetings we’ve scheduled for 2010. The NLA will invite Program Directors in the hosting regions to send their Fellows to participate in the NLA Lipid Management Training Course as well as a half-day mentoring session and reception with the faculty...
Scenes from AHA 2009 Scientific Sessions in Orlando

The National Lipid Association was present at the American Heart Association’s 2009 Scientific Sessions in Orlando. Prior to the opening of the Sessions, the NLA held a Masters Summit conference on “Overcoming Challenges in CVD Prevention: A Focus on the Cardiometabolic Risk Continuum.” With an outstanding faculty of national thought-leaders, this was a “standing-room-only” symposium, as each of the previous Masters Summits have been. This was an excellent introduction to the AHA Sessions as the presentations included looks at CVD prevention from multiple perspectives, including inflammation, hypertension, and diabetes as targets of treatment. If you haven’t attended an NLA Masters Summit, you’re missing out on the highest level of education the NLA offers. Be sure to register and arrive early—seats go quickly.

The big news at the Sessions was the release of data from the ARBITER 6 trial. The New England Journal of Medicine printed the results Sunday evening and the author of the paper, Dr. Allen Taylor, gave a presentation the next day on November 16. There was a lively panel discussion of the study findings, and the NLA has established discussion areas and blogs at lipid.org where we invite you to weigh in with your own thoughts on the impact of the ARBITER 6 trial.

Two past presidents, Dr. Anne Goldberg of NLA (L) and Dr. Diane Becker of SELA (R), were on hand at the Sessions and visited with the NLA at our booth in the exhibit hall. Dr. Becker remembers the early days when she helped to found the Southeast Lipid Association and is pleased to see the growth of the NLA. “The development that has most interested me,” she says, “is the certification process in clinical lipidology. Our field is both an art and a science and now we are teaching this.” She also notes that the NLA is strongly oriented toward networking and helps members integrate into a professional community where they can stay in touch. Dr. Goldberg adds that the NLA has helped female members advance in the medical community, being an egalitarian organization. “The Sessions at AHA are a bit smaller this year,” she says, “but the quality is tremendously high.”

The Director of NLA Marketing and Associate Director of the Foundation of the NLA, Karen Kent, meets with Dr. Marcus Lipp, who is speaking to other physicians about homozygous familial hypercholesterolemia, which he can address from a patient’s perspective and about which he is raising awareness.

There was much interest among attendees at the Sessions about the NLA and we expect to have increased our membership as a result of exhibiting. Clinical lipidology is a key facet of cardiovascular disease treatment and prevention. We’ll be exhibiting next at the American College of Cardiology conference, March 14–16 in Atlanta, Georgia. We hope to see you there.
Online Activities
Available at www.lipid.org/education

Webcast: Should an LDL-C Less Than 70 mg/dL and a CRP Less Than 2 mg/L Be Dual Targets of Therapy? Pro and Con
Sponsored by the NLA

Webcast: Lipid Insights from AHA 2009: Implications for Clinical Practice
Sponsored by the NLA

Webcast: Lipid Insights – Implications of the ARBITER-6 HALTS Trial
Sponsored by the NLA

Online Self-assessment Programs
4 Complex Lipid Management SAPs are available:

- Clinical Applications of Advanced Lipoprotein Testing, Inflammatory Markers and Non-invasive Assessments of Atherosclerosis
- Management of Low HDL-C
- Management of Dyslipidemia—Focus on Combination Therapies
- Pharmacology and Safety of Lipid-Altering Therapies

These programs are available online at: www.lipid.org/education/online

2010 Meetings and Courses

February 19–21, 2010
NLA 2010 Winter Clinical Lipid Update
(hosted by the Pacific and Southwest Regional Chapters)
The Palace Hotel
San Francisco, CA
www.lipid.org

March 13, 2010
NLA Masters Summit: Progress in Prevention: Global Approaches to CVD Risk Assessment and Treatment
Atlanta, GA
www.lipid.org

March 14–16, 2010
American College of Cardiology 59th Annual Scientific Sessions
Atlanta, GA
www.acc.org

May 13–16, 2010
NLA 2010 Annual Scientific Sessions
(hosted by the Midwest Regional Chapter)
Sheraton Hotel and Towers
Chicago, IL
www.lipid.org

August 27–29, 2010
NLA 2010 Summer Clinical Lipid Update
(hosted by the Southeast and Northeast Regional Chapters)
The Mayflower Hotel
Washington, DC
www.lipid.org

NLA Professional Development Courses

February 18–19, 2010
- Lipid Management Training Course
- Comprehensive Cardiometabolic Risk Reduction Course—Phase III
- Masters in Lipidology Course
The Palace Hotel
San Francisco, CA
www.lipid.org/education

May 12–13, 2010
- Lipid Management Training Course
- Comprehensive Cardiometabolic Risk Reduction Course—Phase III
- Masters in Lipidology Course
Sheraton Hotel and Towers
Chicago, IL
www.lipid.org/education

August 26–27, 2010
- Lipid Management Training Course
- Comprehensive Cardiometabolic Risk Reduction Course—Phase III
- Masters in Lipidology Course
Mayflower Hotel
Washington, DC
www.lipid.org/education
The Foundation of the National Lipid Association is the charitable arm of the National Lipid Association. The Foundation served as an education and research, with an emphasis on serving professional, community and public health interests.

Since its inception in December 2008, the primary focus of the Foundation has been to generate awareness of the grant program and identify public awareness opportunities that align with our mission.

Foundation Grant Program
The Foundation’s grant program provides education, research and community outreach grants to applicants who meet the criteria. (See inset on page 29). In 2009, we provided three grants to support local CME education programs:

<table>
<thead>
<tr>
<th>Grant Name</th>
<th>Grant Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>16th Annual Clinical Management of Heart Disease - Cardiology Update 2009</td>
<td>Cardiovascular Institute of Philadelphia</td>
</tr>
<tr>
<td>2nd Annual Cardiovascular Disease Update: Strategies for Successful Care of the Cardiovascular Patient (see below)</td>
<td>UMC Native American Cardiology Program</td>
</tr>
<tr>
<td>Cardiovascular Disease Protection Through Clinical Lipidology: A Primer with Contemporary Issues</td>
<td>Orange County Membership of the Pacific Lipid Association</td>
</tr>
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A Closer Look
In October 2009, the National Lipid Association Foundation issued a grant to help support a conference titled, “The Second Annual Cardiovascular Disease Update: Strategies for Successful Care of the Cardiovascular Patient.” The conference was held in Scottsdale, Arizona, and organized by the Native American Cardiology Program, a collaboration between the University Medical Center at Tucson, Arizona, and the Indian Health Service. The target audience were primary care providers and clinical staff, mainly from Indian Health Service facilities, and tribal and urban clinics. The goal of the conference was to bring providers the most up-to-date information on the evaluation and treatment of cardiovascular diseases, with particular emphasis on practical diagnostic and therapeutic strategies for treating patients with such common conditions as chronic angina, dyslipidemia, chronic kidney disease, and peripheral vascular disease.

The conference was attended by 65 participants, including primary care physicians and cardiologists, nurses, nurse practitioners, and physician assistants. The Indian Health Service Clinical Support Center was the CME accrediting organization. After a brief overview of the epidemiology of diabetes and heart disease among Native Americans, the first half day focused on acute care situations. Dr. Timothy Ingall, a neurology consultant at the Mayo Clinic in Scottsdale, discussed the evaluation and management of a patient presenting with new neurological symptoms and possible stroke. Dr. Karl Kern, director of the Cardiac Catheterization Laboratory at the Arizona Health Sciences Center and a leader in the field of resuscitation research, discussed the care of the cardiac arrest patient, focusing on the science of effective resuscitation, hypothermia and prompt catheterization to improve intact neurologic survival. Dr. Eric Brody, the assistant director of the Native American Cardiology Program, reviewed the key components of managing patients with acute myocardial infarction at rural facilities.

The second conference day was devoted to care for chronic conditions and began with discussion of the COURAGE trial. The presentation compared and assessed medical therapy and revascularization for patients with chronic stable angina. Following this were lectures on the management of patients with chronic kidney disease, congestive heart failure, and atrial fibrillation. Dr. Wm. James Howard, a principal investigator in the Strong Heart Study and the SANDS Trial and Professor of Medicine at...
George Washington University School of Medicine, gave an excellent lecture titled, “From STRONG to SANDS: Managing Lipids and Blood Pressure Among Native Patients—Yes We Can!” Following was a roundtable case discussion with the faculty where audience-generated cases and questions were reviewed. Dr. Joseph Mills and Dr. David Armstrong, co-directors of the Southern Arizona Limb Salvage Alliance based at the Arizona Health Sciences Center, spoke on the evaluation and management of patients with diabetes foot ulcers and strategies for decreasing amputation rates. There was also a brief review on lipid-lowering therapies and antihypertensive and anti-thrombotic medications. Lipid management was a thread woven through most of the lectures, given its central role in primary and secondary prevention.

The conference was well received. The majority of the attendees rated the course and educational objectives as excellent. More than half of the participants noted that they would change their management of lipids based on what they learned during the conference. Overall it was an extremely successful educational conference that will help optimize care for a population with very high rates of diabetes and premature death from coronary disease.

The grant from the Foundation of the National Lipid Association helped to make the conference possible and allowed us to invite nationally known faculty from outside the region. [Beth Malasky, MD, FACC of the Arizona Health Sciences Center, University Medical Center, Tucson, Arizona, contributed to this report. –ed.]

**Support the Foundation**

Replenishing the funds for the Foundation of the National Lipid Association grant program is essential to future viability and health of our organization. Take a moment now to help by investing in the future of the FNLA. Your donation will help support professional outreach and education and promote public awareness of critical issues in public health. You can make a tax-deductible donation online at [www.lipidfoundation.org](http://www.lipidfoundation.org) or make a contribution the next time you renew your dues.

**FNLA Grant Criteria**

**Parameters for all FNLA Grants**

- Will fund up to $5000 or less.
- Applications must be submitted at least 60 days prior to the date funds are needed.
- Funds must be used for activities within 90 days of grant approval.
- Funds cannot be used for small, exclusive or commercial events such as dinner programs among physicians.
- Grants will be considered for activities that focus in the therapeutic areas of Dyslipidemia, Cardiometabolic Disorders, CV Risk Reduction, and related efforts to reduce morbidity and mortality associated with dyslipidemias.

**Community Outreach Grants**

- Funding will be used to develop educational materials for patients and the public.
- Grants will only be approved if the requester is a non-profit organization or if the activity is sponsored by a non-profit organization.

**Research Grants**

- Must be original research in the areas of Dyslipidemia, Cardiometabolic Disorders, CV Risk Reduction, and related efforts to reduce morbidity and mortality associated with dyslipidemias.

**Education Grants**

- Educational grants will only be accepted for CME or CE certified activities approved by and accredited provider of continuing medical education.

To apply online or learn more, log onto [www.lipidfoundation.org](http://www.lipidfoundation.org) and click on “Grants.” If you have any questions, please call Karen Kent at 904.309.6211.
“It’s like TurboTax® for CMS quality reporting!”

Maximize Your PQRI Incentive Payment!

The PQRIwizardSM is a simple step-by-step online solution for participating in the CMS Physician Quality Reporting Initiative (PQRI)

The PQRIwizard Makes PQRI Reporting Quick & Easy:

✔ Earn a 2% Incentive Payment – on all Medicare Part B professional services for the entire year
✔ No Claims or Coding – requires as few as 30 patient records
✔ Saves Time – complete and submit your entire PQRI report online in just a few hours
✔ Maximize Your Incentive – automatically validates your practice data & notifies you when the report is ready to submit
✔ Still Time for 2009 - Participation is available until February 1, 2010 (data must be for patient visits in 2009)

In 2008, 100% of eligible professionals that relied on the PQRIwizard, and submitted valid patient data, received their incentive payment from CMS.

Visit https://nla.pqriwizard.com for more information.
atherosclerosis in many cases has had a remarkable impact on physician behavior and patient motivation, an area that deserves more research. It is the strong opinion of this clinician and many others with expertise in atherosclerosis imaging that CIMT is ready for clinical application.

References


From the Files cont. from page 14


[Note: The views expressed in this article are those of the author. The NLA invites members to provide scientific and medical opinion which does not necessarily represent the policy of the National Lipid Association or its chapters.]
measures define a minimum level of control (i.e., a “floor”) and should not discourage clinicians from more intensive treatment, if deemed appropriate in the context of the individual patient’s cardiovascular risk and supported by evidence. The potential impact of these performance measures is large. Using NHANES data, Kahn, et al. estimated last year that 78% of US adults aged 20–80 years are candidates for at least one prevention activity (although some of these were individuals with established disease). They further estimated that 36% of myocardial infarctions and 20% of strokes could be prevented if prevention activities across the country would match those achieved by the best health care delivery systems. While implementation of the primary prevention performance measures will be challenging, I believe that we simply cannot afford not to go forward.

What do you think about these competency and performance measure statements? Do they go too far or do they not go far enough? Were any critical aspects omitted? How will the statements affect you in day-to-day practice? Let’s discuss these and other aspects at www.lipid.org. Look for the NLA Community logo to discuss articles online at www.lipid.org.

**Table 2: Performance Measures for Primary Prevention**

- Lifestyle/risk factor screening
- Dietary intake counseling
- Physical activity counseling
- Smoking/tobacco use risk assessment
- Smoking/tobacco cessation
- Weight/adiposity assessment
- Weight management
- Blood pressure measurement
- Blood pressure control
- Blood lipid measurement
- Blood lipid therapy and control
- Global risk estimation
- Aspirin use

**References**


**News and Notes cont. from page 25**

and Program Directors in attendance. There will be no fee for attending and travel scholarship grants (up to $500) will be provided to help cover the cost of Fellow travel and hotel stays. Contact Lindsay Otto by e-mailing her at lwotto@lipid.org for more details about this program.

**Annual NLA CME Needs Assessment Survey—Member Response Essential!**

Keep an eye on your e-mail, because we’ll be sending you an invitation soon to participate in our annual CME Needs Assessment Survey. This is your opportunity to tell us what you need most in education, and how we can best meet your needs. As you can see, we directly apply your preferences in the design of our educational activities. We want to meet your needs so take a few minutes when you see the survey invitation and help us to help you more. Incentives will be offered to those who participate!

**UPDATED: Comprehensive Cardiometabolic Risk Reduction Course—Phase III**

This newly defined NLA program focuses on the practical aspects of office-based weight management for patients with cardiometabolic risk. The role and benefits of weight loss approaches in cardiometabolic risk reduction will be reviewed, and expert insight regarding their clinical implementation will be provided. This 3-hour course incorporates case vignettes and basic quality improvement strategies to assist you in setting standards-based performance goals for managing various patient populations. Program tools will support patient education and management. The course will be offered 3 times in 2010: February 19 in San Francisco, CA; May 14 in Chicago, IL; and August 27 in Washington, DC. For more information and to register, visit www.lipid.org/education.
effects on LDL-C and other atherogenic lipoproteins are additive to those of Therapeutic Lifestyle Changes and statin drugs. The dietary adjuncts recommended by the NCEP ATP III can help many patients achieve LDL-C and non-HDL-C treatment goals without drug therapy, or with lower dosages of drug therapy, and should be recommended more often than appears to be the case at present.

References
**Clinical Lipid Update – Winter 2010**

**Jointly Hosted by the Pacific and the Southwest Regional Chapters**

**February 19–21, 2010**

**Palace Hotel • San Francisco, CA**

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### Guest name(s), if attending meeting:

______________________________

### Membership status:

- I am currently a member.  
- My application for membership has been submitted and confirmed.  
- I will apply at www.lipid.org  
- Please send me membership information.

### Payment Method

- VISA  
- MC  
- AMEX  
- Check

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**Signature**

______________________________

Name on Card

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### Important Information

- **Master’s Course**
  
  To purchase related study materials or the NLA-SAP’s please go to: www.lipid.org/education/nlasap.

- **Registration:**
  
  Registration and payment must be received no later than February 5, 2010. After this date a syllabus and name badge cannot be guaranteed- so register TODAY!

- **Cancellation:**
  
  Telephone Cancellations will not be accepted. A written notice of cancellation must be received no later than February 5, 2010. This includes Social Events and Guest Fees.

- **Special Needs:**
  
  ____________________________
  
  **ADA Compliance:**
  
  Attendees who need additional reasonable accommodations or who have special needs should contact the NLA at 904-998-0854.

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### 3 Easy Ways To Register

**Mail To:**

National Lipid Association  
6816 Southpoint Parkway, Ste 1000  
Jacksonville, FL 32216

**Fax To:**

NLA at 904-998-0855  
Fax with credit card number and signature

**Online:**

www.lipid.org

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### Circle fee based on attendee type

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<th>Non-Member</th>
<th>Trainee</th>
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<td>$395</td>
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**Clinical Lipid Update**

**Winter 2010**

**February 19–21, 2010**

Includes course syllabus and one admission badge to Exhibit Hall for all food functions.  
*(Saturday Night Dinner NOT Included)*

- I Join NLA and register for Clinical Lipid Update

| N/A | $495 | $75 | N/A |

**Ancillary Courses**

- Master’s Board Review Course*
  
  **February 18–19, 2010**

  | $695 | $895 | $595 | $1,200 |

- Lipid Management Training Course
  
  **February 18–19, 2010**

  | $395 | $585 | $195 | $900 |

- Comprehensive Cardiometabolic Risk Reduction Program
  
  **February 19, 2010**

  | $0 | $0 | $0 | $0 |

**Registration Fee Total**

| $____ | $____ | $____ | $____ |

### Social Events and Guest Fees

- Saturday Night Dinner-Registrant

  | $125 | $____ |

- Saturday Night Dinner- Guest(s)

  | $125 | X____ | $____ |

*Please note: $25 of your Dinner Ticket will be donated to the Foundation of the National Lipid Association.*

- Exhibit Hall Pass-Guest(s)

  | $80 | X____ | $____ |

**Social Events and Guest Total**

| $____ | $____ |

**Combined Total Sections 2,3 & 4**

| $____ | $____ |

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**Register at www.lipid.org**

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35
Translating the Evidence into Practical Lipid Management
What Is the Take-Home Message?

February 19-21, 2010
Palace Hotel • San Francisco, CA
Register at www.lipid.org

Program Highlights

- Controversies in Dyslipidemia Management and Atherosclerosis Prevention
- Markers, Imaging Techniques, and Advanced Testing to Improve Risk Stratification
- How to Achieve Plaque Regression and Stabilization
- Diet, Exercise, Lifestyle Changes - What Works and What Doesn't
- Predictions and Updates on New Treatment Guidelines
- The Role of HDL-C Mapping and Functionality in CVD Risk and Management
- Treating Diabetic Dyslipidemia: Getting All Lipid Parameters to Goal
- Practical Pearls and Take-Home Strategies for Your Practice
- Case Studies on Special Populations

See page 35 for registration information