Clinical Feature:

Apolipoproteins A-I, B and C-III in the Oklahoma Cherokee

—Piers R. Blackett, MD
—Petar Alaupovic, PhD
—Elisa T. Lee, PhD

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President

The NLA is in the lead

Looking back over my past year as President of the NLA, I can report that we have made substantial gains as an association. Always at the forefront of our thinking is our 5-Year Strategic Plan, a document we use as a road map of where we are going as an organization. While we haven’t completed every item on our list of goals—yet—we continue to make progress and here are some of the accomplishments we’ve enacted on behalf of our regional chapters and you, our membership.

Leadership and Organization: On this front we have been successful in establishing an In-Training Member on 3 of our 5 regional boards. We hope to complete this initiative soon. By bringing in more fellows at an early stage in their careers, we broaden input on our boards and also help these members obtain a unique perspective from the viewpoint of medical association management.

Liaisons and Lipidology Promotion: With respect to establishing international liaison for the promotion of NLA education, we have been active and have met with our European counterparts in a number of countries. There is considerable interest abroad in our courses and training materials and, through our role as a constituent of the International Atherosclerosis Society, we expect to make significant progress in the coming year. You may already have noticed that this year’s NELA Scientific Forum is being held in Boston, June 12–14, in conjunction with the XV International Symposium on Atherosclerosis. We plan on meeting with our counterparts to coordinate our efforts with other countries.

Education and Professional Development: Regarding our initiative to establish control over all symposia presented at NLA events, I’m happy to say we have accomplished this important goal, as it eliminates the perception of bias and enhances our ethical credibility as an organization. Another item in this category, the need to adjust our regional meetings, is underway and for 2010 we are scheduling two
regional meetings instead of four, which will help us conserve resources in this challenging economic climate. Also in this category, we have adopted a Core Curriculum in Clinical Lipidology. This is an extremely important document that outlines the very nature of our branch of medicine and helps us to better design and evaluate our educational programs. You can view the Core Curriculum yourself online at www.lipid.org/core_curriculum.php.

Communication and Public Policy: One of the first accomplishments last year was the creation of the NLA Rapid Response Committee. Establishing this protocol has allowed us to form the right kind of teams that can respond to time-critical and press-related issues in the appropriate timeframe. As breaking issues and controversies have arisen over the past year, the NLA has been able to draft and promulgate statements to our members and the public in a timely way, which keeps our Association relevant. As for social networking—a key goal in this area—we are proud to show you the new lipid.org website. More than a cosmetic change, the homepage of the NLA at lipid.org is now a robust tool for social exchange and networking, and we have new tools for you to use. You can listen to podcasts of our radio program, Lipid Luminations, you can read articles from the Journal of Clinical Lipidology, and read the latest news breaking in lipidology and metabolism. New features like member blogs and a user-editable lipid-wiki are on the way. Keep visiting lipid.org often to watch for new changes. And for those of you who use Twitter, the NLA is now broadcasting. Login into Twitter and start following nationallipid.

Administration and Finance: I am very pleased to announce that we have launched the Foundation of the National Lipid Association. This charitable foundation will help us extend key messages to our profession and the public, and it also allows us to make grants to deserving applicants who seek funding for research and education in the realm of clinical lipidology and cardiometabolic disease prevention and treatment.

Also during the year past, we have held a series of meetings that continue to improve in scope and quality, and we’ve had a visible presence at the AHA and ACC annual meetings. The prominence and influence of the NLA have continued to grow due to our continuous efforts at staying in the lead of clinical lipidology. Thank you for your support and participation in our Association.
Apolipoproteins A-I, B and C-III in the Oklahoma Cherokee

PIERS R. BLACKETT, MD
Professor of Pediatrics
Department of Pediatrics
University of Oklahoma Health Sciences Center
Oklahoma City, OK

PETAR ALAUPOVIC, PHD
Professor Emeritus, Department of Biochemistry
Oklahoma Medical Research Foundation
Oklahoma City, OK

ELISA T. LEE, PHD
George Lynn Cross Professor of Biostatistics and Epidemiology
Director, Center for American Indian Health Research
College of Public Health
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Introduction
The occurrence of increased cardiovascular risk in Native Americans is concerning, because this population is susceptible to insulin resistance, which plays a role in developing dyslipidemia and is leading to their high rates of type 2 diabetes. The association of diabetes with increased cardiovascular risk and mortality is particularly tragic since they appear to lose their innate protection from atherosclerosis following the development of insulin resistance and diabetes.1 Also, because the insulin-resistant state is increasingly common in childhood and is associated with obesity, it is more likely to lead to cardiovascular risk and diabetes in early adulthood. For these reasons, it is important to study both traditional and novel risk factors in Native American populations and to identify the risk markers that manifest at early ages and have potential for reversal. Following an initial pilot study to establish feasibility, studies were planned to determine possible associations of apolipoproteins with risk factors for type 2 diabetes and cardiovascular disease. A primary purpose was to determine prevalence in relation to age so that the data might serve to reveal early predictors and provide rationale for intervention strategies.

The Cherokee Indians
Because the Cherokee are the largest of more than 60 Oklahoma tribes, they were selected as being the most suitable to study potentially reversible risk factors for type 2 diabetes and cardiovascular disease. The Cherokee were one of 5 tribes who settled in Oklahoma between 1830 and 1842, after being forcibly removed from their homelands in the southeastern United States. The Cherokee removal in 1838, during which thousands perished during the long journey, later became known as “The Trail of Tears.” Despite formidable setbacks, they have retained their cultural assets in keeping with their historical traditions and continue to excel in several fields such as the arts, literature, education, medicine, farming, commerce and ranching. Similar to other American Indian populations, they have shown susceptibility to becoming insulin resistant and developing type 2 diabetes. This predisposition may result from the effect of a westernized lifestyle on their inherited susceptibility, which is common with other tribes such as the Arizona Pima, who have an even higher prevalence of type 2 diabetes.

Diabetes and the Tendency to Be Overweight
Of those who were available for recruitment, as previously described, 2205 volunteered for the Cherokee Diabetes Study. The age-adjusted prevalence of type 2 diabetes was 4.3% in females and 4.8% in males aged 5 to 40 years. Among the 89 individuals who had type 2 diabetes, 31 were newly diagnosed. Thirty-two (1.5%, 18 females and 14 males) were found to have an impaired fasting glucose. The prevalence of type 2 diabetes and impaired fasting glucose increased with age, number of parents with diabetes, obesity, degree of Indian heritage, high triglyceride value, and low HDL cholesterol. Thus, the increasing prevalence of type 2 diabetes in these young subjects with American Indian heritage is alarming, and it warrants early detection programs and preventive measures.

The relative tendency to gain weight in this population of
Cherokee children and adults, known to be predisposed to type 2 diabetes, plays a role in the onset of the metabolic syndrome as reflected by correlations of the criteria with the adiposity parameters such as the BMI Z-score and waist circumference. We have previously shown that Cherokee children and adolescents tend to have BMI Z-scores greater than 1, using NHANES norms derived from a national population sample, and that Native American children tend to become relatively more obese than the national norms at an early age. These observations have been confirmed and the increased BMI is known to be associated with insulin resistance in childhood.

Among other parameters pertaining to the metabolic syndrome, apolipoproteins were assessed on the basis that they can provide evidence that obesity and associated insulin resistance can lead to increased cardiovascular risk. Abnormal findings could potentially alert physicians, healthcare workers and the local community to initiate preventive measures.

**ApoC-III**

We were interested in apoC-III bound to apoB-containing particles as determined by heparin precipitation, as heparin precipitates apoB and separates apoB-containing particles from apoA-I-containing lipoproteins. In addition to its known capacity to inhibit lipoprotein lipase, inhibition of apoB binding to the LDL receptor and facilitation of apoB binding to proteoglycans in the arterial wall, apoC-III has recently been shown to enhance monocyte binding to endothelial cells, potentially linking associated hypertriglyceridemia to inflammatory processes in the arterial wall.

We assessed the association with heparin-precipitated lipoproteins containing apoC-III that we have designated apoC-III HP, representing apoC-III bound to heparin-precipitated apoB-containing lipoproteins. ApoC-III was measured in the precipitate because this measurement has previously been associated with cardiovascular risk, and in some papers has been designated LpB:C-III. In the Monitored Atherosclerosis Regression Study (MARS), apoC-III HP was shown to be stronger than triglycerides as an independent predictor of lesion progression, particularly for lesions with less than 50 percent stenosis, which progress to subsequent clinical events. Also, we have shown apoC-III HP to be related to insulin resistance in children and adolescents, and we demonstrated a trend for apoC-III HP to increase throughout the HOMA-IR quartiles in children and adolescents, suggesting that apoC-III HP is associated with insulin resistance at an early age. Recent studies have supported an association of apoC-III with the metabolic syndrome in adolescents and young adults. Logistic regression modeling for both adolescent and young adult groups showed that apoC-III HP had a higher association with the metabolic syndrome than the B:A-I ratio and there were significant trends for log apoC-III HP, B:A-I ratio, triglyceride:HDL-C ratio and HOMA insulin resistance to increase with the number of metabolic syndrome criteria (Figure 1). Furthermore, the prevalence of the metabolic syndrome increased by apoC-III HP quartile (see Figure 2 on page 18). These findings support evidence that increased VLDL production, characteristic of insulin resistance, results in relatively more apoC-III in VLDL and consequently in non-HDL. Furthermore, apoC-III HP correlated with HOMA-IR, BMI Z-score and waist circumference, but most strongly with waist circumference, supporting a role for apoC-III in forming triglyceride-rich particles in the arterial wall.
so-called “hypertiglyceridemic waist” syndrome. It is also possible that the strong relationship of apoC-III HP to obesity and insulin resistance can be attributed to an insulin response element in the C-III gene’s promoter region. ApoC-III production is normally down-regulated by insulin via the transcription factor, FoxO1. However, ApoC-III production increases in insulin resistance.

ApoB and ApoB:A-I Ratio
The significant trend for apoB to increase with the number of syndrome criteria in adolescents and young adults demonstrates that an increasingly severe presentation of the syndrome is associated with higher levels of atherogenic particles and supports evidence that apoB is an independent risk factor for cardiovascular disease.7 Also in children and adolescents, we have demonstrated a progressive increase in apoB for each homeostasis index (HOMA-IR) quartile in 5–9 year olds, 10–14 year olds, and in 15–19 year-olds for both genders.

In addition, the inverse association of apoA-I with the severity of the syndrome suggests that a deficiency of apoA-I-containing particles is a significant characteristic of the syndrome, because decreased apoA-I is also known to be independently associated with cardiovascular disease.7 It follows that the apoB:A-I ratio, representing the combination of the 2 risk factors, is strongly associated with the syndrome.7 The increase in apoB in relation to insulin resistance is associated with the increase in fatty acids transported to the liver. Therefore, the trend for apoB levels to increase with the number of criteria may indicate increasingly severe insulin resistance associated with more peripheral fatty acid mobilization.

HDL-C, LpA-I and LpA-I:A-II
Since low HDL-C is a known predictor of cardiovascular disease and high levels are protective in adult populations, it follows that low levels in childhood may increase cardiovascular risk at an early age. This is supported by post-mortem studies on the formation of atherosclerotic plaques at ages 15 to 34 years in the Pathological Determinants of Atherosclerosis in Youth (PDAY) study, in which the size and composition of the plaques were inversely related to the HDL-C levels. BMI was inversely correlated with HDL-C in Pima Indian men and women.9 Because Native American populations are prone to obesity in association with insulin resistance, we investigated whether BMI would influence high density lipoproteins at a young age.

We assessed Cherokee children and adolescents aged 5 to 19 years to determine how obesity is associated with LpA-I and LpA-I:A-II, respectively, corresponding to the larger HDL₂ and smaller HDL₂ particles. Correlations of waist circumference, a surrogate measure of visceral fat, with HDL cholesterol, LpA-I, and LpA-I:A-II, supported an influence of visceral fat on the tendency to decrease high density lipoproteins with age. Visceral fat is first acquired in childhood and is proportionate to a general increase in body fat, and when present in adolescence it is associated with post-mortem evidence of coronary artery pathology, suggesting its importance as a therapeutic target because it is potentially reversible. The influence on insulin resistance is of more significance in Native Americans in view of their predisposition to diabetes.

We concluded that the obesity-related lowering of HDL-C occurs as early as age 5 years. In general, the decline in HDL-C values with BMI Z-score quartiles was significant for all age groups of Cherokee children and adolescents; but declines in LpA-I and LpA-I:A-II were less remarkable. The finding is analogous to a predominant decrease in the cholesterol “load” for the respective HDL apolipoprotein “transport vehicles,” which remain relatively constant. Multiple regression modeling supported a negative influence of adiposity on HDL-C and, to a lesser extent, on LpA-I and LpA-
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**

I was consulted about a 50-year-old Asian, menopausal, non-smoking woman with reasonable weight who was, for quality-of-life issues, using Activella®, which is a combined continuous estrogen/progestogen replacement therapy (EPT) consisting of estradiol 1 mg and 0.5 mg of norethindrone acetate (a lower dose formulation is also available). The patient was doing well and is normotensive. On follow-up examination, a lipid/metabolic panel was performed:

- **TC** = 238 mg/dL
- **TG** = 80 mg/dL
- **HDL-C** = 54 mg/dL
- **LDL-C** = 168 mg/dL
- **VLDL-C** = 16 mg/dL
- **Non-HDL-C** = 184 mg/dL (TC – HDL-C)
- **TC/HDL-C** = 4.40
- **TG/HDL-C** = 1.48
- **Apo B** = 135 mg/dL
- **LDL-C/Apo B 168/135 >1.2**
- **Lp (a) 12 mg/dL**
- **FBS = 84 mg/dL**

The patient was asked to modify her diet and do more walking, but wondered if additional therapy was warranted.

**Discussion**

The 2007 AHA Guidelines on Women and CHD\(^1\) remind us that women age 50 or above with a single cardiovascular disease (CVD) risk factor have a 50% lifetime chance of having a clinical event, even though their 10-year risk of an event (as determined by Framingham Risk Scoring or FRS) is low. Even cursory examination of the lipid panel reveals several risk factors. Framingham data reveal that most women with CHD have high TG or high TG with low HDL-C,\(^2\) but the other one-third of women having CHD have elevated LDL-C. Clearly, this patient has CV risk and now the lipidologist must decide exactly what that risk is and determine if treatment should be therapeutic lifestyle or if lipid-modulating drugs are also indicated. The first step is Framingham Risk Scoring (FRS):\(^3\)

- **Age = 6 points**
- **Normotensive, nonsmoker = 0 points**
- **TC = 4 points**
- **HDL-C = 0 points.**
- **Total score of 10 points classifies her as a low-risk woman (1% 10-year risk)**

The treating clinician has a dilemma—the patient has low ten-year risk, but high lifetime risk of CVD. I believe we need to look deeper at the data. We know the risk of atherosclerosis is primarily related to the number of circulating potentially atherogenic particles that contact and enter the arterial wall.\(^4\) Each of those particles is enwrapped with a single molecule of apolipoprotein B (apoB), which provides structure, stability and solubility in plasma. The apoB also serves as a ligand for the LDL-receptor (LDLr). ApoB is also the only apolipoprotein that is with the particle from its point of synthesis to its point of degradation. It is non-transferable in contradistinction to all other apolipoproteins, which can jump between various lipoproteins. The apoB concentration is quite elevated at 135 mg/dL. Using Framingham Heart Study (FHS) population cutpoints,\(^5\) it is between the 90th and 95th percentile. In other words, the vast majority (90–95%) of adults would have a lower level. The 20th percentile (desirable for a high-risk patient) is 80 mg/dL, and the 40th percentile is 90 mg/dL. A 90th percentile apoB means this woman has severe hyperbetalipoproteinemia. This extreme elevation of a single CVD risk factor elevates her to the high-risk category.

What if the provider had not ordered an apoB level? There are values in her lipid profile that serve as surrogates of atherogenic apoB particles.\(^6\) Total cholesterol is the mg of cholesterol (in this case 238) that exists within all of the lipoproteins in a deciliter (dL) of plasma. The vast majority...
(80% or more) is usually trafficked within the apoB particles because they are so much larger than HDL (apoA-I containing) particles. The volume of spherical particles is \( \frac{4}{3}\pi r^3 \). Therefore any patient with a TC > 200 mg/dL should be suspected of having a high apoB. In early Framingham and MR FIT data, CVD events started to happen at TC levels > 200 mg/dL. 90% of apoB particles are typically LDL particles because of their long half life or plasma residence time (2–3 days). Thus an LDL-C of 168 (the 85th percentile population cut-point in FHS) strongly suggests a significant apoB elevation. Lastly, the elevated non-HDL-C is actually the best surrogate of atherogenic apoB particles whether the TG is above or below 200 mg/dL. The non-HDL-C value of 184 mg/dL is the 78th percentile cut-point in the FHS. Therefore, even without apoB testing one would be reasonably confident that this woman has a serious apoB problem without actually ordering the test. It is important to note that discordance between apoB and non-HDL can be significant (~30%) in patients with elevated TG, but that is not the case in this woman.

Nowadays, LDL particle size testing is readily available, but do we really need such data to help us make clinical decisions? The answer is no. All apoB-containing LDL particles are atherogenic if they exist in excess concentration. Large LDLs penetrate the arterial wall as easily as do smaller species; even VLDL and chylomicron remnants and IDLs are found in plaque and those particles are considerably larger in diameter than are LDLs. Using data that we have in this woman one could easily predict that the LDLs are large by one of two methods: A TG/HDL-C > 3.8 is associated with an 80% chance of having small LDLs; the ratio in this patient is much lower consistent with large (Pattern A) LDLs. Dividing LDL-C by apoB (in normal people the ratio is 1.0). Any ratio >1 indicates there are fewer particles than there is cholesterol and the particles are therefore large. Conversely a ratio < 1.0 suggests small LDL particles. The ratio in this woman is > 1. Her hyperbetalipoproteinemia is thus due to too many large LDL particles and she is at increased risk of CVD compared to a woman with normal LDL particle (apoB) concentration.

It would be reasonable to instruct this woman more carefully with therapeutic lifestyle suggestions and perhaps encourage her to supplement her diet with a plant stanol (sitostanol or Benecol) available as a spread or chews. I prefer not to advise plant sterols (sitosterol) as some data indicates menopausal women can over-absorb them. Because I believe this woman is at high risk, I would closely follow the apoB level. If after 3–6 months an apoB of 80–90 (20th–30th population cut-point) is not achieved, then drug therapy is indicated. It should be rather easily to normalize apoB by upregulating hepatic LDL receptors. Any therapy that depletes hepatic cholesterol pools will stimulate the sterol regulatory element binding proteins (SREBPs) to promote LDLr upregulation and enhance hepatic clearance of the excess apoB-containing lipoproteins (mostly LDLs in this case). Hepatic removal of apoB-cholesterol containing particles is termed indirect reverse cholesterol transport. Three drugs are available that reduce apoB (non-HDL-C and LDL-C) by upregulating LDLr, namely statins, ezetimibe and bile acid sequestrants (of which colesevelam is the most tolerable).

We will need a 30% reduction of apoB and thus we should initiate therapy with drugs capable of achieving
that goal. Typically a moderate dose statin would do that unless the patient is a hyperabsorber of cholesterol in which case there is often a hypo-response to the statin. Only trial and error would determine that as we do not routinely measure markers of absorption (sitosterol, campesterol). One should note that this patient is an Asian and they often respond to much lower doses of statins. Therefore I would start a lower dose of a statin and see the response. If goal is not achieved one can titrate the statin or add ezetimibe (also available as a combination tablet) or coleselam, which would likely get her to goal. Adding either ezetimibe or coleselam would upregulate more LDL receptors and further lower apoB or its lipid surrogates than would doubling the dose of the statin. The EPT that has been prescribed is one of the few EPT preparations that actually lowers apoB.9

Case Two

I was asked how the following patient should be approached. This case is very appropriate because of recent data from the JUPITER trial. The patient is a 45-year-old perimenopausal Caucasian female. She is currently on hydrochlorothiazide 25mg/day, Toprol-XL 25mg (metoprolol), and Ativan. The blood pressure is stable at 122/68. She is 5’4” and weighs 215 pounds. Lab testing shows the following:

- TC = 182 mg/dL
- LDL-C = 113 mg/dL
- HDL-C = 45 mg/dL
- TG = 157 mg/dL
- Non HDL-C = 137 mg/dL
- VLDL-C = 31 mg/dL
- TC/HDL-C = 4.0
- TG/HDL-C = 3.48

NMR LipoProfile

- Total LDL Particle # (LDL-P) = 1221 (desirable depends on risk)
- LDL size = 20.9 (Large or Pattern A)
- Large HDL = 4.0 (desirable > 9.0)
- Large VLDL = 4.1 (desirable < 0.5)

- hs-CRP = 5.17 mg/dL (n < 2.0)
- Lipoprotein (a) = 9 mg/dL
- Fasting Glucose = 97 mg/dL
- 2-hour post glucose challenge = 152 mg/dL

Discussion

This is a very typical presentation of a perimenopausal/ menopausal woman. As already discussed in the previous case, two-thirds of women in the Framingham Heart Study (FHS) who had an event over a 12-year period had an LDL-C < 140 mg/dL, but also had hypertriglyceridemia (>200 mg/dL) or hypertriglyceridemia with low HDL-C.2 All too often, such women are ignored or under-treated because their LDL-C is unremarkable. Lipidologists know that with the near epidemic emergence of insulin resistance (cardiometabolic risk), men or women with TG/HDL axis disorders often have considerable risk above and beyond what their LDL-C predicts.

If one applies the NCEP ATP-III guidelines3 to this patient, she is insulin resistant and has 4 of the 5 needed criteria: TG > 150 mg/dL, an HDL-C <50 mg/dL, obesity and hypertension. She does not yet have impaired fasting glucose but does have impaired glucose tolerance. The elevated hs-CRP is also very common in insulin resistant patents. In the Women’s Health Study, the presence of at least 3 of 5 components of the metabolic syndrome predicts incident cardiovascular events in apparently healthy women and the more components of the metabolic syndrome that are present, the higher the CRP. This is also true with atherogenic particles, as in the FHS the more components of the metabolic syndrome, the higher the LDL-P.11 JUPITER was a trial of rosuvastatin versus placebo with low-risk persons, but that risk assessment was based on FRS and normal LDL-C. However, 40% qualified for the diagnosis of metabolic syndrome and likely many more were insulin resistant without meeting all of the criteria. Therefore, it should be no surprise that the CRP was high in all and mean apolipoprotein B was 110 mg/dL (70th percentile population cut-point) and the patients were at considerably higher risk than it appears at first glance.12

The presence of least 3 of 5 components of the metabolic syndrome predicts incident cardiovascular events in apparently healthy women.
Analysis of the lipid profile should make one suspect that too many atherogenic particles and too few antiatherogenic particles (HDLs) are present. Clues to the atherogenic particles are the presence of metabolic syndrome, a high TC/HDL-C ratio, a borderline high TG/HDL-C ratio and elevated non-HDL-C. Looking at the lipoprotein analysis, the presence of large VLDLs and the reduced large HDLs are typical in such patients. The overproduction and secretion of large VLDLs is associated with increased blood viscosity, decreased endothelial nitric oxide, elevated fibrinogen and PAI-1. The large VLDLs have increased plasma residence time, which allows for cholesteryl ester transfer protein ( CETP) to exchange for cholesteryl ester (CE) from HDLs and LDLs. With respect to lipid concentrations, such patients have higher VLDL-C, lowering of LDL-C and HDL-C and, put them all together, a higher non-HDL-C (apoB or LDL-P surrogate). Surprisingly, this patient has large LDLs. Normally the LDL particles in such people are small, because the LDLs that have acquired TG at the expense of losing CE become small when further lipolysis occurs as the particles exposed to hepatic lipase. In data from FHS, at a TG level of ~150 mg/dL approximately 50% of patients will have increased LDL-P in the high-risk level (>1600 nmol/L) but 50% will not. Most likely her LDLs are somewhat but not too severely TG-rich and CE poor, and even after hepatic lipolysis they remain large. Large LDLs are more efficaciously removed by LDL receptors than small ones, and perhaps that is why her LDL-P is not higher.

NCEP guidelines strongly advocate that this type of patient obtain aggressive treatment, both lifestyle and pharmacologic. The lipid/lipoprotein goal of therapy in such patients is to normalize LDL-C (<100 mg/dL) and non HDL-C (130 mg/dL); the lipoprotein goals are to normalize LDL particle (apoB of 90 mg/dL² and LDL-P goal of 1000 nmol/L). Based on JUPITER, it may be important not only to get lipids/lipoproteins (apoB) to goal, but there were better outcomes in those who also had CRP reduced to < 2.0 mg/dL . If lifestyle modification does not get the patient to goal, a statin would be the appropriate first-line therapy and the mild elevation of non-HDL-C and LDL-P suggests the response to a generic statin would get her to lipid goal. If it does not, adding niacin or ezetimibe would further lower the non-HDL-C and LDL-P. Niacin would also increase total HDL-P. Adding niacin or ezetimibe to the statin would also further reduce CRP. Although in the VA-HIT trial (a study of men) the benefit of gemfibrozil was related to the presence of insulin resistance and not to the baseline or on-treatment TG or HDL-C level, there is little other trial evidence that a fibrate would be of benefit in patients with TG < 200 mg/dL.

[Attention readers: If you enjoy the cases files of Dr. Dayspring, you can request a free subscription to his biweekly Lipidaholics Anonymous Cases newsletter by e-mailing the author at tdayspring@oal.com. Former cases are archived at www.lipidcenter.com under the “professionals” tab. – ed.]

References
Hypertension and Dyslipidemia: A Rigadoon

A definition of rigadoon reads: “A couple dance in lively duple time, dating from 17th-century Provence and named after a dancing master from Marseilles.” This word brings me back to the 7th grade, when it was first introduced into my vocabulary by my never-normal general language teacher as “a lively dance for two.” Many years later, it now serves to remind me of how hypertension and dyslipidemia interact, how they together contribute to cardiovascular risk, and how the treatment of one often impacts the other.

It has been estimated in various studies that up to 30–40% of patients with hypertension also have dyslipidemia. Data from the Framingham offspring study show that more than 55% of adult men and women have 2 or more cardiovascular risk factors, including hypertension and dyslipidemia. When both risk factors are present, their effects are more than additive, such that patients with only mild to moderate elevations in cholesterol and blood pressure exhibit cardiovascular event rates often equal to the patients with very high levels of either single risk factor. The majority of hypertensive patients have LDL-cholesterol (LDL-C) levels above 100 mg/dL, and both ATP 3 and JNC 7 make mention of the importance of hypertension and dyslipidemia in risk evaluation and medication selection. In a scientific statement published in Circulation in 2007 on the treatment of the high-risk hypertensive patient, it is suggested that the more aggressive goal of 130/80 mm Hg also be targeted in those patients whose 10 year Framingham risk score is > 10%. Finally, in 2008 both the ADA and ACC in a consensus statement agreed that in patients with cardiometabolic risk (of which hypertension is one important component) aggressive LDL-C and Non-HDL cholesterol goals should be achieved. They also recommend targeting aggressive lipoprotein goals for the first time. In a recent “Get with the guidelines” publication it was noted that while the average LDL-C for patients admitted to the hospital with cardiovascular diagnosis was only 104 mg/dL, more than 50% of these patients where hypertensive.

Patients with dyslipidemia are more likely to develop hypertension. One study followed men for 18 years and showed that those patients in the highest quintile for Non-HDL-C had a 55% increased risk of developing hypertension. Similar studies in women have shown that the presence of atherogenic dyslipidemias is associated with the subsequent development of hypertension.

Treatment of these conditions is also interlinked. Statins have been shown to lower blood pressure in hypertensive patients, as well as impacting arterial compliance and systemic vascular resistance, possibly through nitric oxide mediated pathways. Patients with elevated LDL-C have been shown to have increased sensitivity to angiotensin II. Interestingly, dietary salt restriction in hypertensive patients has been shown to worsen dyslipoproteinemia. Elevated levels of angiotensin II or increased sensitivity to angiotensin II results in endothelial injury, perhaps facilitating lipoprotein entry into the vascular wall. Elevated angiotensin II levels promote oxidation and modification of LDL-C, thereby enhancing macrophage uptake. Studies in rodents have demonstrated angiotensin II inhibition of macrophage expression of the ABCA-1 transporter and decreases in HDL levels. This effect can be inhibited by AT1 blockade. In addition, studies on vascular endothelial cells have shown that oxidized LDL cholesterol down regulated ABCA-1 expression and promoter activity.

The clinical implications of this “lively dance” have been well demonstrated in clinical trials. Treatment of hypertensive patients with additional risk factors with normal LDL-C with statins in the ASCOT study showed significant outcome benefits, and most recently in the JUPITER trial, patients with normal baseline LDL-C levels, had average baseline systolic blood pressures of 134 mm Hg.

In our lipid clinic, one of our most common interventions in dyslipidemic patients is to change medications for other conditions that may be worsening the lipid profile. Both diuretics and beta-blockers may worsen LDL-C, HDL-C, and triglyceride levels. Use of ARBs, ACE inhibitors, CCBs or more cardioselective/vasodilating beta-blockers in these patients is recommended. The interaction and associations between even mild elevations in blood pressure and cholesterol is an important one that impacts the evaluation and management of the cardiovascular risk to which they contribute. Aggressively detecting and then managing to appropriate goals with the correct medications is necessary so as to negate or at least minimize the effects of this “lively dance for two.”

Remember the Rigadoon!

Reference
Rosuvastatin Prevents Vascular Events in Men and Women with Elevated C-Reactive Protein but Without Elevated Low-Density Lipoprotein Cholesterol

Post-hoc analyses of several statin intervention trials over the years, including CARE, ALLHAT, REVERSAL and PROVE-IT have suggested that the cardiovascular disease (CVD) benefit of statin therapy is influenced by a marker of heightened sub-clinical inflammation, namely high sensitivity C reactive protein (hs-CRP), such that the reduction in major CVD events is greatest in individuals with elevated CRP levels. This might reflect either (1) that elevated CRP levels identify at-risk individuals who have a robust response to statin therapy and/or (2) that independent benefit accrues from a statin-induced fall in CRP levels. The latter possibility would then suggest that in addition to the accepted target of statin therapy, namely low-density lipoprotein cholesterol (LDL-C) CRP levels might constitute a second target through which statins produce CVD benefit. The recent publication of The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER),\(^1\) tested possibility (1) above by addressing the question of whether apparently healthy persons with levels of LDL-C below current treatment thresholds, but with elevated levels of high-sensitivity CRP, might benefit from statin therapy.

The JUPITER investigators randomized 17,802 apparently healthy men and women with LDL-C levels of <130 mg/dL and CRP levels of ≥2.0 mg/dL to rosuvastatin, 20 mg daily or placebo, and followed them for the occurrence of the combined primary endpoint of myocardial infarction, stroke, revascularization, hospitalization for unstable angina, or death from CVD causes. At baseline, the median age was 66 years, 39% were women, 71% white, the median BMI was 28.3, BP 134/80 mm Hg, CRP 4.2 mg/L, LDL-C 108 mg/dL, HDL-C 49 mg/dL, triglyceride 118 mg/dL, fasting glucose 94 mg/dL, HbA1c 5.7%, eGFR 73 ml/min/BSA and 41% had the metabolic syndrome. The median on-treatment LDL-C and CRP values in the rosuvastatin group were 55 mg/dL and 2.2 mg/L respectively, representing a 55% reduction in LDL-C, and a 37% reduction in CRP levels by rosuvastatin compared to placebo. Median triglyceride values were 17% lower and HDL-C 4% higher than placebo levels. Although planned for an average follow-up period of 4 years, the trial was stopped early after 1.9 years because a clear-cut result had been obtained at that point as a result of the unexpectedly large rosuvastatin effect size. The rates of the primary endpoint were 0.77 and 1.36 per 100 person-years in the rosuvastatin and placebo groups respectively, yielding a relative risk reduction of 46%. Significant benefits were seen for MI (54%), stroke (48%) and death from any cause (20%) among the secondary endpoints. Subgroup analysis also showed significant benefits in those considered to be at low risk e.g. LDL-C ≤100 mg/dL, Framingham risk scores ≤10%, those with no other major risk factors (apart from age) or without the metabolic syndrome. The only adverse events of note was a significant reduction in deaths from cancer (35 vs. 58, p<0.02) a slight increase in HbA1c values (5.9% vs. 5.8%) and in newly diagnosed diabetes (270 vs. 216; p<0.01).

What to take from this interesting and provocative study? First, this is the first prospectively designed study in subjects without CVD or diabetes to demonstrate that when elevated CRP levels are used to identify individuals at risk, even with LDL-C values below the levels recommended for treatment, not only is statin therapy beneficial but the effect size seems to exceed the average reported CVD reduction in statin trials in which a particular LDL-C level is targeted for treatment (about 20% relative risk reduction for each 30 mg/dL [1 mmol/L] LDL-C). Thus, an elevated CRP level identifies at-risk individuals who have a robust response to statin therapy. Importantly, this does not prove that the CVD benefit is due to the reduction in CRP. It should be remembered that this was a highly selected older population in which only 1 in 5 screened subjects was randomized. Second, 40% of the population had

Perhaps most important is the question as to whether the results of the JUPITER trial should be translated to clinical practice.

Continued on page 19
“You’re going to die!”

My name is Paul Bradley. I’m an internist in Savannah, Georgia, in a hospital affiliated practice for the past 20 years. I’ve always had a special interest in obesity and its many complications, especially diabetes, hyperlipidemia, and hypertension. We have all experienced the frustration of seeing an overweight patient with “bad” laboratory values, knowing that you could right them with just diet and exercise. At the urging of a friend 3 years ago, I decided it was time to offer my patients an alternative to a never ending list of medications. I coaxed forty of my physician colleagues to help fund a center where we would make diet and exercise as easy and painless as possible. We originally called ourselves Hourglass Weight Loss and Fitness with the thought that we would appeal more to women than men. We represented different specialties and even competing medical groups.

At the first facility we offered circuit training for exercise, fresh ready-to-eat calorie-controlled meal plans that followed ADA guidelines, visits with registered dieticians, and nurse practitioners who booked in extended time blocks to do extensive diabetic and lipid instruction and management. Our goal was to create a black box that the community’s physicians could refer their patients to for those services for which the physicians did not have the time or resources. Patients could pick and chose what services they needed. The meal replacement plans made dieting easy. Available at two caloric levels, 1200 and 1700 per day, the meals were fresh and required heating for only a few seconds in a microwave oven. Menus changed daily and the food was delicious and was a wonderful example that drove home the message that you could eat great-tasting food that was nutritionally appropriate. As patients went on and off of the diet there was never a transition as everyone was eating real food. Patients, as a result, learned visually by example. Both patient feedback and results have been very good. As we have grown and learned from our patient’s experiences, we have changed our image and our name and are more co-ed in our services. Now we are OurLife (www.ourlifehealth.com) and have three offices in Savannah, all of which feature diet and exercise.

Last year, through a stroke of good luck, we were thrown into the national spotlight. My associate had come to me and said that he had a 500 pound 5’9” patient named Ruby who had heard of our weight loss plan and just knew that if we were to change her diet that she could lose weight. She admitted she did not know what she was supposed to be eating, how to shop for groceries, or how to cook. She didn’t know what a calorie was, much less which foods had high or low values. She claimed that she was on disability and had no money, but a reality TV production company in Hollywood wanted to film her struggle to lose weight. It turned out to be true, but the production company was actually only shooting a pilot. They had virtually no budget to work with and still had to sell the pilot to a network. Ruby is a remarkably compelling individual, though, so we agreed to sponsor her in the program. The production company came as promised, shot for a few weeks, and then left. The program starts with my associate and myself telling Ruby that she was going to die if she did not lose weight. Ruby began her OurLife program. She was placed on our 1700-calorie plan and gently started to exercise. Two months went by. While Ruby was doing great, we had not heard back from the film crew. Just when we were beginning to doubt that we would ever hear back from them, we got a call that Style Network had bought the series.

Ruby Gettinger had had diabetes for many years. On starting the diet she had an A1c of 9.8 and a cholesterol of 160 with triglycerides of 160, an HDL of 41 and LDL of 88. She was supposed to be taking metformin 1000 mg twice a day, glypizide ER 10 mg a day, and Byetta 10 micrograms a day, as well as simvastatin 10 mg a day. Four months later she had lost 60 pounds and her A1c was down to 6.7. She had stopped her simvastatin on her own and her cholesterol at that point was 194 with triglycerides of 202, an HDL of 39, and an LDL of 114.
Her glypizide ER was stopped and she continued on the diet without the statin. Her weight loss continued. Five months later and now off of the metformin her A1c was down to 5.7 and her cholesterol was at 172, triglycerides at 118, HDL at 39, and LDL at 109. We are now a year from the start of her diet, and Ruby is down to 349 pounds! She is due back for another set of labs soon and has remained faithful to her diet.

The TV program Ruby has become a remarkable phenomenon. It is the top-rated program in the history of Style Network (www.mystyle.com). The first season is over and shooting for the second season has begun. She has even been featured on Oprah twice. I act as Ruby’s weight-loss specialist on the series. The program has remained medically correct, stressing that one can lose weight by just eating “right” and exercising regularly. Ruby is one of television’s few morbidly obese females and, I believe that as such, she is appealing to the two-thirds of American women that are overweight. Ruby’s message is clear: it’s not OK to be overweight—or as she puts it, “we all have to conquer the beast within.” So as America watches Ruby eat her nutritionally balanced meals and exercises, she is literally inspiring hundreds of thousands of others to do so as well. As for her long-term goal, Ruby wants to get down to 150 pounds and she won’t hear from me that that may not be realistic. She fully understands that she will need cosmetic surgery in the future. As for her cholesterol, she wants to just see what happens with diet for now. So we continue to follow it off of the statin.

While Ruby was inspiring America to lose weight, we had another unique opportunity: The local county government agreed to sponsor a three-month trial with 34 of its high-risk employees to lose weight if we could promise them that we could be budget neutral. The idea was to put them through the same program that Ruby was using. The employees would be provided OurLife meals at either the 1200- or 1700-calorie level, they would exercise regularly with a trainer, they would meet with a dietician, and would have their medications adjusted both at the beginning and end of the trial to the most cost-effective choices possible. As a bonus to the employee, any medication that could be purchased for $4 or less a month would be free as would the costs of the entire program. We were convinced that through the judicious use of generic alternatives and the benefits of diet and exercise, we could achieve significant savings. The criteria for enrollment was simple: participants had to be overweight and be on at least one maintenance medication. It turned out to be quite a diverse group with members ranging from the county attorney to county maintenance workers.

Roughly one third were male, two thirds female. Twenty percent were diabetic. By the end of the trial, everyone had lost weight. Remarkably, all 34 completed the program. Collectively, the group lost 550 pounds with an average weight loss of 16.3 pounds and a maximum loss of 34.8 pounds. The group lost an average of 4.1 inches in their waistlines. A1c levels consistently fell. Both of the insulin-requiring diabetics came off of their insulin during the 3 months (one had been on insulin for over 20 years). Many were on high potency branded statins at the start. Most were changed to lower potency generics. The end result was that lipid profiles remained stable and did not worsen. The program had a total cost of $66,000, most of which was related to the cost of the food. The savings from the medication changes alone when annualized amounted to $105,000. That did not include the future health savings, decreased time off work, etc.

Our goal has been a simple one: Create a model that allows the primary care physician, using currently accepted national standards, to help their patients with diet, exercise, and disease education. In the process we would see better blood glucose control and improved lipids while at the same time minimizing medication costs.

So far, so good.
Announcing the NLA vClinic—Interactive CME

As part of our 2.0 Web initiatives, we have launched the NLA vClinic, which allows NLA members to work up and manage virtual patients over multiple visits. These test cases are designed to enable you make treatment decisions and then compare them with other learners. In a manner similar to the NLA-SAP program, this online tool enables you to assess your level of clinical expertise. What’s more, you can compare your performance against that of other practitioners and obtain advice from NLA expert faculty.

To participate, visit www.lipid.org and follow the link from the homepage, or go directly to the vClinic at www.lipid.org/vclinic. In this engaging CME activity, you’ll meet a patient and obtain labs and other critical information. Then, after an introduction from a faculty member, you’ll be asked to make treatment decisions and obtain immediate feedback on your choices. In the event you’d like to consult with an expert, online help is available. A unique feature of this program is that you are able to follow a given virtual patient over time and see the results of your treatment decisions. This is the future of online learning, here today. Visit lipid.org/vclinic to learn more about this remarkable program, free for NLA members.

The Foundation of the National Lipid Association

It is with great pleasure that we announce the opening of the Foundation of the NLA. This is a major initiative of the Association that was conceived last year as a way to promote education and research in clinical lipidology, with a focus on professional and community public health improvement. The Foundation is now ready to conduct educational activities designed to enhance and promote the key messages surrounding medical efforts to prevent cardiovascular events and death from the perspective of addressing dyslipidemia and related cardiovascular disorders.

The Foundation of the NLA has several priority objectives:

- Conduct professional educational outreach programs on lipidology.
- Create small grant opportunities for professional education.
- Develop and issue statements on key issues in public health related to our mission.
- Develop solid, medically evidenced patient information and work with related foundations and similar organizations to inform patients and the public.

The Foundation offers grants at multiple levels: Research Grants for original research in our field, Medical Education Grants for CME or CE-certified activities, and Community Outreach Grants for educational initiatives aimed at healthcare professionals and the public. All grants will be considered up to a maximum funding level of $5,000. Complete details are available at the Foundation website: lipidfoundation.org.

Dues Reminder

If you haven’t paid your dues yet for 2009, we encourage you to do so immediately. Members who are in arrears on their dues will not be listed in the NLA Membership Directory and will not receive a subscription to the Lipid Spin or the Journal of Clinical Lipidology. Compared to other associations, our dues are very affordable and with NLA membership you have access to all areas of our website at lipid.org, online educational activities, discounted fees to live events and meetings, updates to our self-study programs, and many more benefits that come with being connected to your peers in clinical lipidology.

Pay your dues online at www.lipid.org. If you’d like to pay over the phone, call us at 904-998-0854 and we’ll be happy to assist you.

Continued on page 19
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
The National Lipid Association is very excited about our new educational initiative, the NLA vClinic™ available online now at lipid.org/vclinic.

The Virtual Lipid Clinic replicates real-world experiences of the busy clinician. Learners meet multiple “virtual patients” with different presentations, and manage them across multiple visits and care settings. Within each visit, learners make clinical decisions and interact with subject matter experts and peers.

The NLA vClinic™ is a personalized environment that presents new patients and visits to each learner. Through a unique knowledge management platform, you can track your progress and benchmark your performance with other learners.

Virtual patients from the vClinic will be frequently discussed at the NLA’s symposia and conferences to uniquely connect online and live educational experiences. This service is a benefit of NLA membership.

**NLA vClinic**
Welcome to the NLA vClinic. Here, you’ll have the opportunity to work-up and manage virtual patients over multiple visits, with input from leading clinical experts. Be sure to use the vClinic forums to share your opinions about key clinical decisions, and the CMECompanion that accompanies these activities to assess your clinical mastery and compare your performance with other learners.

Visit the NLA vClinic today at www.lipid.org/vclinic

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I:A-II. HOMA-IR was negatively associated with LpA-I:A-II. Therefore, its role as a cholesterol acceptor from lipoprotein and cellular sources appears compromised. The trend for HDL-C, LpA-I and LpA-I:A-II to decrease with age in boys more than in girls supports a gender-specific effect of puberty and suggests that boys become at higher risk during puberty, particularly when they are obese and insulin resistant.

Conclusions
The finding that apoC-III HP, apoB, and apoA-I are associated with the severity of the metabolic syndrome supports their use as markers of early interventions designed to detect and treat reversible cardiovascular risk at an early age. Correlations of HOMA-IR with apolipoproteins, criteria of the syndrome and the number of criteria present suggest that the outcomes result from pathways influenced by insulin resistance. Furthermore, epidemiological evidence suggests that the apolipoproteins, particularly those containing apoC-III in the heparin precipitate, are involved in propagating early vascular lesion formation. This is an important observation for the Cherokee, because their tendency to gain weight and develop insulin resistance appears to coincide with the development of the metabolic syndrome at young ages when detection and prevention is needed.

In general, the apolipoproteins apoA-I, apoB, and apoC-III appear related to insulin resistance and associated adiposity and support an emphasis on lifestyle as a means to prevent obesity and insulin resistance in childhood, particularly in populations predisposed to obesity and insulin resistance such as the Cherokee. The need to increase HDL in boys is particularly important because lowering during puberty is more marked.

Acknowledgements
The Cherokee Diabetes Study was supported by grant R01 DK47920 from the National Institute of Diabetes and Digestive and Kidney Diseases, of Bethesda, Maryland.

The authors wish to express their appreciation to the Cherokee people and to the health care and administrative officials of the Cherokee Nation in Tahlequah, Oklahoma, for their support and assistance. The authors also thank the administrators and staff of the Sequoyah High School, and the Cherokee Nation clinics at Stilwell, Salina, Sallisaw, and Jay. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the Indian Health Service or the Cherokee Nation. The manuscript was approved for publication by the Cherokee Nation Institutional Review Board.

References
Keep Up with Changes at Lipid.org

You may have noticed our new look at lipid.org. We are adding new features at a steady pace and we strongly encourage to visit our website often to see the most recent developments. New features include a daily news carousel with our breaking top stories, a news feed of the top stories in lipidology, and direct access to articles in the Journal of Clinical Lipidology—now available to read online with a single mouse click. If you want to know what is happening in our field of medicine and what your Association is doing, Make www.lipid.org a daily stop when you go online.

Take the NLA Surveys

Please visit the NLA homepage and complete our surveys. There is a link to “Practice Trends Surveys” in the news carousel, or you can just go directly to www.lipid.org/survey/ to fill them out. The first two are practice trend surveys that help us to design curricula that meet your needs. The third survey asks about cholesterol ratios and your practice. Each takes only a minute to complete, but will help us immensely. If you’ve already taken them, you have our thanks. All responses are confidential.

Breaking News: For those who use the Twitter service to get breaking news and notes delivered to their desktop computers or cell phones, the NLA is now broadcasting.

Login into Twitter and start following national lipid. To learn more about Twitter and to register an account, visit www.twitter.com.

Lipid Luminations cont. from page 12

the metabolic syndrome, and although the fasting glucose was normal, the HbA1c level suggests a sizable number of participants had glucose intolerance, so they may have been selected to some extent for increased cardiometabolic risk by virtue of age and metabolic factors. Third, the absolute benefit for the primary endpoint was quite small—142 primary events in the rosuvastatin group versus 251 in the placebo group out of 8901 subjects in each group and 120 participants needed to be treated for 1.9 years to prevent 1 primary outcome event. Fourth, the finding of a deleterious effect on glucose tolerance is of concern and needs further work, since it is not the first such observation in a statin intervention trial.

Perhaps most important is the question as to whether the results of the JUPITER trial should be translated to clinical practice. It should be remembered that while the CRP test is reproducible over time, there are many other factors that cause a rise in CRP levels, including mild infection, arthritis, cigarette smoking, weight gain, and estrogen treatment, and while these effects may have been diluted and controlled for in JUPITER, they could have substantial effect in the single patient visiting the office. This means requiring a second inconvenient and expensive test at least 2–4 weeks distant from the first after ensuring that there are no confounding factors to ensure that an elevated value is stable. In addition, there is confusion in practice as to what kind of CRP test is needed; the standard CRP test is too insensitive to read in the relevant 0–10 microgram/L range, and many third-party payors will not reimburse the patient for the test. Thus, while the results of JUPITER are compelling reading and certainly strengthen the case of CRP as a CVD risk marker, it is difficult to conclude that these results are poised for widespread use in primary prevention.

Reference

You are cordially invited to attend the Fifth Annual Scientific Forum of the Northeast Lipid Association on June 12–14, 2009 at the Seaport Hotel in Boston. Our focus on Translational Lipidology will present you with the latest lipid science and show you how to apply it to your clinical practice. Earn up to 10 continuing education credits by attending our forum and extend your knowledge by participating in the pre-conference professional development courses offered by the NLA (see page 5).

Our program faculty gathers top thought leaders and contributors to the field of lipidology who will report on critical recent studies. The forum begins on Friday with a keynote address by Dr. Virgil Brown on the current state of clinical lipidology and an overview of where the field stands to grow internationally. Make plans to attend the welcome reception on Friday evening and join us for a very special Gala event on Saturday where we will enjoy one of the city's finest cultural experiences—the Boston Pops at Symphony Hall.

June is one of the best times of year to visit Boston, so be sure to set aside time to explore the city while you are there. Or, make plans to stay on for the International Atherosclerosis Society’s ISA conference in Boston after the sessions conclude on Sunday.

Up-to-date meeting information is posted at www.lipid.org. We look forward to welcoming you at the meeting!

Seaport Hotel
One Seaport Lane
Boston, MA 02210
For reservations call 800-440-3318

The Seaport Hotel’s fresh and inviting surroundings along Boston’s historic waterfront district will give you a glimpse of all that Boston has to offer. Conveniently located within miles of the Logan Airport and Boston’s downtown, the Seaport Hotel is also within walking distance of world-class shopping and gourmet dining.

Rooms have been reserved for NELA meeting attendees for $226/night (plus tax) per night. The cutoff date is May 21, 2009, or until the room block is filled. After this date, reservations and rates are subject to availability.
NORTHEAST LIPID ASSOCIATION
5TH ANNUAL SCIENTIFIC FORUM
SEAPORT HOTEL • BOSTON, MASSACHUSETTS
JUNE 12–14, 2009

First Name  Middle Initial  Last Name

Mailing Address

City  State or Province  Zip  Country

Phone  Emergency Contact/Phone

Email

Check all that apply:  MD  DO  PhD  RN  NP  PA  RPh  PharmD  RD  Other _____________

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

IMPORTANT INFORMATION

*Syllabus
NLA goes green. You must pre-order a syllabus with printed slides in order to receive one on-site. There will be a limited number available. Access to slides online available at no extra charge.

**Slides:
You may bring a flash drive to download an electronic copy of the presentation slides for free.

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

Registration:
Registration and payment must be received no later than May 27, 2009. 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 May 27, 2009. Includes Social Events and Guest Fees. There will be a cancellation fee of $25.

Special needs:

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

Register at www.lipid.org/nela
## Scientific Program

### Friday, June 12

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>8:00 AM–5:00 PM</td>
<td><strong>MASTERS IN LIPIDOLOGY ADVANCED TRAINING AND BOARD REVIEW COURSE</strong></td>
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<tr>
<td>8:00 AM–3:00 PM</td>
<td><strong>LIPID MANAGEMENT TRAINING COURSE</strong></td>
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</table>
| 4:00–5:00 PM     | **Keynote Address:** Professional Competence in Clinical Lipidology—Current Progress But a Growing Need  
W. Virgil Brown, MD |
| 5:00–6:00 PM     | **OPENING NIGHT INTERNATIONAL RECEPTION**                           |
| 6:00–9:00 PM     | **COMPREHENSIVE CARDIOMETABOLIC RISK REDUCTION COURSE**              |

### Saturday, June 13

<table>
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<tr>
<td>8:00 AM–4:00 PM</td>
<td><strong>MASTERS IN LIPIDOLOGY ADVANCED TRAINING AND BOARD REVIEW COURSE</strong></td>
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<tr>
<td>8:00 AM–12:00 PM</td>
<td><strong>LIPID MANAGEMENT TRAINING COURSE</strong></td>
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<tr>
<td>7:00–8:00 AM</td>
<td><strong>BREAKFAST</strong></td>
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| 8:00–8:10 AM     | Welcoming Remarks  
Penny Kris-Etherton, PhD, RD |
| 8:10–10:15 AM    | **MANAGEMENT OF DYSLIPIDEMIA AND OBESITY IN PEDIATRIC/ADOLESCENT PATIENTS** |
| 8:10–8:40 AM     | Pediatric Guidelines for Lipid Management  
Stephen R. Daniels, MD, PhD |
| 8:40–9:10 AM     | Obesity in Children and Adolescents  
Samuel S. Gidding, MD |
| 9:10–9:40 AM     | Pediatric Genetic Syndrome  
Peter O. Kwiterovich, MD |
| 9:40–10:15 AM    | Case Study Approach to Managing Children  
Susan E. Lynch, MD |
| 10:15–10:45 AM   | **BREAK**                                                            |
| 10:45 AM–12:25 PM| **GENETIC TESTING AND GENOMICS OF CVD**                              |
| 10:45–11:10 AM   | Understanding the Inherited Basis for Heart Attack  
Sekar Kathiresan, MD |
| 11:10–11:35 AM   | The Genetics of Statin Myopathy  
Paul D. Thompson, MD |
| 11:35–12:00 PM   | Novel Genetic Tests—In Which Patients Is Testing Appropriate and How Will Genetics Impact Clinical Therapy?  
Christie M. Ballantyne, MD |
| 12:00–12:25 PM   | Case Discussion and Panel Q&A                                        |
| 12:25–1:30 PM    | **LUNCH**                                                            |
| 1:30–1:45 PM     | NELA Business Meeting                                                |

Register at www.lipid.org/nela
### Saturday, June 13 Continued

<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>1:45–3:25 PM</td>
<td><strong>Residual Risk and Biomarkers</strong></td>
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<tr>
<td>1:45–2:10 PM</td>
<td>Recent Findings from the JUPITER Trial</td>
<td>Paul M. Ridker, MD</td>
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<tr>
<td>2:10–2:35 PM</td>
<td>Triglycerides as an Important Biomarker in CHD Risk Assessment</td>
<td>Michael C. Miller, MD</td>
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<tr>
<td>2:35–3:00 PM</td>
<td>HDL Structure—Function and Dysfunction</td>
<td>Stanley L. Hazen, MD</td>
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<td>3:00–3:25 PM</td>
<td>Case Discussion and Panel Q&amp;A</td>
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<td>3:25–3:50 PM</td>
<td>Lp-PLA2 as a Marker and as a Treatment Target</td>
<td>Michael H. Davidson, MD</td>
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<tr>
<td>3:50–4:15 PM</td>
<td>New Anti-Lipidemic Therapies in Early Development</td>
<td>James M. McKenney, PharmD</td>
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<tr>
<td>7:00–11:00 PM</td>
<td>NELA President's Dinner</td>
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### Sunday, June 14

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<th>Time</th>
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<tbody>
<tr>
<td>7:30–8:00 AM</td>
<td>Breakfast</td>
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<tr>
<td>8:00–8:30 AM</td>
<td>An Analysis of Lipid Fractions Among US Adults – Report from the NLA</td>
<td>Mark Cziraky, PharmD</td>
</tr>
<tr>
<td>8:30–9:00 AM</td>
<td>Improving Compliance Through Effective Counseling and Motivational Interviewing</td>
<td>Geoffrey C. Williams, MD, PhD</td>
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<tr>
<td>9:00–10:30 AM</td>
<td>Concurrent Workshops (each 45-minute workshop is repeated one time)</td>
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<tr>
<td>9:00–9:45 AM</td>
<td><strong>Workshop A</strong></td>
<td>Janet Long, MSN, ACNP, Karen E. Aspy, MD</td>
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<td>Managing the Complex Lipid Patient</td>
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<td><strong>Workshop B</strong></td>
<td>Jennifer Fleming, MS, RD, Penny Kris-Etherton, PhD, Wahida Karmally, RD, DrPH</td>
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<td>Personalized Diet Assessment and Application to Virtual Patients</td>
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<td>9:45–10:30 AM</td>
<td>Workshops A&amp;B Repeat</td>
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<td>10:30 AM</td>
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**Evening with the Boston Pops**

Saturday, June 13
7:00–11:00 PM
$100 (includes ticket, transportation and hors d’oeuvres)

Join your colleagues for an unforgettable evening with the Boston Pops. Enjoy the Pops while celebrating our nation’s triumphant achievement and the 40th Anniversary of the Apollo 11 Moon Landing. Historic footage of the lunar landing provided by NASA will accompany a program of stirring patriotic music and music about our universe including Holst’s *The Planets*. Special seats on the symphony floor will be provided and you will take pleasure in light bites, libations and live music. Transportation to and from the Symphony Hall will be provided.

This is a ticketed event—please see the registration page to sign up. Guests may purchase tickets.

Register at www.lipid.org/nela
Multiple events are being held in Boston in June. See below for details.

### Online Courses

**Online: Sept. 2008–Sept. 2009**
**Webcast:** Clinical Insights into the Management of Mixed Dyslipidemia: Targeting Hypertriglyceridemia to Reduce Cardiovascular Disease Risk
Sponsored by the National Lipid Association
Sponsored – CME
Available at www.NLACME.com

**Online: October 2008–October 2009**
**Webcast:** NLA Cardiometabolic Risk Reduction Online Case Studies
Sponsored by the National Lipid Association
Sponsored – CME
Available at www.NLACME.com

**Online: Jan 2009–Jan 2010**
**Webinar:** Cardiometabolic Risk Reduction Program—Case Studies
Sponsored by the National Lipid Association
Sponsored – CME
Available at www.NLACME.com

### Meetings and Events

**June 12–14, 2009**
**NELA 5th Annual Scientific Forum**
Boston, MA
Sponsored – CME
www.lipid.org

**July 24–26, 2009**
**SWLA 4th Annual Scientific Forum**
Oklahoma City, OK
Sponsored – CME
www.lipid.org

**September 25–27, 2009**
**MWLA 6th Annual Scientific Forum**
Cincinnatti, OH
Sponsored – CME
www.lipid.org

**June 14–18, 2009**
**XV International Symposium on Atherosclerosis**
Boston, MA
Sponsored – CME
www.isa2009.org

This Symposium, held triennially under the auspices of the International Atherosclerosis Society, offers the world’s largest and most prestigious forum for the presentation of new research and clinical findings on arterial disease.

**Who Should Attend**
Practicing physicians and clinical researchers involved in the diagnosis and treatment of lipid, cardiovascular, metabolic diseases, and disorders, basic scientists, epidemiologists, nutritionists, geneticists, public health specialists, general practitioners, and other healthcare professionals.

The XV International Symposium on Atherosclerosis – Boston 2009 is jointly sponsored by National Lipid Association and Giovanni Lorenzini Medical Science Foundation.