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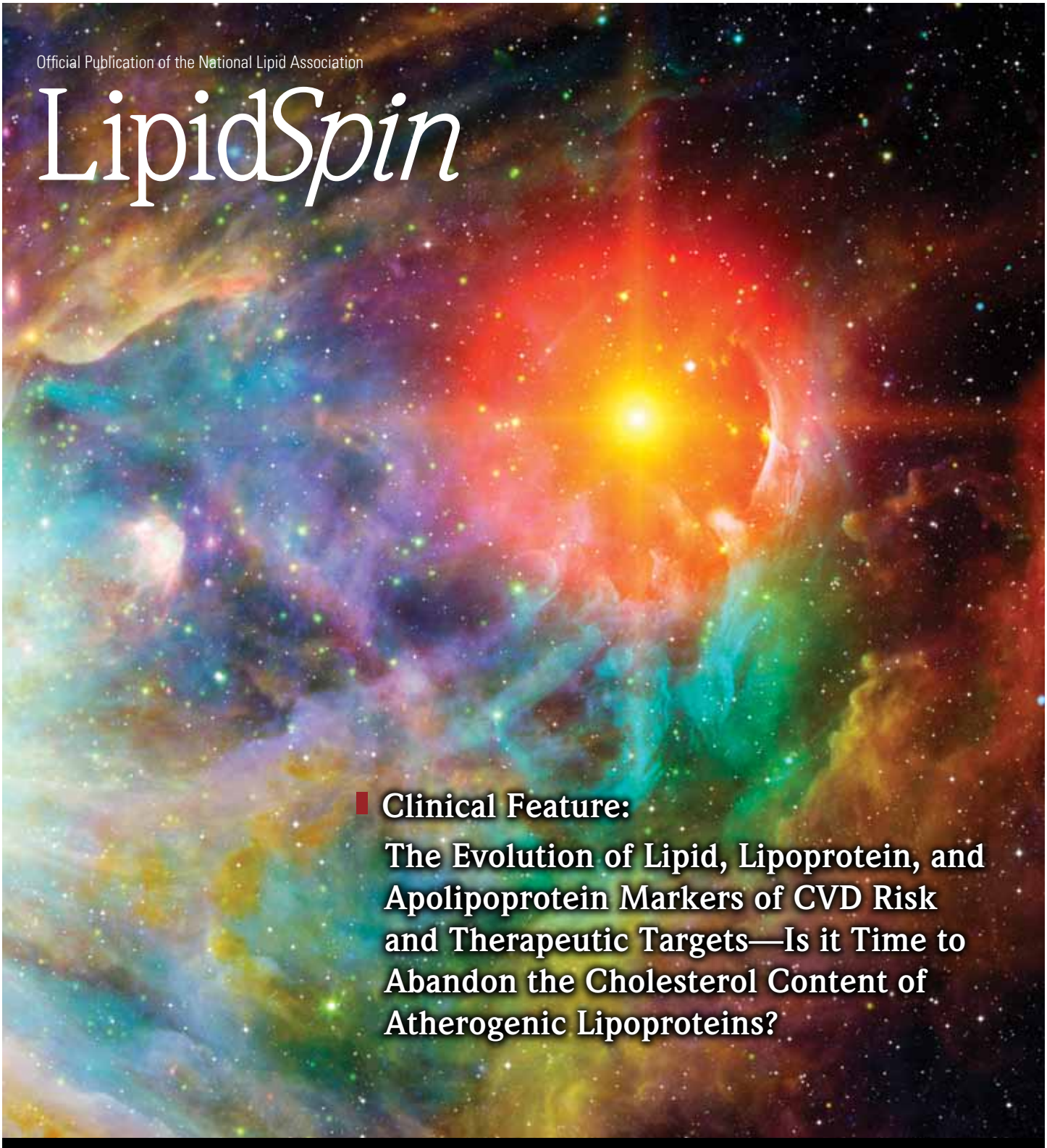
LipidSpin



Clinical Feature:

The Evolution of Lipid, Lipoprotein, and Apolipoprotein Markers of CVD Risk and Therapeutic Targets—Is it Time to Abandon the Cholesterol Content of Atherogenic Lipoproteins?

Also in this issue:

"HDL-P vs. ApoA1 vs. HDL-C" in Context of the HDL-Hypothesis Controversy

The Role of Remnant Lipoproteins in Atherogenesis

This issue sponsored by the Pacific Lipid Association

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From the NLA President:
Our Pursuit Continues

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The NLA has consistently held a determined focus on promoting the highest levels of education and professional development. We are defined by the quality of our outstanding leadership, members, partners and staff. As a result, we are continuously challenged to assess and refine our work in an attempt to produce the best and most innovative programming in Clinical Lipidology, leading to a direct and measurable impact in our medical community and across the globe.

With our core mission in mind, a group of NLA leaders met in Miami from February 8-10 for biannual strategic planning, where we were faced with important topics about resources and positioning the association far into the future. I am gratified to report that we emerged with clear priorities in the areas of Professional Education, Policy Statements, and Practice Management and Research. Additionally, we discussed ongoing and new endeavors in the areas of Communications and Membership.

We have made targeted recommendations regarding Leadership Development and Member Responsibilities. In particular, chapter leaders and members at the regional levels will be given greater responsibility for projects, and chapter leaders will develop annual plans. Chapter bylaws will be made uniform so they are consistent throughout the association. In addition, some NLA committees will review and refine their charges and initiatives.

The strategic planning recommendations will be brought before the NLA Board for consideration during our Annual Scientific Sessions in Las Vegas this coming May. I look forward to sharing our strategic plan with you once adopted and approved.

Additionally, the NLA hosted yet another successful regional meeting, the Spring Clinical Lipid Update, in New Orleans this past February. The conference was co-hosted by the Midwest Lipid Association and Southwest Lipid Association, who provided key expertise in the planning and execution of the Spring CLU. After the conference concluded, Foundation of the NLA President **Anne Goldberg, MD**, hosted some of our partner organizations during our inaugural FH Roundtable in New Orleans. At the Roundtable, these groups discussed forming a collective identity known as the FH Consortium, with the goal of further moving FH awareness to the national stage and assisting patients with finding treatment.

Moving ahead, I look forward to seeing you at our Annual Scientific Sessions in Las Vegas from May 30-June 2. I always enjoy the NLA meetings because they are characterized by people who are passionate about ideas and who share common values and intellectual energy. Let's gather once again to share with and learn from one another in our pursuit of new knowledge as well as personal and career achievement. ■

From the PLA President:
Apolipoproteins in Clinical Practice

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I am pleased to present to the National Lipid Association the Spring 2013 issue of the *Lipid Spin*. The Pacific Lipid Association serves the states of Washington, Oregon, California, Idaho, Montana, Nevada, Utah, Alaska, and Hawaii. The theme of this Spring issue is "Roles of Common Apolipoproteins in Cardiovascular Disease (CVD) and How They Affect Our Clinical Practice." The authors discuss apolipoproteins, their relevance, a review of the literature and the implications for clinical practice. I am proud of the contributions of our PLA members.

I am honored that pioneering lipid researcher, **Daniel Steinberg, MD, PhD**, professor emeritus of medicine at the University of California-San Diego, is featured in this issue as the member spotlight. Dr. Steinberg is one of the original proponents of the cholesterol hypothesis of atherosclerosis. San Diego, California is my hometown.

At this midterm juncture of my presidency, I am thankful for the support of **B. Alan Bottenberg, DO**, President-elect; **Paul D. Rosenblit, MD, PhD**, Treasurer; **Wayne S. True, MD**, Secretary; and Immediate Past-President **John R. Nelson, MD**. For this issue of the *Lipid Spin*, I am also thankful for the work of the editors, **Jamie Underberg, MD**, and **Robert Wild, MD, PhD**. This issue would not have been completed without the assistance of the NLA staff and, in particular, **Megan Seery**.

An important mission of the PLA and NLA is to promote responsible outreach to all regions of the country to make available the benefits of the NLA in every community. I encourage all of our members to continue our collective effort in achieving this goal.

We invite you to attend the 2013 NLA Annual Scientific Sessions in our own Las Vegas, Nevada, from May 30-June 2. The PLA will serve as the regional host for the sessions at the Red Rock Hotel in Las Vegas. You will not want to miss out on the latest in lipid research and applications. ■

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Letter From the *Lipid Spin* Editors:
The Times They Are A-changin'

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…the times they are a-changin' **~Bob Dylan**

These are exciting times for Lipidologists! We can always count on change as the one sure thing in life.

Our field is changing. As health care evolves, the NLA is doing its part to position our field to take advantage of the changes that our system demands. Our leaders are providing new ways to navigate systems to the benefit of our patients. As a multidisciplinary organization, we now have even more ways for our many disciplines to contribute to accomplishing our goal: improving the practice of Clinical Lipidology. In addition to mainstream primary care, we also have taken efforts to educate within Pediatrics, Ob/Gyn and Geriatrics.

We all know that reimbursement affects the care of our patients. I am excited to see that the Centers for Medicare and Medicaid Services are now rewarding efforts to deliver lifestyle interventions in a practical and meaningful way. I am also pleased to see that as ATP IV progresses, recommendations are being developed based on a thorough and systematic examination of existing evidence. Happily, we are living in times that are more influenced by evidence rather than opinion. The NLA has developed task forces to deal with each aspect of ATP IV, recognizing that this is a wonderful way to get our message out based on the best evidence available for risk assessments and therapy.

As you will learn in this issue, many of us participated in a strategic planning session in Miami in February. We came away from the meeting energized. The NLA is consolidating; you will note more evenness in the governance of each region. There are new efforts to recognize regional leaders for their hard work. While we recognize that each region has unique challenges, we also know that uniform rules of governance are more efficient.

Our mission is to educate all professionals who practice Clinical Lipidology so that in turn our patients' lives will be improved. Steps are under way to bring you the best evidence available to integrate clinical judgment and patient preferences with systems management. We are making strides to streamline the process, and targeting our educational offerings to move towards mature learning principles. We are looking at newer and better ways to communicate our message.

At the strategic planning meeting we discussed newer and better ways to make the *Lipid Spin* even more meaningful. We have the fortunate problem of having to turn down submissions! However, this has created a challenge. During the editorial process, we receive submissions that do not fit within an issue's regional theme or scope. Many of the submissions are of good quality, yet do not fit into the theme of an upcoming issue. We are working hard to develop a solution and look forward to sharing it with you in the coming months. In the meantime, we hope you continue to look to the *Lipid Spin* as a practical resource to help your practice.

…the times they are a-changin'…and the times are exciting! Prevention is finally earning its spot in the limelight. At the NLA we recognize that an ounce of prevention is worth a pound of cure. Let's embrace the concept and work even harder to spread our message. ■

Clinical Feature:
Is it Time to Abandon the Cholesterol Content of Atherogenic Lipoproteins?

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The year 2013 marks the "Silver Anniversary" of three key announcements that identified relationships among various lipid fractions, lipoproteins, apolipoproteins, non-lipid disorders and cardiovascular disease (CVD) risk. In1988, NCEP ATP I[1] recognized evidence that high levels of low density lipoprotein cholesterol (LDL-C) contributed to increased CVD risk and subsequently this has become the primary lipoprotein lipid target to reduce CVD.[2-4] They recognized that high density lipoprotein cholesterol (HDL-C) was associated with reduced CVD risk.[5-7] The 1988 NCEP 'expert laboratory panels' also provided guidelines for measuring LDL-C[9], HDL-C[10], and triglycerides (TG).[11] Both HDL-C and calculated LDL-C have remained cornerstones of lipoprotein lipid measurements for guiding lipid-lowering therapy for over 25 years.

In the second key 1988 announcement, Gerald Reaven, MD, described the etiology of known clustered metabolic CVD risks as, primarily, a consequence of resistance to insulin-stimulated glucose uptake and resistance to insulin-stimulated suppression of adipose tissue lipolysis. Insulin resistance, secondarily, leads to compensatory hyperinsulinemia, impaired glucose tolerance (IGT), elevated circulating free fatty acids and TG and decreased circulating HDL-C. He suggested that the insulin resistance 'syndrome X' played a central role in the pathogenesis and clinical course of type 2 diabetes mellitus (T2DM), hypertension, and CAD, and "likely explained most ofthe CVD risk in the general population" including many obese, overweight, or physically inactive individuals, as well as, those

individuals with T2DM.[12] The third 1988 key announcement shed doubt on the simplicity and predictability of LDL-C per se. Researchers from Lawrence Berkeley Laboratory introduced the Atherogenic Lipoprotein Phenotype (ALP) concept, with the identification of two distinct lipoprotein phenotypes; (Pattern A) characterized by a predominance of large, buoyant LDL particles and (Pattern B) characterized by more circulating small, dense LDL particles. They found that, compared with the Pattern A, Pattern B phenotype was associated with greater risk of myocardial infarction.[13-15] Pattern B dyslipidemia was also associated with increased apolipoprotein B (ApoB), VLDL, hypertriglyceridemia, and decreased levels of HDL-C and apolipoprotein A-I (ApoA1) levels.[13]

A link was established between Syndrome X, T2DM, and ALP.[16,17] Having plasma TG concentration >130 mg/dL, a TG/HDL >3.0 and insulin concentrations (>109 pmol/L) aided in the identification of overweight individuals who were sufficiently insulin resistant to be at increased risk for CVD outcomes.[18] An increased TG/HDL ratio, a surrogate of insulin resistance, was highly predictive of a first coronary event, regardless of BMI value.[19]

The Copenhagen Prospective Cardiovascular (Male) Study, estimated that approximately 35% of the population-attributable CVD risk, associated with high TG and low HDL-C levels, was independent of LDL-C level, hypertension, smoking history, or level of physical activity.[20] The Helsinki Heart Study (HHS) reported a link between the high TG and low HDL-C and greater risk for CHD. They found that while there was an overall 34% relative risk reduction among gemfibrozil users for the entire HHS cohort (mean TG 176 mg/dL); almost the entire benefit of gemfibrozil (a 56-71% RRR) was noted in the group defined by either low HDL-C or high TG or both. The investigators suggested a personalized or individualized targeting or "tailoring of drug therapy" with fibrates, for this high risk group.[21] The early monotherapy fibrate studies may have influenced the NCEP ATP III panel's recommendations for fibrate use in these subgroups.

> Once the standardization of these biomarkers is no longer debatable, particle concentrations are likely to become mainstream measurements.

Although hypothesis-generating observations (in need of a dedicated clinical trial to test this hypothesis in this population as the primary cohort) similar results were obtained in four subsequent fibrate studies. There was remarkable consistency noted in all of the post-hoc subgroups analyses from each primary study (usually analyzing <20% of the entire primary cohorts). Three independent meta-analyses, combining 'moderate dyslipidemia' subgroups, in all five trials (HHS, VA-HIT, BIP, FIELD, ACCORD-Lipid), demonstrated the consistent highly significant fibrate benefit.[22-24]

Metabolically circulating LDL-C must first undergo some modification and this affects the structure of its apolipoprotein B (ApoB) moiety. This is necessary for it to become a ligand for the scavenger receptors of monocyte macrophages. As a gradient-driven diffusion process, the more LDL-ApoB particles present in the circulation, whether by overproduction or by reduced clearance, the more LDL-ApoB particles infiltrate arterial walls. This sets in motion the cascade of events that leads to atherosclerosis.[25] The intimal retention of LDL-ApoB particles is thought to reflect an imbalance between the entry and the efflux of lipoproteins via the media and its adventitia.[26-28]

Recognizing the importance of all atherogenic lipoprotein particle concentrations, the NCEP ATP III (2001) identified non-HDL-C as a secondary target for therapy, after LDL-C goals have been met, in patients who have elevated triglyceride levels >200 mg/dL. Non-HDL-C is a surrogate for all of apolipoprotein-B-containing particles, carrying cholesterol into the arterial wall [LDL-C, VLDL-C, IDL-C, chylomicrons, chylomicron remnants, and Lp(a)]. Another secondary target identified by ATP III is having the 'Metabolic Syndrome.' ATP III also suggested that advanced cardiovascular panels could include, testing for 'emerging risks' such as ApoB and lipoprotein (a), ApoA1.[29]

Since LDL particles vary in both their cholesterol and triglyceride contents, LDL-C, per se, does not always provide a precise and/or accurate measure of the circulating concentration of heterogeneous LDL particles. This is particularly true in the hypertriglyceridemic environment, when LDL particles are particularly cholesterol-depleted, small in size and large in number. Nuclear magnetic resonance (NMR) spectroscopy, which measures lipoprotein particle concentrations directly has been utilized to study the significance of elevated low density lipoprotein particle concentrations (LDL-P). NMR analysis of the Framingham Offspring Study demonstrated a significant

	Population	LDL-P, nmol/L	LDL-C, mg/dL	CIMT, mm	Incidence CV Events per 1000 person-years
LDL-P>LDL-C	25%	1372	104	0.958	12.5
Concordant	50%	1249	117	0.932	10.1
LDL-P<LDL-C	25%	1117	130	0.917	7.3

Table 1. CIMT and CV Events According to LDL-C-LDL-P discordance and concordance among patients in the MESA study.[32]

discordance between LDL-C and LDL-P in patients with low levels of HDL-C. This implied that the excess CAD risk likely results from an excess of cholesterol-depleted LDL particles and suggested that many patients with normal levels of LDL-C, but low-levels of HDL-C, would benefit from LDL-lowering therapy.[30] The Framingham Heart Study data also found that LDL-P>LDL-C discordance is strongly linked to all five metabolic syndrome markers. Thus the enhanced risk of patients with metabolic syndrome may come from underappreciated or unrecognized LDL-P elevations. Of interest, in contrast to a graded association of increased small LDL-P with presence of more components of the metabolic syndrome, LDL-C concentrations per se, did not show a stepwise increase.[31]

The Multi-Ethnic Study of Atherosclerosis (MESA) trial analysis suggested that distinguishing concordance and the extremes of discordance [Discordant LDL-P <LDL-C, Concordant LDL-P ≃ LDL-C and Discordant LDL-P > LDL-C] can aid in identifying the need for aggressive treatment.[32] While LDL-C and LDL-P levels were both associated with overall incident CVD in the MESA trial (HR 1.20, and 1.32, respectively), among those with discordant levels, only LDL-P was associated with incident CVD (HR 1.45) vs. LDL-C (HR 1.07). Carotid intimal media thickness (CIMT) also tracked with LDL-P, rather than LDL-C in this study. The adjusted mean CIMT found in the LDL-P>LDL-C discordant subgroup (25% of studied population) was thickest at 0.958 mm. In the concordant subgroup (50% of studied population) was 0.932 mm. In the LDL-P<LDL-C discordant (25% of the population) subgroup was thinnest 0.917 mm with the differences persisting after adjustment for LDL-C (p=0.002), but not LDL-P (p=0.60).

During follow-up, 160 CVD events were experienced by individuals with concordant LDL-C and LDL-P. Event rate was 10.1 per 1000 person-years, adjusted for age, gender, and race. This contrasted with 101 and 58 events (adjusted rates of 12.5 and 7.3 per 1000 person-years, respectively; P .0025) for those with LDL-P>LDL-C and LDL-P<LDL-C discordance. Mean levels of LDL-P in the three subgroups tracked positively with atherosclerotic risk (increased CIMT and CVD events); whereas LDL-C levels were inversely related to risk. Thus, for individuals with discordant LDL-C and LDL-P levels, the LDL-attributable atherosclerotic risk was better predicted by LDL-P in the MESA study (Table 1).

Accumulated studies have demonstrated strong evidence that Non-HDL-C is a surrogate measure for atherogenic particle measurements in assessing at-risk 'populations.' However, support that particle via ApoB or LDL-P measurement is a better measure for predicting 'individual' risk exists as well. There is a very large 2011 meta-analysis of 15 independent published analyses, from 2004-2009, identifying a total of 233,455 subjects and 22,950 events.[33] The author-investigators calculated the number of clinical events prevented by a high-risk treatment regimen of all those greater than the 70th percentile of the US adult population using each of the three atherogenic markers. Over a 10-year period, using non-HDL-C as a surrogate would prevent 300,000 more events than a strategy that targets only LDL-C. This article suggests that using ApoB as a surrogate would prevent 500,000 more events than using a non-HDL-C strategy alone (Figure 1). These authors argue "the dispute about choice of markers is a dispute with consequence."

Describing the observations and conclusions from studies of ApoB as the best atherogenic marker, the authors provide four major arguments for using particle concentration as the preferred risk marker for predicting risk in managing individual patients:

1. ApoB identifies major LDL particle abnormalities not evident when LDL-C alone is used. In patients with T2DM and/or metabolic syndrome LDL-C level may be normal, but ApoB level may be elevated. The predictive power of non-HDL-C is related more to LDL-P than to inclusion of VLDL particles.[34]

2. Not all hypertriglyceridemic patients have elevated ApoB and not all hypertriglyceridemic patients have elevated ApoB. LDL-P and ApoB are often normal in patients who present with low HDL-C and otherwise normal lipids.[35,36] ApoB and LDL-P measurements allow individuals with elevated LDL-C,but normal ApoB levels, to be recognized.[37] Identification all of the atherogenic dyslipoproteinemias can be accomplished by measuring ApoB, along with TChol and TG levels, including familial combined hyperlipidemia and familial

dysbetalipoproteinemia.[38]

3. Recognized errors in the measurement of HDL-C, a component of the Friedwald equation, may in turn affect the accuracy of non-HDL-C measurement.[39] Clinical assays for ApoB, on the other hand, have become reliable, robust, and can be measured on non-fasting samples at low cost.[40] Accordingly, ApoB is superior to LDL-C and non-HDL-C as a laboratory analysis and reducing laboratory error will in turn reduce clinical errors in individual patient care.

4. While in large statin trial populations, non-HDL-C and ApoB are generally equivalent risk markers, ApoB is superior for identification of the individual that will benefit from an increased dose of statin. In statin-treated 'populations,' ApoB level identifies more individuals at increased risk, compared with LDL-C measurements.[41]

Based on the most recent statin clinical trials, Sniderman, Williams, Contois, et al.[32], in 2011, suggested that in patients at 'very high risk,' the ApoB target should be <70 mg/dL, with no lower limits. They suggested for those patients at 'high risk' an appropriate ApoB target should be <80 mg/dL and for the 'moderately high risk' patients, the ApoB target would be <120 mg/dL. For non-HDL-C the targets are <100mg/dL, <130 mg/dL and <190 mg/dL, respectively; and for LDL-C <70mg/dL, <100 mg/dL and <160 mg/dL, respectively (Table 2).

A key concept is the inverse relationship that exists between HDL-C and ApoB or LDL-P, such that lower levels of HDL-C tend to be associated with higher levels of ApoB.[42] Both HDL and LDL can

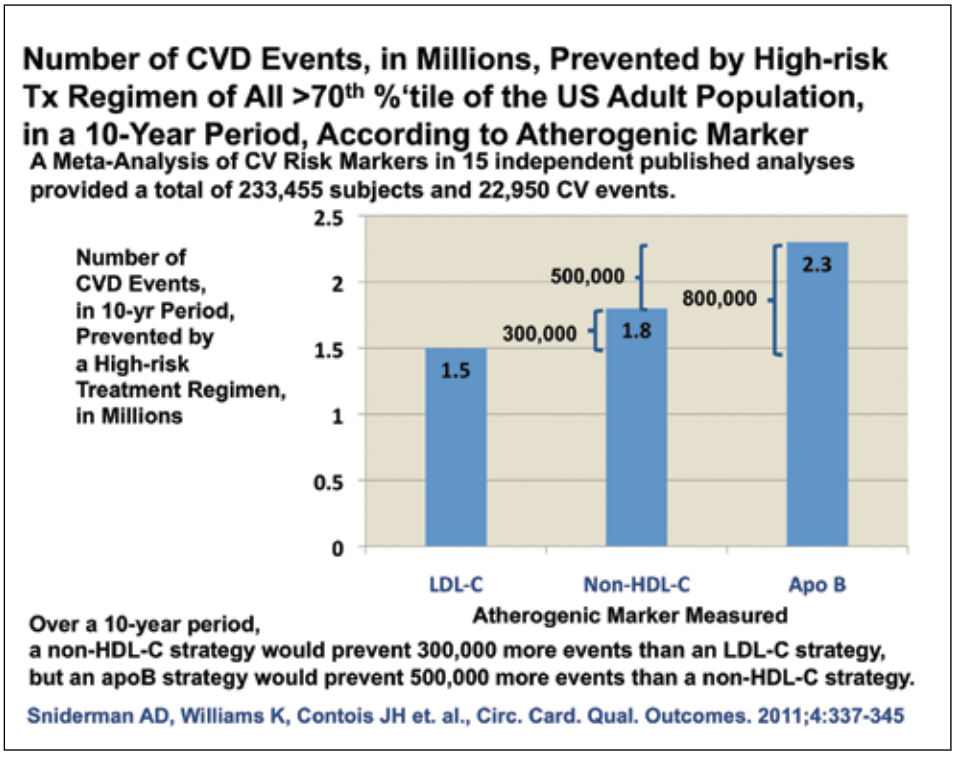

Figure 1.

participate in cholesteryl ester transfer protein (CETP)-mediated lipid exchange where the VLDL-triglyceride moves to the HDL and LDL particles in exchange for cholesterol ester moving to the VLDL fraction. Thus, a higher HDL-C points to less core lipid exchange and greater concordance between LDL-C and ApoB. Conversely, a lower HDL-C points to more core lipid exchange and, therefore, greater *discordance* between LDL-C and ApoB. When ApoB and LDL-C are concordant, they predict risk equally, whereas when they are discordant, ApoB will be superior. Therefore, compositional changes related to CETP mediated lipid exchange explain much of the variance in predictive power between LDL-C and ApoB.

Considerable controversy continues to exist with regard to the need for additional markers beyond LDL-C and non-HDL-C. Not all studies show this superiority of ApoB over non-HDL-C. Among statin-treated patients (n=38,153), on-treatment levels of LDL-C, non-HDL-C, and ApoB were each associated with risk of future major cardiovascular events, but the strength of association, relative to LDL-C (HR 1.13) was greater for non-HDL-C (HR 1.16, p = 0.002) than for ApoB (HR 1.14, p=0.02).[43]

In a very large analysis (n=302,430) of people, without initial vascular disease, from 68 long-term prospective studies, mostly in Europe and North America, involving 2.79 million person-years of follow-up, there were 8,857 nonfatal myocardial infarctions, 3,928 coronary heart disease [CHD] deaths, 2,534 ischemic strokes, 513 hemorrhagic strokes, and 2,536 unclassified strokes. The analysis[44] demonstrated that lipid risk assessment can be simplified by measurement of either cholesterol levels or apolipoproteins, without the need to fast, and without regard to triglyceride. This conclusion derives from several findings including:

1. Hazard ratios (HRs) with non-HDL-C and HDL-C that were nearly identical

to those seen with ApoB and ApoAI, ultimately suggesting that vascular risk assessment should consider cost, availability, and standardization of assays.

2. HRs for vascular disease with lipid levels were at least as strong in participants who did not fast as in those who fasted.

3. Non-HDL-C and direct LDL-C measurements HRs were similar.

4. Triglyceride concentrations were not independently related with CHD risk after controlling for HDL-C, non-HDL-C, and other standard risk factors, including null findings in women and under non-fasting conditions in both genders. Hence, for population-wide assessment of vascular risk, triglyceride measurement provided no additional information about vascular risk given knowledge of HDL-C and TChol levels. The exception may be the triglyceride measurement performed to prevent pancreatitis.

Summary

Given the absence of clinical trials targeting the population where this issue matters most, and given divided expert opinions, it would be unreasonable to abandon measurements of lipoprotein cholesterol content, LDL-C and Non-HDL-C as predictors of risk. However to move the science further, the NCEP or NHLBI expert 'laboratory panels' will need to establish recommendations for standardization and analytic performance targets for apolipoprotein B and lipoprotein particle numbers, as in the past for lipids and lipoprotein measurements. Once the standardization of these biomarkers is no longer debatable, we believe that measurement of particle concentrations is likely to become mainstream. Management guidelines, after all, require an evidence-based approach and each lipid modifying agent should undergo a pre-specified designed RCT to demonstrate their comparative effectiveness for atherogenic biomarker reduction coincident with CV events. A caveat is in order: one of the issues with future prospective RCT may be insurmountable. Now considered unethical by many, prior RCTs on this issue were placebo-controlled. Because residual risk is an important issue, each new or existing drug class will need to demonstrate effectiveness against secondary targets (i.e., non-HDL-C) and then either ApoB or LDL-P in comparison.

The superiority of these surrogates when applied to selected individuals, as opposed to evaluation in large populations, appears to be particularly important in persons with cardiometabolic risk, i.e., moderate hypertriglyceridemia in the setting of elevated ApoB, as in the metabolic syndrome and diabetes. Thus, many, but not all, lipid specialists recommend a greater focus beyond non-HDL-C, to assess residual CVD risk in statin-treated patients. Changes in LDL-C can result either from changes in LDL particle concentration or cholesterol content, or both. Common lipid-modifying treatments affect both LDL lipid composition and particle number, causing the magnitude and even direction of changes in LDL-C and LDL-P to differ. Statins reduce LDL particles, but reduce LDL cholesterol content more. This issue is very clinically relevant because other lipid-modifying therapies that increase LDL size (niacin, fibrates, omega-3 ethyl esters, glitazones and therapeutic lifestyle) reduce LDL-P more than LDL-C. To date, no trial has yet been carried out that specifically targets the high-risk 'discordant' individuals, likely responsive to these agents. However, support for this concept is suggested by significant benefit seen in post-hoc subgroup analyses and independent meta-analyses of the high TG (>200 mg/dL) and/or low HDL-C (<40 mg/dL) fibrate trial subgroups.[22-24]

Marker, in mg/dL	LDL-C	Non-HDL-C	ApoB
Risk			
Very-high	<70	<100	<70
High	<100	<130	<80
Moderately High	<160	<190	<120

Table 2. 2011 Goals for Atherogenic Markers Based on Coronary Risk Factor Levels.[33]

Assessment of individuals at risk has evolved from simple lipids (cholesterol and triglycerides) to lipoproteins (predominantly VLDL-C, LDL-C, and HDL-C), to lipoprotein size determinations, to surrogates of atherogenic cholesterol (non-HDL-C), to lipoprotein-associated apolipoproteins (predominantly ApoB and ApoA1), and to LDL particle numbers (as LDL-P or ApoB), as well as non-lipid biomarkers and imaging assessments. There is recent evidence to suggest that increased HDL particle number (HDL-P) is a better measure of cardiovascular

Once applicable, genetic testing will be utilized to identify risk and also to dictate appropriate treatment modalities.

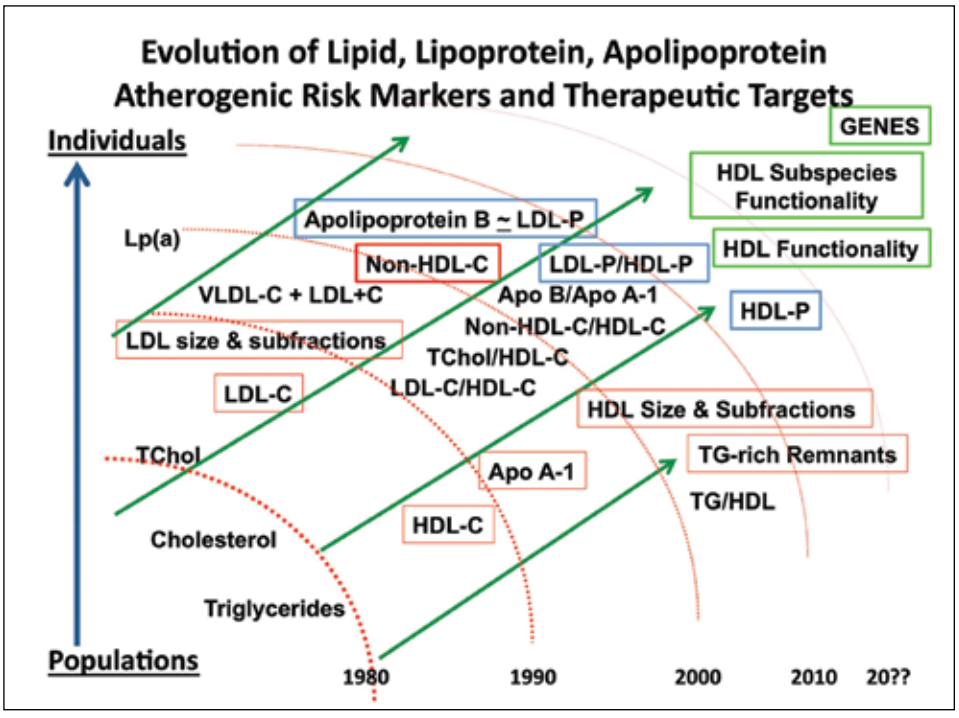

Figure 2.

risk than HDL-C.[47] This raises the possibility that when therapies increase HDL-P, regardless of changes in HDL-C, HDL functionality, such as macrophage cholesterol efflux, or other beneficial properties attributable to HDL, might also improve.[42] In this regard, at least as monotherapy, fibrate benefit was associated with both increased HDL-P and reduced LDL-P, in the low-HDL targeted VA-HIT trial population.[48]

Identification of optimal biomarkers of risk are clearly important to optimum risk assessment. Individualized therapies based on pharmacologic-induced outcome benefits using HDL sub-species functionality may be in the future. Once proven to be clinically relevant, genetic testing may be utilized to identify risk and also to dictate appropriate treatment modalities for individuals (Figure 2). The future may also bring new ethical dilemmas associated with polymorphism identification that facilitates genetic engineering to avoid (cardiovascular) disease. ■

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The Evidence: Risk, Treatment and Outcomes

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Guest Editorial:
The Role of Remnant Lipoproteins in Atherogenesis

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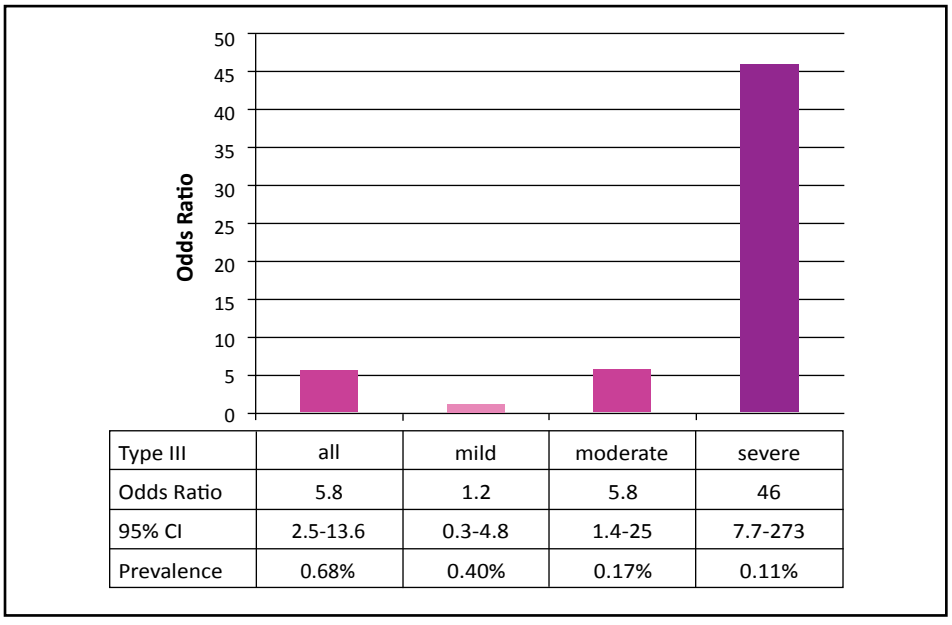
Remnant Lipoproteins Promote Foam Cell Formation

Atherosclerosis is characterized by accumulation of inflammatory foam cells whose formation is promoted by the subendothelial retention of ApoB-containing lipoproteins. Plaques develop in predisposed areas of the arterial tree where blood flow is either slow or has a back and forth pattern (thus coronary arteries are particularly prone).[1] In these predisposed areas endothelium displays increased susceptibility to inflammation as well as greater permeability to lipoproteins with subendothelial retention in these locations. Resident subendothelial dendritic cells may be the first cells to take up retained lipoproteins to become foam cells. Some dendritic cell subtypes suppress while others promote inflammation.[2] Hyperlipidemia initiates greater endothelial expression of inflammatory adhesion molecules (by multiple mechanisms) followed by macrophage and neutrophil transmigration into the subendothelial space. Eventually, macrophages as well as activated smooth muscle cells begin to accumulate and are converted to foam cells. Surprisingly, early acquisition of cholesterol by macrophages actually suppresses inflammatory responses, leading to a reparative macrophage phenotype.[3] However, continued cholesterol accumulation, particularly with excessive intracellular unesterified cholesterol combined with stimulation of innate immune receptors (such as toll-like receptors), results in predominantly inflammatory macrophages. Further accumulation of macrophages (and other inflammatory cell types) ensues, followed eventually by wholesale apoptosis and necrosis with formation of the necrotic core and an unstable plaque.[4] These vulnerable plaques have a high cholesterol content, many macrophages at the shoulders, thinned fibrous caps, and are prone to rupture, leading to acute coronary events.[5] The physical expansion caused by sudden cholesterol crystallization in such plaques may be a major driving force for their rupture.[6]

Excess cholesterol accumulation can lead to initiation, promotion, and progression of atherosclerotic lesions and may even precipitate plaque rupture and acute coronary events, but where does the cholesterol come from? In classical in vitro studies, incubation of macrophages with native LDL (low density lipoprotein) did not result in foam cell formation due to downregulation of the LDL receptor.[7-9] However, after LDL were oxidized or acetylated they were avidly taken up by

macrophages with conversion to foam cells. Importantly, in these same studies, triglyceride-rich remnant lipoproteins (TGRL) from cholesterol-fed rabbits or dogs (referred to as β-VLDL) needed no modification to promote foam cell formation. Note that β-VLDL are TGRL with abnormal composition and are not equivalent to IDL (intermediate density lipoproteins). They are composed of both intestinal (with ApoB48) and hepatic (with ApoB100) TGRL remnants. β-VLDL have density less than 1.006 (the density of plasma) and float upon ultracentrifugation whereas IDL do not float. Unlike normal VLDL which have pre-β mobility, β-VLDL have β mobility upon electrophoresis, that is, they move like LDL. Finally, β-VLDL are abnormally enriched in cholesterol (mostly esterified) due to prolonged transit time and exchange of cholesteryl ester for triglycerides through the action of cholesterol ester transfer protein (CETP).[10]

The contribution of various forms of oxidized LDL (including minimally modified LDL) to foam cell formation in vivo continues to be debated.[11] In the meantime, a number of additional LDL modifications that promote foam cell formation may even be more quantitatively important than oxidation. These include proteoglycan binding and aggregation, especially after exposure to various phospholipases (including LpPLA2) or sphingomyelinase, which result in so-called electronegative LDL.[12] Besides β-VLDL, several other types of TGRL have also been shown to promote foam cell formation, including human VLDL from hypertriglyceridemic subjects[13], human chylomicron remnants[14], and remnant-like particles (RLP) isolated by incubation with immunoaffinity gels directed against a specific epitope on ApoB and ApoA1 with the intention to remove nascent TGRL and HDL.[15,16] TGRL have been directly isolated from human aortic intima.[17,18] In one study, 36% of the cholesterol isolated from aortic plaque in patients undergoing aortic



Type III	all	mild	moderate	severe
Odds Ratio	5.8	1.2	5.8	46
95% CI	2.5-13.6	0.3-4.8	1.4-25	7.7-273
Prevalence	0.68%	0.40%	0.17%	0.11%

Figure 1. Risk of premature CAD (MI, CABG, or PTCA by age 60 in men or 70 in women) associated with type III hyperlipidemia among 1170 premature CAD cases and 1759 population-based controls. Type III was defined as measured VLDL-C / total triglycerides ≥ 0.30 with total triglycerides > 150 mg/dL. Risk associated with meeting this criteria (versus not) is given as "all." Those with type III were further broken down as mild, moderate, and severe, defined as estimated β-VLDL cholesterol <50, 50-79, and 80 mg/dL or more, respectively. Risks were calculated by logistic regression adjusting for age, gender, measured LDL-C, HDL-C, fasting triglyceride category (excluding type III – see Figure 2), hypertension, diabetes, and history of cigarette smoking.

reconstruction was from very low density lipoprotein (VLDL) and intermediate dense lipoprotein (IDL).[18]

Chylomicron remnants (CR) are cholesterol-rich TGRL remnants produced from the hydrolysis of chylomicrons. These ApoB48-containing particles vary greatly in size and composition, becoming denser and less negatively charged as they lose triglycerides and their associated ApoC lipoproteins while increasing their concentration of cholesteryl ester. Human CR are in the range of 50 to 150 nm in diameter.[19] Small VLDL and IDL are TGRL remnants produced from the hydrolysis of triglyceride-rich VLDL. Gradient density ultracentrifugation reveals small VLDL and IDL in the Sf (Svedberg flotation rate) 20 to 60 and 12 to 20 ranges respectively.[10] The diameter of LDL, small VLDL, and IDL particles are, respectively, 20 to 25 nm, 30 to 80 nm, and 25 to 35 nm. The density of IDL is greater than 1.006, but less than 1.019 g/mL with a diameter of 27.5 to 30 nm in individuals without dyslipidemia. Approximately 15% to 20% of the total cholesterol is carried in IDL and a normal plasma concentration of IDL is 5 to 15 mg/dL and a total mass of 10 to 30 mg/dL.[10] Lipoproteins greater than 75 nm in diameter are thought to not enter the arterial wall.[20] These considerations suggest that small CR and other TGRL remnants can enter the arterial wall and contribute to atherogenesis.

These findings may support the possibility that postprandial CR contribute to atherogenesis.[21,22] Recently, much more ApoB48 was reported to be present in human carotid plaque than ApoB100.[23] It appears to be the cholesteryl ester component of these remnant TGRL that is atherogenic as demonstrated by ACAT2 deficiency, which almost entirely abrogated atherosclerosis in ApoE null mice. In these knockout mice, there were normal or slightly increased numbers of both ApoB48 and B100 particles having markedly reduced cholesteryl ester and increased triglyceride content.[24]

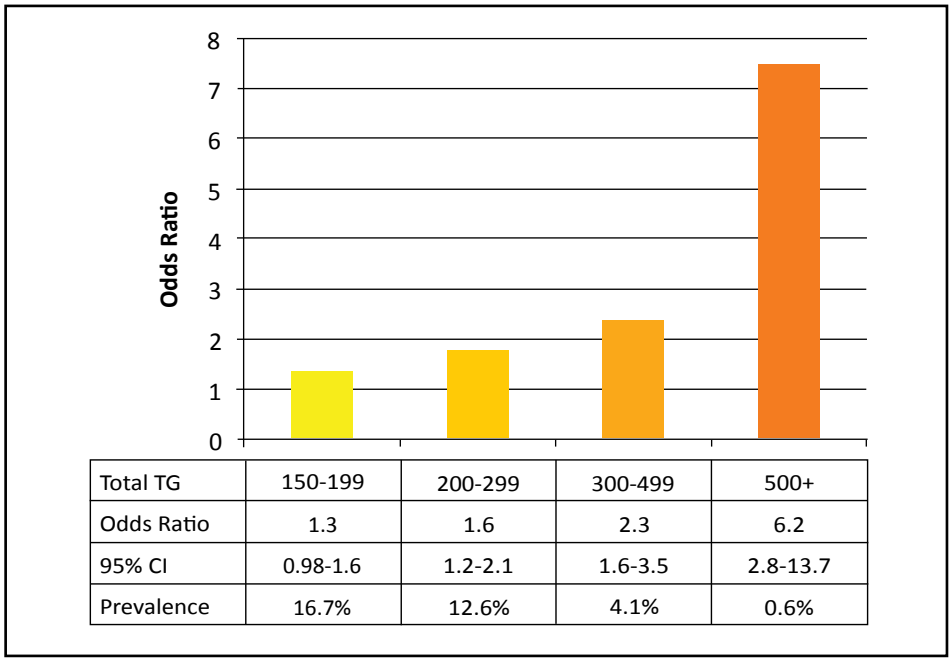
TGRL Remnants Can Initiate Endothelial Inflammation

Upon incubation with TGRL, endothelial cells upregulate their expression of MCP-1, ICAM-1, and VCAM-1.[25,26] MCP-1 is a chemokine that stimulates monocyte integrin activation, allowing firm adherence to ICAM-1 and VCAM-1 while also promoting transendothelial migration. Incubation of monocytes with RLP also promotes their adherence to endothelial cells.[27] RLP adversely affect endothelial function by directly and indirectly inhibiting endothelial nitric oxide synthase.[28] Furthermore, elevated RLP has been shown to be an independent risk factor for impaired flow-mediated, endothelial-dependant dilatation in patients with coronary artery disease.[29] Elevated RLP levels have been associated with impaired coronary vasomotor response and acetylcholine-induced spasm.[30,31] Elevated TGRLs were further found to be cytotoxic and induce apoptosis of endothelial cells.[32]

Hydrolysis of TGRL May Also Activate Endothelial Cells

Hydrolysis of TGRL has been shown to induce endothelial inflammation with production of TNFα, ICAM-1, and increased reactive oxygen species.[33] In this study, it was the free fatty acids derived from the hydrolysis of TGRL, not the cholesteryl ester, triglycerides, free cholesterol or phospholipids that were associated with these effects.

Free fatty acids released during hydrolysis of TGRL can also adversely affect endothelial barrier function and increase subendothelial transfer of lipoproteins. In a study with cultured endothelial cells, exposure to oleic acid resulted in an increased transfer of LDL across the endothelium.[34] TGRL hydrolysis products were reported to increase endothelial permeability by promoting disruption of the zonula occludens-1 complex which is essential for tight junction formation. Increased caspase 3 activation was also seen, which can be associated with apoptosis.[35] In another study, RLP were shown to induce a strong inflammatory response with vigorous NADPH oxidase activation and superoxide formation followed by apoptosis in endothelial cells through activation of the LOX1 receptor.[36]



Total TG	150-199	200-299	300-499	500+
Odds Ratio	1.3	1.6	2.3	6.2
95% CI	0.98-1.6	1.2-2.1	1.6-3.5	2.8-13.7
Prevalence	16.7%	12.6%	4.1%	0.6%

Figure 2. Risk of premature CAD associated with increasing triglycerides. Risks were calculated as described in Figure 1.

Further Observations on Foam Cell Formation

In the subendothelial space, monocytes differentiate into macrophages where they ingest ApoB-containing lipoproteins. The inaugural event is the subendothelial retention of ApoB lipoproteins.[37] In a study of patients undergoing elective carotid endarterectomy, although the influx of LDL cholesterol was 19 times greater than that of TGRL cholesterol, the intimal clearance and fractional loss were similar.[38] In a study of heritable hyperlipidemic rabbits, lipoprotein arterial influx was linearly related to plasma concentration; however, efflux was inversely related to lipoprotein diameter,[39] suggesting the potential for greater retention of TGRL remnants. The main ApoB proteoglycan binding site is between the positively charged basic amino acids on ApoB (residues 3359 to 3369) and the negatively charged sulfate groups on the glycosaminoglycan chains of proteoglycans.[40] Small VLDL and IDL have less affinity for proteoglycans; however, like LDL, sphingomyelinase causes VLDL and IDL to aggregate, fuse, and enhance their binding to proteoglycans.[41] It has been shown that sphingomyelinase-induced aggregation of TGRL leads to foam cell formation.[42]

Although there is much greater penetration of the endothelial barrier by LDL particles, TGRLs carry significantly greater cholesteryl ester molecules per particle. It has been estimated that CR-TGRL of approximately 100 nm in diameter carry 40 times more cholesteryl ester than LDL particles.[43] In a study evaluating TGRL and LDL fractions removed by density gradient ultracentrifugation from thoracic and abdominal aorta tissue at autopsy, it was found that when these fractions were incubated with mouse peritoneal macrophages, TGRL increased incorporation of radioactive oleate into cholesteryl esters by 10-to-20 fold as compared to three-to-four fold for LDL.[17] Similar increases

in cholesteryl ester synthesis by were seen in studies with dogs over 30 years ago.[7] In patients with type III or type IV hyperlipidemia, oxidized β-VLDL or VLDL remnants were found to cause greater macrophage cholesteryl ester formation than oxidized LDL.[44,45]

Coronary Risk Associated with Type III Hyperlipidemia

Type III hyperlipidemia is characterized by increased accumulation of β-VLDL in plasma. This phenotype is commonly thought to be rare, being the result of an apo E 2-2 genotype (about 1 in 100 persons) together with a genetic predisposition to excess VLDL production, such as *APOA5* variants,[46] or acquired overproduction of VLDL as with obesity or hypothyroidism. The prevalence of type III is frequently cited as approximately 1 in 10,000.[47] However, in the Lipid Research Clinics (LRC) Prevalence Study, type III hyperlipidemia was found in 0.4% of men in the general population.[48] This study represents one of the only studies to apply classic criteria to all participants to define type III, namely, the presence of a β-VLDL band upon electrophoresis of the density <1.006 fraction isolated after ultracentrifugation of plasma.

While markedly increased risk of atherosclerotic disease has long been appreciated for patients with type III, a population-based estimate of risk was not available until our recent publication (PNH).[49,50] Additional, previously unpublished analyses utilizing data from the more recent of these studies[50] are presented in Figures 1-3. The study groups consisted of 1759 population-based controls and 1170 cases with onset of clinical CAD by age 60 in men and 70 in women, all with ultracentrifugation performed on plasma samples. Type III hyperlipidemia was defined as present if the ratio of measured VLDL cholesterol/total triglycerides was ≥ 0.30 with total triglycerides > 150 mg/dL.[51]

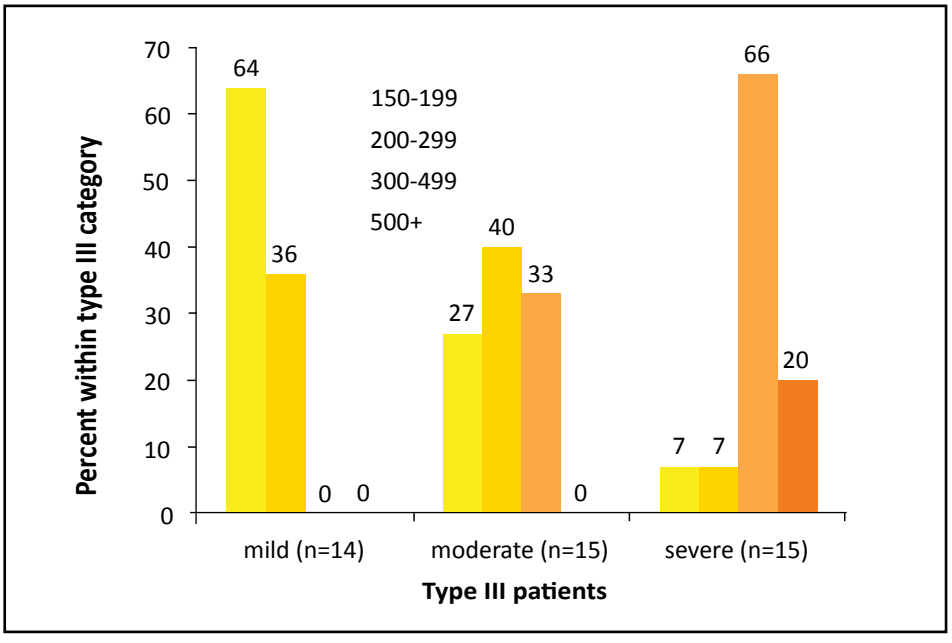


Figure 3. Distribution of type III hyperlipidemia cases (including cases and controls together) according to fasting triglycerides. Note the relatively large number of type III cases with only modest triglyceride elevations.

The prevalence of type III (0.68%) we identified in the control population was very similar to the LRC Prevalence Study estimate, especially in consideration of the increased obesity expected in the population. The prevalence among our cases was 2.7%, almost identical to that reported by Goldstein, et al.[52] In Figure 1, risk associated with the presence of type III is given with adjustment for LDL-C, HDL-C, triglyceride categories (which excluded type III subjects), hypertension, diabetes, and cigarette smoking. In addition to the traditional yes/no definition of type III, we show the markedly increasing risk associated with more severe type III as defined by an algebraic estimate of plasma β-VLDL cholesterol levels. CAD risk was increased over 40-fold in the most severe category. These severe cases represent only about 1/1000 control subjects yet most did not have any xanthomas. Perhaps those with tuberous xanthomas and/or palmar striae would be found as infrequently as 1/10,000. Elevations in triglycerides without type III were associated with increased CAD risk, but to a much lesser extent as shown in Figure 2. Interestingly, many cases of type III hyperlipidemia would have been missed if ultracentrifugation had only been performed in those with triglycerides over 300-400 as shown in figure 3. It should be noted that estimates of risk associated with remnant accumulation can vary substantially, depending on the method or parameter used.[10,53-55]

In summary, despite significantly lower plasma concentrations than LDL, TGRL and TGRL remnants contribute to atherosclerosis plaque formation. With increasing obesity rates, these TGRL-derived particles may play a greater role in the development of atherosclerotic burden. Non-HDL cholesterol goals therefore may become even more important in the management of the dyslipidemic patient. ■

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EBM Tools for Practice:
"HDL-P vs. ApoA1 vs. HDL-C" in Context of the HDL-Hypothesis Controversy

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Recent high-profile interventional studies and a large genetic association analysis have failed to show a benefit of raising high density lipoprotein cholesterol (HDL-C) levels on cardiovascular disease (CVD) outcomes, calling into question the validity of the HDL hypothesis. Among several plausible explanations for these findings, one is that assaying the cholesterol content of HDL (HDL-C) may fail to adequately measure its protective effects. Two potentially better ways to assess the protective effects of HDL are to measure levels of the major HDL apolipoprotein (apo), ApoA1, and to estimate HDL-particle number (HDL-P) by nuclear magnetic resonance (NMR).

The "Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health" (AIM-HIGH) study failed to show CVD benefit from HDL-C raising with niacin.[1] The lack of benefit of niacin in this trial was surprising given the many pre-AIM-HIGH studies demonstrating that niacin reduces CVD events.[2] In patients with low HDL-C and stable coronary artery disease, extended release nicotinic acid (ERNA) was added to statin therapy and subsequent CVD events were assessed. To better understand the impact of the HDL-C raising effect of ERNA, low density lipoprotein-cholesterol (LDL-C) was targeted to 40-80 mg/dL in both groups, leading to higher statin doses and more frequent ezetimibe use in the control group. Low-dose immediate-release nicotinic acid (IRNA) was given to the control group to cause flushing and maintain the study blind. Possible explanations for the surprising lack of CVD benefit included (1) near equalization of LDL-C levels (weighing against the HDL-hypothesis), (2) smaller-than-expected HDL-C difference of only 15% due to IRNA in the control arm, and (3) the short study duration of only 2 ½ years[3] (neither (2) nor (3) weighing against the HDL-hypothesis). Further, in a post hoc subgroup analysis in subjects having both high triglycerides and low HDL-C at baseline, there was a statistically significant 37% decrease in CVD events with high-dose ERNA vs. control. This finding clearly supports the traditional HDL hypothesis.[4] An alternative explanation for the surprising results of AIM-HIGH is that the lack of CVD benefit with ERNA was expected since, despite a robust increase in HDL-C and ApoA1 with ERNA, HDL-P may not increase with ERNA treatment.

Another study with results appearing to weigh against the HDL hypothesis is the "Randomized, Double-blind, Placebo-controlled Study Assessing the Effect of RO4607381 on Cardiovascular Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome" (dal-OUTCOMES) trial.[5] In this study, dalcetrapib, a cholesteryl ester transfer protein inhibitor (CETP-I), failed to lower CVD events despite increasing HDL-C by 31%, (and previously

being reported to raise ApoA1 by 13%, and HDL-P by 9%).[6] The apparent contradiction of the HDL hypothesis in dal-OUTCOMES (by 3 HDL metrics) might be explained, however by consideration of two study findings: (1) a modest inverse trend between CVD risk and the degree of HDL-C increase with dalcetrapib (suggesting that the increase in HDL-C remained somewhat protective), and (2) a statistically significant increase in blood pressure with dalcetrapib (suggesting that the lack of overall CVD benefit was due to modest adverse adrenal effects, analogous to much greater ones seen with another CETP-I, torcetrapib). Ongoing laboratory and statistical analyses may better explain the apparently paradoxical results of dal-OUTCOMES.

A third very recent clinical trial result also seems to weigh against the HDL hypothesis. According to a preliminary report of The Heart Protection Study-2 (HPS-2), ERNA (with a flush-blocker, laropiprant) added to a statin failed to reduce CVD vs. statin alone.[7] Certain problems with the AIM-HIGH clinical trial design were avoided. No IRNA was given to control subjects in HPS-2, since the lack of flushing in the treatment arm did not require flushing in the control arm to maintain the study blind. Also HPS-2 was much larger and longer than AIM-HIGH. Unfortunately, however, baseline HDL-C and triglyceride levels in HPS-2 were even closer to normal than they were in AIM-HIGH. Analyses of HPS-2 subjects with low HDL-C and high triglycerides might show decreased CVD risk similar to the subgroup analysis in AIM-HIGH, which would provide further support for the HDL hypothesis in those important patients.

Beyond these randomized pharmaco-therapeutic trials, a recent Mendelian randomization study also examined the relationship between HDL-C levels and CVD risk.[8] A single nucleotide polymorphism in the endothelial lipase gene was associated with HDL-C levels 5.5 mg/dL (roughly 12%) higher than in non-carriers. Surprisingly, this was not associated with a lower myocardial infarction (MI) rate. Importantly, however, the higher HDL-C was not accompanied by a lower triglyceride level (in contrast to the inverse relationship seen in the general population). Further, polymorphisms in 14 other genes with isolated HDL-C increases (no triglyceride change) also failed to reduce MI. Unfortunately, neither ApoA1 nor HDL-P levels were reported in that study.

As noted above, some of the evidence weighing against the HDL hypothesis might be explained by using different measures of HDL plasma concentration. ApoA1 seems to play many important roles in atheroprevention, and its level is inversely related to CVD, as strongly, or more strongly than HDL-C in many epidemiological studies.[9,10] Similarly, HDL-P, a measure of HDL particle concentration independent of both HDL-C and ApoA1, may inversely predict atherosclerosis and CVD as well or better than does HDL-C.[11,12] An interesting example of this independent prognostic ability comes from a recent analysis from the prospective observational Multi-Ethnic Study of Atherosclerosis (MESA).[13] HDL-P and HDL-C were both strongly inversely associated with carotid intima-media thickness (CIMT) and incident coronary heart disease (CHD), but the relationship with HDL-C was greatly weakened after adjusting for HDL-P and LDL-P (an estimation of LDL particle concentration from NMR). In contrast, adjustment for HDL-C and LDL-P did not affect the relationship of HDL-P with CIMT and CHD. The independence of HDL-P from other lipid/lipoprotein measures is further demonstrated by the fact that it appears to be the only HDL parameter consistently neither increased by niacin treatment nor decreased by high plasma triglyceride levels.

HDL-P was also independent from other HDL parameters in a Mendelian randomization analysis of genetic polymorphisms in the phospholipid transfer protein (PLTP) gene. In this study PLTP-related HDL increases were associated with decreased CVD rates.[14] HDL-C was only modestly and non-significantly increased, whereas HDL-P (especially small HDL-P) was significantly increased and inversely related to CVD.

Although several measures of HDL levels can inversely predict CVD, a dynamic measure of HDL function, such as reverse cholesterol transport (RCT) intuitively might provide even better predictive ability. A recent study by Khera, et al. demonstrated that assaying one aspect of HDL function (cholesterol efflux from cultured cells, related to the first step in RCT) was somewhat more predictive of CIMT and angiographic coronary artery disease than was HDL-C.[15]

This is a challenging time in the evolution of our understanding of the roles of HDL in atherogenesis and CVD risk. Recent studies suggest reconsideration not only of the HDL hypothesis, but also of the optimal methods to measure potential HDL-mediated beneficial effects on atherosclerosis and CVD events. HDL-C measurements are still clinically useful, but adding independent measures of HDL levels such as ApoA1, HDL-P and possibly assays of HDL function, may provide even better prediction of CVD risk. The HDL hypothesis remains "alive and (presumably) well" for now, even though much additional research is needed to validate old and new diagnostic and therapeutic tools to better assess and enhance the many apparently favorable effects of HDL on atherosclerosis and CVD. ■

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Lipid Luminations:
Lipoprotein(a)—Clinical Significance, Evaluation, and Management

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Introduction

Lipoprotein(a), also referred to as Lp(a), is an unusual plasma lipoprotein that was first described by Berg in 1963.[1] The lipoprotein(a) particle consists of a low density lipoprotein (LDL) particle to which a single molecule of apoprotein(a) is covalently bound via a disulfide linkage to apoprotein B-100. The size of the apoprotein(a) moiety varies substantially between individuals because of differences in the number of kringle-4 repeats, as discussed below. Lipoprotein(a) is formed in plasma, possibly on the surface of hepatocytes, primarily from circulating LDL and hepatically secreted apoprotein(a). The distribution of plasma concentrations of lipoprotein(a) in the general population is highly skewed toward zero, with the range varying more than 1000-fold. The median concentration in Caucasians, Asians, and Hispanics is 10 to 20 mg/dL, with levels being 2-3 fold higher among blacks.[2]

The normal function of lipoprotein(a) is uncertain, since there is no clear deficiency state, most animal species do not produce lipoprotein(a) (it is found only in humans, apes, old world monkeys, and European hedgehogs), and most humans have low concentrations of plasma lipoprotein(a). It is has been proposed that lipoprotein(a) may function to deliver cholesterol to sites of injury and repair in various tissues, but there are other mechanisms for accomplishing this task in the absence of lipoprotein(a). Anticarcinogenic properties have been proposed for lipoprotein(a), and the results of one recent study showed a significant association between prospective cancer risk and low concentrations of lipoprotein(a) in 10,413 participants followed for a median of 12.5 years[3], but most studies have shown no association. Lipoprotein(a) is of interest to lipidologists and other health care providers because it is a risk factor for and mediator of thrombosis and accelerated atherogenesis.

Assays for Lipoprotein(a)

Measurements of lipoprotein(a) cannot be interpreted without an understanding of the diverse variations in laboratory methodology. Measurements of plasma lipoprotein(a) concentrations are performed by several different methods, which has been a significant source of ambiguity and confusion in interpreting published data and diagnostic results provided by various laboratories.[4] There has been some success in standardizing the quantitative assays used for measuring lipoprotein(a) concentrations, but variability between laboratories can still produce disparate results.[4] In addition, various laboratories provide results in units that are not directly interchangeable. The three most common assay units utilized are nmol/L of lipoprotein(a) particles, mg/dL of lipoprotein(a) protein (usually a

measurement of apoprotein(a) by ELISA), and mg/dL of lipoprotein(a) cholesterol. The latter two differ about 3-fold, but the results are easily confused because both are expressed in units of mg/dL, often without designation of measurement of protein or cholesterol. One mg/dL of apoprotein(a) protein is comparable to about 2.4 nmol/L of lipoprotein(a), but the proportion varies from 1.8 for large apoprotein(a) size to 2.9 for small apoprotein(a). Other methods of assessing lipoprotein(a) include determination of the apoprotein(a) genotype and quantification of the number of kringle-4 repeats in the apoprotein(a) molecule. It is estimated that the apoprotein(a) genotype alone accounts for 90% of heterogeneity in plasma concentrations of lipoprotein(a), and the results of family studies provide a similar estimate of heritability of lipoprotein(a) levels. Other causes of elevated concentrations of lipoprotein(a) are shown in Table1. The molar plasma concentration of lipoprotein(a) is inversely proportional to the number of kringle-4 repeats in the apoprotein(a) molecule, which means that the largest apoprotein(a) molecules are associated with the lowest concentrations of lipoprotein(a) in plasma. Practitioners need to familiarize themselves with the assay used by their laboratory, including the accuracy and reproducibility of the results, so they can correctly interpret the lipoprotein(a) results from their patients. Reference ranges for lipoprotein(a) are shown in Table 2.

Factors Associated with Increased Plasma Concentrations of Lipoprotein(a)

Genetic inheritance (causes ~ 90% of inter-individual heterogeneity of levels)
Dietary trans fat intake
Hypothyroidism
Menopause
Renal insufficiency
Nephrotic syndrome
Familial hypercholesterolemia

Table 1.

> Lipoprotein(a) elevation is an important risk factor for CVD, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease

Lipoprotein(a) and Cardiovascular Risk

Lipoprotein(a) plays a causative role in atherogenesis and cardiovascular disease (CVD) through several mechanisms related to increased thrombogenesis and lipid deposition in the artery wall.[5-8] The risks of coronary artery disease, cerebrovascular disease, and peripheral vascular disease are all increased in the setting of high levels of lipoprotein(a). Up to 20% of individuals with early onset CVD have high levels of lipoprotein(a) > the 95th percentile, which demonstrates that elevated lipoprotein(a) is fairly common in this patient population.

The apoprotein(a) molecule is a homologue of the fibrinolytic proenzyme, plasminogen, the precursor of plasmin. The presence of high levels of apoprotein(a) can interfere with plasminogen activation and thereby contribute to thrombosis by decreasing fibrinolysis and enhancing clot stabilization. Lipoprotein(a) may also interfere with the function of tissue factor pathway inhibitor, which increases thrombogenesis. Accordingly, very high concentrations of lipoprotein(a) can be associated with spontaneous arterial thromboses, and possibly venous thromboses, but a recent Mendelian randomization study of lipoprotein(a) genotype and plasma concentrations in 41,231 individuals did not demonstrate a relationship between lipoprotein(a) and venous thrombosis except when lipoprotein(a) levels were greater than the 95th percentile.[9]

Lipoprotein(a) also plays an important role in atherogenesis, particularly in the presence of elevated concentrations of LDL or remnant lipoproteins.[10,11] The lipoprotein(a) particle appears to be more readily retained in the artery wall and it accumulates at sites of arterial injury or inflammation. In addition to its atherogenic cargo of cholesterol, lipoprotein(a) is also a carrier of pro-atherogenic oxidized phospholipids and lipoprotein-associated phospholipase A2 (Lp-PLA2; also known as PAF acetylhydrolase). Several lines of evidence suggest that the risk of CVD appears to be related to a synergistic relationship between lipoprotein(a) and LDL, as reflected by the attenuation of risk in individuals with high lipoprotein(a) but low LDL-C[10,11], the enhancement of risk in subjects with heterozygous familial hypercholesterolemia and high lipoprotein(a)[12], and the suppression of risk of CVD events by aggressive LDL-C lowering in patients with pre-existing CVD and high lipoprotein(a) concentrations.[13]

Lipoprotein(a), Aortic Valve Calcification and Aortic Stenosis

The very interesting results of a recent study have suggested that lipoprotein(a) also contributes to aortic valve calcification and incidence of aortic stenosis. Genome-wide associations with the presence of aortic valve calcification were assessed in 6942 subjects in 3 cohorts, which led to the identification of a single nucleotide polymorphism in the lipoprotein(a) (LPA) locus (rs10455872) associated with an odds ratio of 2.05 ($P=9.0 \times 10^{-10}$) for aortic valve calcification.[19] Lipoprotein(a) levels predicted by the LPA genotype also were associated with aortic valve calcification. In a prospective analysis, the LPA genotype also was associated with the incidence of aortic stenosis with a hazard ratio of 1.54 (95% CI 1.05 to 2.27).

Screening for Lipoprotein(a) Elevation

Screening for lipoprotein(a) elevation is indicated in patients with moderate to high CVD risk because it is helpful for CVD risk stratification and helps guide the aggressiveness of treatment of dyslipidemia. Identification of an individual with high lipoprotein(a) also is a marker of genetically mediated CVD risk, which provides the opportunity for detection of first degree relatives who unknowingly may also have increased CVD risk. Screening of seemingly low-risk patients also needs to be considered because the advent of the statin era 25 years ago has substantially reduced the sensitivity of the family history for detection of familial CVD risk. Since an entire generation of patients have markedly reduced their CVD risk as a consequence of effective LDL-lowering by statins, the offspring of these patients (and their health care providers) can no longer assume that a negative family history of CVD implies low CVD risk. The implication of this is that patients who report having no family history of CVD may actually have increased CVD risk related to lipoprotein(a) elevation or other genetically mediated CVD risk factors. The European Atherosclerosis Society Consensus Panel recently advocated screening all individuals with the following conditions: (I) premature CVD, (II) familial hypercholesterolemia, (III) a family history of premature CVD and/or elevated Lp(a), (IV) recurrent CVD despite statin treatment, (V) ≥3% 10-year risk of fatal CVD according to the European guidelines, and (VI) ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines.[8] A family history of hypercholesterolemia could also be considered as an alternative criterion for item (III) because of the reasons described above. The National Lipid Association also convened a panel of clinical experts who issued recommendations regarding the clinical use of various biomarkers in 2011, which included recommendations for lipoprotein(a) that mirrored the recommendations from the European Atherosclerosis Society Consensus Panel.[14]

Reference Ranges for Plasma Lipoprotein(a) Measurements

Measurement	Reference Range
Lp(a) molar concentration	< 75 nmol/L
Lp(a) cholesterol concentration	< 10 mg/dL
Lp(a) protein concentration	< 30 mg/dL

Table 2.

Treatment

There is no direct proof that lowering lipoprotein(a) reduces CVD risk because the studies have not been done. In the meantime, it is reasonable to try to reduce high levels of lipoprotein(a) in selected patients. Niacin is the primary pharmacologic treatment for elevated lipoprotein(a) because it has the greatest lipoprotein(a)-lowering efficacy and it has been shown to reduce CVD events in several patient populations.[15] Unfortunately, the efficacy of this intervention is limited to a 20-40% dose-dependent reduction, which is insufficient to achieve acceptable levels in patients with very high levels. There are reports that statins minimally lower plasma lipoprotein(a) concentrations, but statins are generally ineffective for lipoprotein(a) lowering except in patients with familial hypercholesterolemia, who may achieve modest lipoprotein(a) lowering for unclear reasons (lipoprotein(a) is not cleared by the LDL receptor). A possible mechanism is decreased production of lipoprotein(a) due to a reduced pool of LDL in plasma.

LDL apheresis can acutely lower lipoprotein(a) levels by 50-80% during a 2-3 hour procedure, but the invasiveness of the procedure, high cost, and fairly limited availability are limiting factors. Individuals with very high lipoprotein(a) concentrations and progressive CVD despite aggressive medical therapy may be candidates for initiation of treatment with LDL apheresis. We are currently treating two individuals with LDL apheresis for this indication, one of whom had severely elevated lipoprotein(a) concentrations and developed rapidly progressive internal carotid artery atherosclerotic occlusions necessitating bilateral revascularizations in her early 50s, despite aggressive combination treatment with a statin plus niacin. In an uncontrolled observational study of 120 patients with CVD and lipoprotein(a) levels greater than the 95th percentile, treatment with LDL apheresis was associated with a reduction in CVD events (MACE rate per patient 1.056 vs. 0.144; $P<0.0001$).[16] The results of a more recent randomized trial of LDL apheresis in 32 patients with lipoprotein(a) > 50

mg/dL and LDL cholesterol < 2.5 mmol/L demonstrated increased regression or stabilization of angiographic coronary atherosclerosis (70% vs 43%, p=0.02) compared to usual care.[17]

Treatment with estrogen replacement or estrogen analogues in postmenopausal women is associated with a modest reduction in the plasma concentration of lipoprotein(a), but the predictive association between lipoprotein(a) and cardiovascular risk is attenuated in women taking hormone replacement therapy.[18] Among postmenopausal women with the highest quintile of lipoprotein(a), however, those women taking hormone replacement appeared to have a lower risk of cardiovascular events compared to those not taking estrogen, particularly among women with high LDL cholesterol concentrations above the median.[18] The relationship between estrogen replacement and CVD risk in the general population continues to be controversial, however.

Treatment of hypothyroidism, if detected, and correction of renal insufficiency and proteinuria, if possible, may also have beneficial effects on lipoprotein(a) levels. Anabolic steroids such as stanozolol and danazol may lower lipoprotein(a) levels up to 50% in women, but these agents are not recommended for general use because of adverse side-effects. It is possible that aspirin, L-carnitine, ascorbic acid combined with L-lysine, calcium antagonists, angiotensin converting enzyme inhibitors, and androgens may lower lipoprotein(a) by < 10%[8], but these agents are not indicated as primary treatment for elevated lipoprotein(a). Experimental medications are under development that may lower lipoprotein(a) concentrations by more than 20-25%, such as lomitapide (microsomal transfer protein inhibitor), mipomersen (apoprotein B antisense oligonucleotide), anti-PCSK9 agents, and thyroid hormone analogues. Lomitapide and mipomersen were recently FDA approved for restricted treatment of homozygous familial hypercholesterolemia, but they are still considered experimental for lipoprotein(a) lowering and treatment of other patient populations.

Options for Management of High Lipoprotein(a)

Niacin – first choice
Possible estrogen replacement in postmenopausal women
LDL apheresis
More aggressive LDL lowering
Upcoming experimental therapies?
Renal transplantation in patients with renal failure

Table 3.

Since it is typically difficult to normalize plasma levels of lipoprotein(a), an alternative strategy is to aggressively lower levels of LDL and remnant lipoproteins in patients with high lipoprotein(a). The efficacy of this strategy is not proven, but it is supported by the findings from prospective observational and intervention studies that suggest that the risk of CVD events attributable to lipoprotein(a) may be abrogated when the LDL cholesterol concentration is < 70-80 mg/dL.[10,11,13]

> Niacin is the most efficacious treatment for lowering lipoprotein(a), aside from LDL apheresis.

Summary and Conclusions

Lipoprotein(a) elevation is an important risk factor for CVD, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease, particularly among individuals with the highest levels of lipoprotein(a) in combination with elevated LDL cholesterol or particle numbers. Levels of plasma lipoprotein(a) are rarely quantified outside of lipid disorder clinics, so the majority of patients with high levels are undiagnosed. About 90% of the inter-individual heterogeneity in levels of lipoprotein(a) is genetically mediated, so the disorder is highly heritable, necessitating screening of first degree relatives of affected individuals. The methods for quantifying lipoprotein(a) are not well standardized, so practitioners need to understand how the testing is performed and what is actually measured in their laboratory. All moderate- and high-risk patients should have a lipoprotein(a) determination, and some seemingly low risk individuals may warrant evaluation. Niacin is the most efficacious treatment for lowering lipoprotein(a), aside from LDL apheresis. Aggressive LDL lowering is an alternative strategy for managing patients with elevated lipoprotein(a), since the atherogenicity of lipoprotein(a) appears to be attenuated when the LDL-C concentration is low. Clinical trials are needed to demonstrate the best approach to managing patients with high lipoprotein(a), but in the meantime we need to utilize the available strategies in the context of our current understanding of lipoprotein(a) and CVD risk. ■

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Specialty Corner:
Nephrology Corner—Limitations of Statin Use and Adjuvant Therapies in Stage IV CKD and Dialysis

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Coronary heart disease (CHD) remains the leading cause of death in Western civilizations. The role of abnormal lipid metabolism as a modifiable risk factor for CHD is well documented. The presence of chronic kidney disease (CKD) is also associated with an increased risk of CHD, but the pathogenesis of this relationship is not completely understood. Specifically, it remains unclear whether and to what degree the management of dyslipidemia can affect the risk of CHD in patients with advanced CKD, especially given the higher risk of adverse effects with pharmacological therapy in this patient population.

Epidemiology

Decreased kidney function is associated with an increase in the risk of cardiovascular (CV) death, particularly among those with stage IV and V CKD (Figure 1).[1] Relative to the general population, advanced CKD does appear to be associated with an increase in triglycerides and VLDL-C and a decrease in HDL-C, but LDL-C appears to be relatively unchanged or perhaps a bit decreased. The epidemiological data has led many to suggest that advanced CKD should be considered a CHD risk equivalent. Indeed, the National Kidney Foundation has published guidelines for management of lipids in CKD that set aggressive goals of therapy, similar to those defined by ATP III for other CHD risk equivalents (Table 1).[2]

Pharmocokinetics, Pharmacodynamics and Potential for Drug Interactions

Statins and other lipid-lowering agents have been used clinically for the management of hyperlipidemia and prevention of cardiovascular events in patients with CKD for the past 25 years. Statins with a shorter duration of action should be dosed at night or bedtime since cholesterol biosynthesis undergoes a circadian cycle, with most cholesterol formation occurring while an individual is asleep. The ideal antihyperlipidemic agent should improve patients' lipid profile without increasing the risk of toxicity. The comparison of pharmacokinetics

Dyslipidemia	Goal
LDL-C >100 mg/dL	LDL-C <100 mg/dL
Triglycerides >500 mg/dL	Triglycerides <500 mg/dL
Triglycerides >200 mg/dL	Non-HDL-C <130 mg/dL

Table 1. National Kidney Foundation Guidelines for Managing Dyslipidemia in Adults with CKD.[2]

properties of all antihyperlipidemics agents are listed in Table 2.[3] Most statins rely on both renal excretion and hepatic metabolism for elimination; atorvastatin and fluvastatin rely least on renal excretion. Most statins are metabolized through cytochrome p450-IIIA4 and can result in significant drug interactions. Compared to other statins, pravastatin and pitavastatin are more hydrophilic agents and metabolized through hydroxylation and glucuronide conjugation, respectively. In general, statins should be used with caution in patients with CKD, particularly the elderly population with CKD. Most patients with CKD have a number of co-morbid conditions that can mask early signs and symptoms of myopathy and rhabdomyolysis [osteoarthritis and back pain] or place these patients at greater risk of drug-drug interactions. Recently, the U.S. Food and Drug Administration (FDA) issued recommendations concerning drug-drug interactions for both lovastatin and simvastatin.[4] For example, the use of cyclosporine and simvastain/lovastatin are relatively contraindicated, while pravastatin is considered the safer agent in this setting. The most serious form of myopathy, rhabdomyolysis, is more common in CKD and can be fatal. Gemfibrozil may affect oxidation of statins or act as an inhibitor of the P450 enzyme system, thereby increasing the area under the curve and total drug exposure of most statins, which may explain the high incidence of myopathy observed with this combination.[5] The use of gemfibrozil and statins is considered a relative contraindication. If a fibric acid derivative is needed, fenofibrate is the preferred agent, but dose adjustments are required in patients with CKD. Fenofibrate may increase creatinine production and cause increases in serum creatinine values. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a lower estimated glomerular filtration rate (eGFR), creatinine clearance and higher serum creatinine was reported in the fenofibrate group compared to the control group. However, the elevation of serum creatinine and cystatin C was noted without any changes in tubular function.[6]

	Rosuva	Atorva	Simva	Lova	Prava	Fluva
T 1/2 (hr)	20.8	15-30	2-3	2.9	1.3-2.8	0.5-2.3
Urinary excretion %	10	<2	13	10	20	6
CYP-3A4 metabolism	No	Yes	Yes	Yes	No	No
CYP metabolism	2CY9	3A4	3A4	3A4	sulfation	2CY9

Table 2. Clinical pharmacokinetic profiles of commonly used statins in CKD patients.[3]

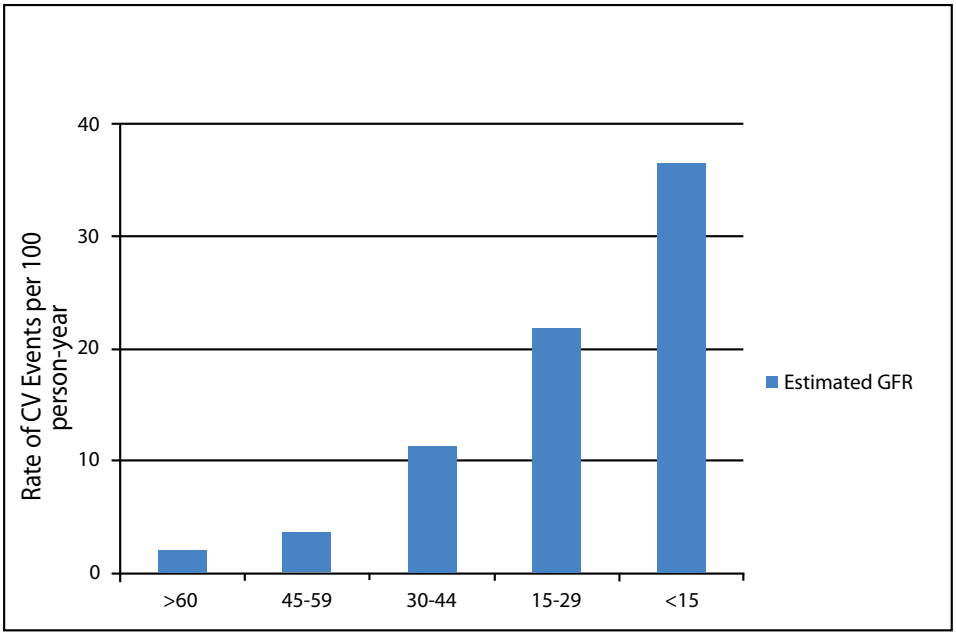

Figure 1. Age Standardized Risks of Cardiovascular Events According to Estimated GFR Among 1,120,295 Ambulatory Adults.[1]

Clinical Endpoints in CKD

While treatment of dyslipidemia has been demonstrated to decrease the incidence of CV events in both primary and secondary prevention, the majority of our landmark prospective clinical trials of lipid-lowering therapy either excluded or enrolled few patients with advanced CKD. As CKD advances the relationship between dyslipidemia and CV risk becomes less clear. Indeed, it has been suggested that the pathophysiology of CV events may be different in patients with more advanced CKD, whereby many CV events could be caused by vascular stiffness and calcification, structural heart disease, increased sympathetic tone, arrhythmia and transient decreases in perfusion across fixed areas of stenosis rather than atherothrombotic plaque rupture.

There have been only three large-scale, prospective, randomized trials of lipid lowering therapy in patients with advanced CKD examining the incidence of clinical CV events (Figure 3). In the first two of these studies, the Die Deutsche Diabetes Dialyze Studie (4D) and the AURORA study, the use of high potency statins (atorvastatin and rosuvastatin respectively)

Study	Year	N	Population	Intervention	Results of Primary Endpoint
4D[7]	2004	1255	Type 2 diabetes mellitus on dialysis	Atorvastatin or placebo	8% non-significant reduction in CV events
AURORA[8]	2009	2776	Dialysis patients	Rosuvastatin or placebo	4% non-significant reduction in CV events
SHARP[9]	2010	9438	SrCr at least 1.7 md/dL in men or 1.5 mg/dL in women or on dialysis	Simvastatin + Ezetimibe or placebo	17% reduction in major CV events (statistically significant

Table 3. Summary of Outcome Studies of Lipid-Lowering Therapy in Patients with CDK.[7-9]

in dialysis patients did not lead to a significant reduction in cardiovascular events despite robust changes in lipid parameters.[7,8]

In the SHARP study, the use of simvastatin-ezetimibe in subjects with stage 3-5 CKD did lead to a statistically significant 17% reduction in CVD events.[9] In subgroup analysis of SHARP, subjects with stage 3 CKD had a statistically significant 25% reduction in CV events; those with stage 4 CKD had a statistically significant 22% reduction in CV events; while those on hemodialysis at baseline did not have a significant reduction in events. Whether the favorable results seen in SHARP were due to the specific combination of lipid-lowering agents used in that study or the inclusion of patients with less advanced CKD (as seems more likely) is unknown. Importantly, although other combinations of lipid-lowering agents, including statin + nicotinic agent or statin + fibrate, are frequently employed in patients with advanced CKD, endpoint data with these combinations is essentially non-existent in this patient population.

A recent meta-analysis of all trials of lipid-lowering therapy that included patients with CKD suggested that lipid-lowering therapy led to a modest decrease in the risk of cardiac mortality (pooled risk ratio [RR] from 6 trials 0.82), CV events (pooled RR from 9 trials 0.78), and myocardial infarction (pooled RR from 9 trials 0.74); however, the majority of subjects in the included studies were stage 3 CKD patients, representing subgroups of larger studies.[6,10] A second meta-analysis demonstrated that statin therapy reduced all cause and CV mortality, major CV events, myocardial infarction and stroke in person with CKD not receiving dialysis by about 20-25%, but that there was little or no beneficial effect on any mortality or CV endpoints with statin therapy in those on dialysis at baseline.[11] Unfortunately, in both meta-analyses, most patients with CKD not on dialysis were stage 3 or lower, and the data was not reported for stage 4 CKD individually.

There are very limited clinical data on the safety and efficacy of combination of statin and nicotinic acid or statin and fibrates therapies in patients with CKD. Due to possible drug interactions and risk of myopathy and recent findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study and AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes, that combination therapy did not result in a significant reduction of cardiovascular events compared with statin monotherapy, care should be taken when combination therapy with these agents is utilized with statins in patients with chronic kidney disease.[12, 13]

While lipid-lowering therapy appears effective in reducing CV events in stage 3 CKD, there is little to no evidence that lipid-lowering therapy reduces CV events in patients already on dialysis. Data specifically in stage 4 patients is quite limited, but based on the SHARP study results, these patients probably do receive a modest benefit.

Safety of Lipid-Lowering Agents in Advanced CKD

In general, cumulative data from both primary and secondary prevention studies of statins indicate that the HMG CoA reductase inhibitors (statins) have an excellent safety record and a favorable risk-benefit profile, with a low risk of significant adverse events (<1% incidence).[14] However, epidemiological studies indicate the discontinuation rates for lovastatin and simvastatin were 3% and 6% respectively, and much higher incidence of myopathy at high doses (80 mg daily).[15]

Myopathy—The clinical spectrum of statin-induced myopathy consists of myalgia, myositis, rhabdomyolysis and asymptomatic increases in plasma creatine kinase (CK) levels. Muscle-related adverse events can be difficult to describe because the terminology used can be inconsistent. Generally, 'myalgia' refers to the tolerability issue of muscle pain or weakness without elevation of creatine kinase (CK) levels, while 'myositis' is defined as the safety issue of muscle pain with considerable elevation of CK levels.[16] Rhabdomyolysis refers to muscle symptoms with markedly raised CK, usually >10x upper limit of normal, and is generally considered a serious medical condition that can lead to hospitalization, renal failure, and even death.[16] For all statins,

Drug Class	Medications	Dosing in Renal Impairment
HMG-CoA Reductase Inhibitor	Atorvastatin	No adjustment is necessary.
	Fluvastatin	Mild-to-moderate renal impairment: No dosage adjustment necessary. Severe renal impairment: Use with caution (particularly at doses >40 mg/day; has not been studied).
	Lovastatin	When CICr <30, Use IR >20 mg daily with caution. Use initial ER 20 mg QHS; (Doses >20 mg daily with caution).
	Pitavastatin	CICr 15-60 (not receiving HD): Initial 1 mg QD; max 2 mg QD ESRD: Initial 1 mg QD; max 2 mg QD.
	Pravastatin	Significant impairment: initial 10 mg/day.
	Rosuvastatin	Mild-to-moderate impairment: No dosage adjustment required. CICr <30: Initial 5 mg/day; NTE 10 mg QD.
	Simvastatin	Manufacturer's recommendations: Mild-to-moderate renal impairment: No dosage adjustment necessary. Severe renal impairment: CICr <30: Initial 5 mg/day with close monitoring. Alternative recommendation: No dosage adjustment necessary for any degree of renal impairment.
Bile Acid Sequestrants	Colesevelam	No dosage adjustment necessary; not absorbed from the GI tract.
	Cholestyramine	No dosage adjustment provided in manufacturer's labeling; however, use with caution in renal impairment; may cause hyperchloremic acidosis.
	Colestipol	No dosage adjustment necessary; not absorbed from the gastrointestinal tract.
Nicotinic Acid	Niacin, etc.	No dosage adjustment recommended; use with caution.
Fibric Acid Derivatives	Gemfibrozil	Mild-to-moderate impairment: Use caution; deterioration of renal function has been reported in patients with baseline SCr >2. Severe impairment: contraindicated. HD: Not removed by HD; supplemental dose is not necessary.
	Fenofibrate	CICr ≥50: No dosage adjustment necessary. CICr <50: Initiate at 45 mg/day. Contraindicated in severe impairment.
Cholesterol Absorption Inhibitor	Ezetimibe	AUC increased with severe impairment (CICr <30); no dosing adjustment necessary.
Omega-3 Fatty Acid		No dosage adjustment provided in manufacturer's labeling (has not been studied).

Table 4. Dosing adjustment for lipid-lowering agents in chronic kidney disease.

the overall risk of rhabdomyolysis is less than 0.5% in the general population.[17] This risk may be higher in patients with CKD, elderly, and in patients taking other drugs or food which inhibit CYP3A4, specifically grapefruit, cyclosporine, azole antifungals, macrolide antibiotics, and fibrates.[18] Although the exact pathogenesis of myopathy has not been determined, several mechanisms have been postulated. Myopathy may be due to mitochondrial dysfunction and muscle protein degradation. The genetic marker SLCO1B1 is among the strongest predictors of myopathy risk.[19]

Hepatotoxicity—Previously, hepatocellular necrosis and hepatotoxicity induced by statins were considered a myth.[20] A recent study has concluded that idiosyncratic hepatotoxicity may be associated with the use of statins.[21] Asymptomatic hepatic transaminase elevation (greater than three times the upper limit of normal) may occur in 1-2% of patients on an HMG-CoA reductase inhibitor and in general is dose related. In most patients, elevation of transaminase enzymes are resolved spontaneously with continued therapy, although discontinuation may be required in some patients. Based on current recommendations from the FDA, routine monitoring of transaminases is no longer

necessary unless the patient exhibits transaminase abnormalities at baseline, has other risk factors for hepatotoxicity, or clinically abnormalities are suspected.

Dosing—With the increasing incidence of chronic renal disease, regular renal function monitoring and dosage adjustment of lipid-lowering agents according to eGFR and pharmacokinetic data are of major importance.[3,22] Because large studies of the safety of these agents in patients with CKD is lacking, drug-drug interactions and dosage adjustment recommendations need to be regularly updated following the results of epidemiological and observational studies. Patients with significant renal disease should be started on low doses of statins and other lipid-lowering agents, with doses titrated up only when clinically indicated. Due to the risk of significant drug-drug interactions, for the renal transplant population fluvastatin has been demonstrated to be safe in a large clinical endpoint trial where tacrolimus was the most common immunosuppressant used, but pravastatin may be a more suitable agent when cyclosporine is used (Table 4).[23]

Summary

While far from conclusive, the available clinical trail evidence supports the hypothesis that lipid-lowering therapy may provide diminishing benefit as CKD advances. In stage 4 CKD and dialysis, the potential for benefit from statin therapy needs to be weighed carefully against the increased risk for adverse effects seen in this patient population. With the exception of statin-ezetimibe, combination lipid-lowering therapy has not been well studied in this patient population and should be used only with careful monitoring for adverse events. Future studies are needed to help clinicians appropriately balance the benefits and risks of lipid-lowering therapy in CKD, particularly for the increasing number of patients with Stage IV CKD and concomitant dyslipidemia. ■

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Practical Pearls:

Cardiac Auscultation for the Lipidologist: A Systolic Murmur You Do Not Want to Miss!

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It is typically silent, but sometimes you can hear it, a soft systolic ejection murmur heard over the aortic area during cardiac auscultation on physical examination. As cardiovascular risk reduction specialists, we do not to want to miss this cardiac murmur. It is not innocent or benign; this is the murmur of aortic valve sclerosis (ASc). In addition, there is a normal split of the second heart sound, a normal carotid upstroke, and a peak transaortic systolic gradient noted on Doppler transthoracic echocardiography (TTE) typically less than 16 mmHg. The characteristic M-mode tracing on echocardiography is seen in Figure 1. ASc is characterized by calcification and thickening involving the aortic valve cusps with no hemodynamically significant transaortic systolic gradient noted on TTE. ASc shares many of the same clinical risk factors for coronary heart disease (CHD) including age, hypertension, and cigarette smoking.[1]

ASc is prevalent among the elderly. Of 5,176 subjects ≥65 years of age enrolled in the prospective Cardiovascular Heart Study undergoing adequate echocardiographic study, 26% were found to have ASc.[1] Aortic valve stenosis was identified in 2% of the subjects. ASc is even more common among patients with known coronary heart disease. The prevalence is approximately 40%.[2,3] In a study of 425 patients presenting to the emergency room with chest pain, the prevalence of Asc was even higher at 49%.[4] In patients undergoing coronary angiography for chest pain, the prevalence was related to the degree of obstructive coronary artery disease present. In patients with no obstructive CHD, single vessel CHD, double or triple vessel CHD prevalence respectively was 14%, 28%, and 58%.[2] Interestingly, ASc was found to be a more powerful predictor of obstructive CHD in patients <60 years of age than in those >60 years.[2]

In a study of 338 consecutive patients undergoing myocardial perfusion single photon emission computed tomography (SPECT) and TTE, ASc was significantly associated with an abnormal SPECT.[5]

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Among mitral and aortic valve sclerosis calcification sites, the odds for an abnormal SPECT in younger patients (≤55 years) for 3 sites was nearly 4 times higher than for patients without calcium. In older patients (>55 years of age), the odds were only 1.94 times as high. After univariate analysis, CRP has been found to be associated with ASc ($p<0.05$) in 425 patients presenting to the emergency room with chest pain.[4] After one year, in patients with established ASc, there was a marked decrease in event-free survival for those at the highest tertile of CRP (>1.18 mg/dL) compared to the patients at the lowest tertile (<0.32 mg/dL). The odds for an abnormal SPECT in patients with multiple calcific deposits, diabetes mellitus or multiple cardiac risk factors was striking for women when they had these factors. The OR was 20.00 in younger women (≤55 years of age) vs. 10.00 for older women (>55 years of age) compared to women with no multiple calcium deposits without diabetes mellitus or multiple cardiac risk factors. ASc has important clinical ramifications. Not only can ASc progress to aortic valve stenosis; it is independently associated with adverse cardiovascular events.

In a study of 2,131 patients with ASc over a mean follow-up of 7.4 years, 10.5% developed mild, 2.9% developed moderate and 2.5% developed severe aortic valve stenosis.[6] In the Cardiovascular Health Study, 9% of 1,091 subjects followed for a mean 5-year period developed aortic valve stenosis.[7] ASc was independently associated with new coronary events (risk ratio 1.8) in a prospective study of 1980 subjects.[8] In the large prospective Cardiovascular Health Study of over 5000 men and women ≥65 years of age, followed for 5 years, ASc was independently associated with increased risk of cardiovascular death and myocardial infarction (MI).[9] ASc has been shown to be an independent predictor of MI in patients with known CHD also. In a prospective study of 814 patients with CHD, 40% having prevalent ASc had a 2.4 fold increased risk of MI during 4-years of follow-up.[3]

ASc is associated with lipid accumulation inflammation in addition to calcium deposition in the valve. Low density lipoprotein (LDL) and lipoprotein (a) [Lp(a)] were found in lesions of aortic stenosis.[10] Elevated circulating Lp (a), and low high density lipoprotein (HDL) cholesterol have been shown to be independently associated with ASc.[11,12] LDL-C is associated with aortic valve stenosis[13-16] in patients with Familial Hypercholesterolemia, however the association in the general population has been inconsistent. In the Cardiovascular Health Study[17], increased LDL-C was associated with ASc but not in the SPARC (Stroke Prevention: Assessment of Risk in Community)[18] or in the Helsinki Aging Study.[19]

ASc is associated with systemic endothelial dysfunction as demonstrated by significantly lower flow mediated dilatation (FMD).[20] Recently, it has been shown that ASc is associated with platelet resistance to NO.[21] Over a 4-year follow-up period, progression of ASc was also independently associated with tissue resistance to NO.[22]

ASc lesions have histologic similarities with coronary atherosclerotic plaque including inflammatory cells: specifically macrophages and T-lymphocytes, in addition to lipid accumulation and disruption of the basement membrane.[23,24] After univariate analysis, CRP has been found to be associated with ASc ($p<0.05$) in 425 patients presenting to the emergency room with chest pain.[4] After one year, in patients with established ASc, there was a marked decrease in event-free survival for those at the highest tertile of CRP (>1.18 mg/dL) compared to the patients at the lowest tertile (<0.32 mg/dL). In patients without CHD or ASc and a CRP in the upper two tertiles, the cardiac death and MI incidence at 1 year was 0 versus 41% in patients with CHD and ASc. In this study, ASc was not an independent predictor. The presence of CHD and elevated CRP was associated with the adverse cardiovascular events however. Specifically, the increasing tertile of CRP was an independent predictor of cardiac death and nonfatal MI (HR 2.2). However, in a lower risk, prospective population study, CRP was not found to be associated with the development of ASc.[7]

In addition to inflammation and lipid accumulation, aortic ASc is associated with calcification. Calcification involving the aortic valve is an active osteogenic process which has been characterized as an osteoblast-like phenotype.[25] Compared to normal human aortic valves, explanted calcified aortic valves at the time of transplantation were shown to have increased levels of the proteins: Osteocalcin, Osteopontin, bone sialoprotein and the transcription factor Cbfa-1 all characteristics of osteoblast activity.[26] Furthermore, in patients with aortic valve stenosis undergoing surgery or routine echocardiography, increased plasma levels of Osteopontin were associated with the presence of aortic valve calcification and stenosis.[27] In addition to Osteocalcin and Osteopontin, low-density lipoprotein receptor-related protein 5 (Lrp5) was found to be increased in explanted calcified aortic valves by protein and gene expression at the time of surgical valve replacement.[27] Lrp5 is an important receptor in the activation of skeletal bone formation. In a study of hypercholesterolemic rabbits with aortic valve calcification, atorvastatin decreased Lrp5 and the aortic valve calcification.[28] Just recently, for the first time, a

circulating osteogenic precursor cell in human blood has been identified to be associated with calcification of the aortic valve.[29]

Patients with ASc are at higher risk for myocardial infarction and CHD and should be assessed for underlying CHD. Multiple retrospective studies[30-34] have shown statins to be beneficial in reducing progression of aortic valve stenosis; unfortunately, prospective, randomized[35-37] and non-randomized[38] clinical trials have not confirmed these observations. Furthermore, there has never been reported a randomized placebo controlled trial in patients with ASc with a TTE Doppler gradient of less than 16 mmHg. The average peak transaortic systolic gradient was at least 36 mmHg in all of these prospective trials. It still remains unknown whether statin therapy will reduce the progression of ASc to aortic stenosis in patients with milder forms of ASc. Of interest is a recent study in hypercholesterolemic mice with early aortic valve disease demonstrating that reducing plasma lipid levels by genetic inactivation normalizes oxidative stress, reduces pro-osteogenic signaling, and halts the progression of aortic valve disease.[39]

We believe that in patients with a cardiac murmur, when there is reasonable suspicion of valvular or structural heart disease, it is appropriate to obtain an echocardiogram.[39] It is also helpful to add on the TTE request: "Please evaluate for Aortic Valve Sclerosis/Stenosis." It is also appropriate to obtain an echocardiogram for routine surveillance (≥3 years) of mild valvular stenosis or (≥1 year) for moderate or severe valvular stenosis without a change in clinical status or cardiac exam.[40] If a patient is identified with ASc then intensive risk factor modification should be instituted including a regular exercise program. In a LDL receptor deficient mouse model, regular exercise training prevented ASc through several aspects including reduction and inflammation, oxidative stress and also an inhibition of the osteogenic pathway.[41] This may be relevant to humans.

Patients with CHD, or CHD risk equivalents including diabetes mellitus, will all need to be on statins regardless of their LDL-C levels or the presence of ASc. We are looking forward to the future as studies address molecular targets for valvular calcification. **ASc is an important murmur that we do not want to miss!** ■

Disclosure statement: Dr. López has received honoraria from Abbott Laboratories, Aegerion, Amarin Corp., AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo Inc., Forest Pharmaceuticals, Gilead Pharmaceuticals, GlaxoSmithKline, Kowa Pharmaceuticals America, and ZonaHealth. Dr. Nelson has received honoraria from Abbott Laboratories, Amarin Corp., AstraZeneca, Atherotech, Bristol-Myers Squibb, Daiichi Sankyo Inc., GlaxoSmithKline, Gilead Pharmaceuticals, Kowa Pharmaceuticals America, Merck & Co., Pfizer Inc., and Novartis Pharmaceuticals.

Case Study:
Digging Deeper—A Case for Apolipoproteins and Lifestyle in Office Practice

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R.E. is a 58-year-old Asian male who finally quit smoking one month ago, and is now being treated for hypertension to goal with the combination amlodipine/benazepril. He has type 2 diabetes and takes metformin 500 mg bid. His initial lipid panel revealed a TC=230 mg/dL, LDL=140 mg/dL, HDL=35 mg/dL and TG=265mg/dL and his Non HDL- was 195. His BMI was 29, FBS=109mg/dL and his HbA1C=6.8. In general he has led a sedentary lifestyle. He was placed on Simvastatin, 40 mg q HS and three months later his lipid profile was: TC=145mg/dL, LDL=89mg/dL. HDL=31mg/dL, and TG=166mg/dL, and non-HDL-C=114.

Because he has multiple risk factors including diabetes, using ATP III guidelines he has an LDL goal of <100mg/dL and a non-HDL-C goal of <130.

Additional data from an NMR lab obtained on the same blood sample: ApoB=97mg/dL, (optimal <60)*LDL-P=1531 nmol/L, (high risk >1000)* sdLDL 32 mg/dL, (optimal <21)* ApoA1=111 mg/dL (optimal >150)*, ApoB/ApoA1 Ratio=0.87 (high risk >0.81)*. He is relatively sedentary and followed no particular diet consistently. Is this additional information useful in clinical practice?

LDL-C concentration, commonly calculated, is simply the amount of cholesterol in the LDL fraction of plasma, and has become the major target for preventing vascular disease associated with dyslipidemia. ApoB is a measure of the total number of atherogenic particles and in some studies it is a more precise marker for risk of vascular disease. The cholesterol content of the LDL particle can be quite variable. In patients with type 2 diabetes and obesity associated with high triglyceides, this discrepancy seems to amplify. Cholesterol ester transfer protein, (CETP) transfers triglycerides from triglyceride-rich VLDL to cholesterol containing LDL and HDL lipoproteins in exchange for cholesterol. LDL-C may be deceptively lower as the cholesterol content is decreased but the particle number has not changed. When triglyceride-rich LDL particles are then exposed to hepatic lipase, triglycerides are cleaved from the LDL particle creating small dense LDL. Small LDL particles may be more subject to

oxidation and entry into blood vessel walls potentially accelerating the atherosclerotic process.

Are apolipoproteins better CVD risk predictors than lipids? The INTERHEART study suggested that the ApoB/ApoA1 ratio was more strongly associated with risk for acute myocardial infarction in all ethnic groups, in both sexes, and at all ages. Additionally, ApoB, and the ApoB/ApoA1 ratio were strongly associated with more fatal myocardial infarction in men and women. ApoA1 was noted to be protective in the AMORIS trial.Analysis from this trial suggested that these values should also be measured to evaluate cardiac risk. Some data, but not all, suggests that this ratio is superior to non-HDL-C calculation {Total Chol – HDL-C= non-HDL-C}. The area remains controversial because the collaborative meta-analysis utilizing individual patient data could not find that ApoB was superior to predicting MI. Although non HDL-C and ApoB are highly correlated in large groups, they may be only moderately concordant for some individuals.

In another study looking at the association between ApoB, ApoA1, the ApoB/ApoA1 ratio, and ApoA1 in the prediction of myocardial infarction in middle-aged men and women, only ApoB and the ApoB/ApoA1 ratio were strong predictors of coronary events. ApoA1 did not add significantly to the estimation of coronary risk.

Patients taking statins need to intensify CVD risk reduction lifestyle measures through proper diet, exercise, and avoidance of tobacco. In a study published by Kokkinos et al., statin treatment and increased fitness were independently associated with lower mortality among dyslipidemic patients. The combination of statins and increased fitness resulted in lowest quartile of mortality risk than either alone.

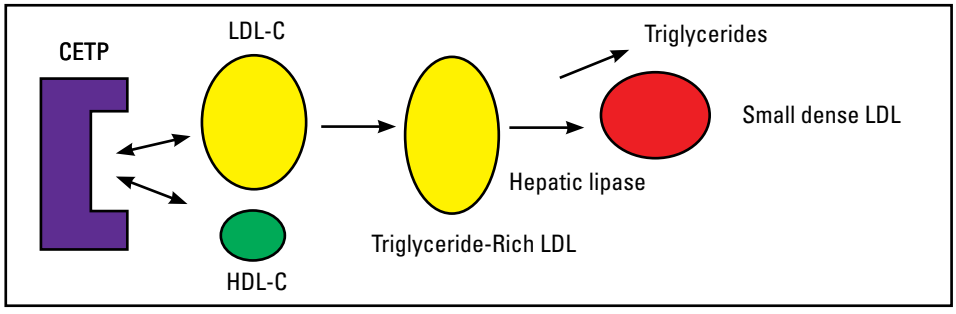

Figure 1. Not shown here: HDL is also subjected to hepatic lipase and becomes sdHDL which is rapidly degraded and excreted renally.

In our case, we felt there was justification for intensifying drug therapy and life-style intervention measures. The initial lipid panel results in contrast would not have lead us to demand a more vigorous approach for him.

Our primary goal was to further reduce LDL particle number and ApoB levels and improve his ApoB/ApoA1 ratio. Rather than increase simvastatin to 80mg (not recommended by the FDA), we chose to change the statin to rosuvastatin 20 mg, and intensify lifestyle changes. We expect that with cigarette cessation, our patient's HDL will increase as valuable enzymes in the HDL molecule may have been inhibited by smoking. Regarding lifestyle, we asked him to incorporate exercise into his busy work schedule by purchasing an inexpensive pedometer and use parking spaces further away, and stairs whenever possible. We asked him to find time during his lunch break to walk for at least 15 min, and when possible to devote this amount of time either before or after work. On weekends he was able to walk for an hour each day with his wife. He was instructed to avoid "anything white" in his diet such as breads, rice, and potatoes, as well as sweets. At our request, he purchased a recommended book to learn more about low glycemic index foods. Four months later, he lost ten pounds and repeat labs demonstrated that his FBS was 94mg/dL, HbA1C=6.1, Total Chol=137mg/dL, LDL-C=75mg/dL, TG=120mg/dL, HDL-C=38mg/dL, non-HDL-C=99. Pt's BMI dropped to 27 and his lipoprotein data now revealed an ApoB=80, LDL-P=950nmol/L, ApoB/ApoA1=0.70.

> "What makes us normal is knowing that we are not normal."
> ~ Haruki Murakami

In today's world of medicine, properly assessing patients and treating to achieve optimal risk reduction is a moving target. Which risk-assessment formulae do we use? Is 10-year or lifetime risk assessment best? Patient adherence and compliance are made more difficult by the endless plethora of readily available information and misinformation to which our patients are exposed on the internet and elsewhere.

As clinicians, we read studies that tell us that we are "under-treating" and we are "soft" on lifestyle changes. We encounter barriers to aggressive and multi-drug combinations due to patient reluctance to take "more meds," the high cost of pharmaceuticals, and formulary roadblocks. Despite this, discovery and innovation continue.

What are "normal" lipids? What will be the "new normal?" What will not change, however, is that as clinicians, we will always be required to use our sound judgment in interpreting and applying the best available evidence with honesty and compassion for our patients. ■

Disclosure statement: Ms. Given has no disclosures to report. Dr. Greenfield has received honoraria from Abbott Laboratories and Merck & Co.

Chapter Update:
Pacific Lipid Association

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As President-elect of the Pacific Lipid Association, it gives me a great pleasure to present our chapter update. Our members continue to be very active in their communities as well as throughout the NLA. Our own **Matthew Ito, PharmD**, will become the NLA President this May.

March of last year, our immediate past president, **John Nelson, MD**, held his annual CME conference in Fresno, California. The conference, entitled "Treatment of the High Risk Patient with Low HDL Cholesterol," was attended by 234 people. Several PLA members presented at the meeting.

The PLA, along with Dr. Nelson's leadership, has recently spearheaded a drive to develop an Advocacy Committee in the NLA. This committee would address specific issues faced by individual members of the NLA. Dr. Nelson is currently working with the State of California on SB866, a two-page electronic prior authorization form. This would allow practitioners to use a single form for all insurance prior authorizations. Insurance companies would be given two business days to respond to the completed document. This would save physicians a great deal of time as well as improve the timeliness of patient care.

PLA Board member, **Julie Bolick, RD**, is working with the Patient Adherence Subcommittee to create a patient toolkit for practitioners. She has also convened a meeting of NLA dietitians.

In September, our current chapter president, **J. Antonio G. López, MD,** hosted the live *Lipid Insights* program entitled "CETP Inhibition—An Important Potential Strategy in Reducing Cardiovascular Events." Dr. López, along with **Eliot Brinton, MD**, and **Benjamin Ansell, MD**, presented a lively debate focused on the relationship between CETP and atherosclerosis.

Dr. López continues as Chair of the NLA Honor's and Awards committee. **Wayne True, MD**, is Chair of the NLA Membership Committee.

Drs. Eliot Brinton and Matt Ito were among the four faculty members to participate in the successful USAGE manuscript and statin adherence public relations campaign (**www.StatinUSAGE.com**), which included a paper published in the *Journal of Clinical Lipidology* this past June.

This past October, **Paul Rosenblit, MD, PhD**, along with **Brian Chesnie, MD, Rob Greenfield, MD,** and **Nathan Wong, PhD**, held the 4th Annual Orange County Symposium in Newport Beach, California. This conference, jointly sponsored by the NLA and the American Society for Preventive Cardiology, focused on expanding knowledge with regard to the role of Clinical Lipidology in the primary and secondary prevention of cardiovascular disease.

The 10th Annual World Congress on Insulin Resistance, Diabetes, and Coronary Artery Disease Symposium was held in Los Angeles this past November. **Yehuda Handelsman, MD**, and colleagues assembled a unique multidisciplinary program dedicated to the management of cardiovascular risk factors and disease. This year's program introduced new aspects

of bone, fat, leptin and adeponectin interactions, as well as mitochondria and associated proteins, to metabolic impairment in human disease.

Our PLA is currently working with the NLA to host the 2013 Annual Scientific Sessions in Las Vegas, Nevada from May 29-June 2. Our NLA President, **Peter Toth, MD, PhD**, and Drs. Ito, López and I will serve as the program's co-chairs. The preliminary schedule and faculty look outstanding.

We are also working to invite lipid experts from the Pacific Rim nations to participate in the Spring 2014 Clinical Lipid Update on Maui. More information will be forthcoming.

The PLA remains an active and dynamic group. I have thoroughly enjoyed my interactions with both the PLA and NLA and recommend all those interested to become more involved. ■

Member Spotlight:
Daniel Steinberg, MD, PhD

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Like many young clinicians starting out, Daniel Steinberg, MD, PhD, did not intend to build a career in Clinical Lipidology. But the Harvard-trained biochemist had motivation to pick a field quickly: it was 1950, the Korean War had just broken out, and he had served less than two years in World War II. His thesis supervisor, Christian B. Anfinsen, MD, had just accepted a position at what was the newly created National Heart Institute—if Dr. Steinberg accepted a job there, he would not need to enlist in the war.

The NHI's first director, James Shannon, MD, took interest in the research on lipoproteins and heart disease conducted by John Gofman, MD, PhD. His curiosity trickled down to Dr. Anfinsen, who put together a group of clinically oriented researchers, including Dr. Steinberg, to work on cholesterol and lipoproteins in relation to coronary heart disease. The work of that group and others around the world strongly suggested a causal relationship but the final proof awaited a randomized, double-blind clinical trial. In 1974, the Coronary Primary Prevention Trial (CPPT) launched with 3,600 male subjects who had high cholesterol. Half were given cholestyramine and half were given a placebo; subjects who had taken the bile acid sequestrant had a statistically significant decrease in heart attack risk. The success of the CPPT—the first large-scale, double-blind trial to show that lowering cholesterol decreased heart attack risk—helped position the National Institutes of Health to make the lowering of blood cholesterol levels a major public health goal.

When Dr. Steinberg went to the University of California-San Diego in 1968 he wanted to find out just how LDL led to atherosclerotic heart disease at the molecular level. In the 1980's, Michael Brown, MD, and Joseph Goldstein, MD, published a paper showing that the macrophages would not take up low-density lipoproteins (LDL) very quickly, which was surprising since macrophages tend to become loaded with cholesterol in atherosclerosis. Drs. Brown and Goldstein postulated that LDL molecules must first undergo some chemical or physical modification before they could be rapidly taken up by the macrophage. Dr. Steinberg and his colleagues showed that oxidation of LDL converts it to a form recognized by specific receptors, receptors that don't recognize native, unmodified LDL.

Dr. Steinberg now serves as a professor emeritus for the University of California-San Diego, where he worked for the past four decades. Many people would be surprised to learn that, at age 90, he still goes into the office on weekdays and writes avidly—in 2007 he published *The Cholesterol Wars,* and he just completed a book on "missed Nobel prizes."

Recently, Dr. Steinberg wrote to the ATP IV Panel, urging its members to be more aggressive in recommending treatment for hypercholesterolemia at a much earlier age. Looking ahead, he hopes research will shed light on why high-density lipoprotein appears to be a negative risk factor. The mystery of HDL is important, Dr. Steinberg said, "because the epidemiology is so clear cut that a breakthrough in this area could yield some of the most promising developments." ■

Education and Meeting News and Notes

Strategic Planning Update

NLA leaders met in February to discuss and develop new strategic initiatives for the NLA. A key focus of the discussions was improving ways for members to actively participate in committees and Boards and encouraging more member-led projects. There were also recommendations related to developing processes to evaluating the benefit of new ideas, improving relationships with other organizations, membership development, communications, and several other areas. The NLA will report on these initiatives in the coming months.

Lifetime Membership

For the first time, the NLA is offering a Lifetime Membership program with rates based on the duration of your involvement with the NLA. All Lifetime Memberships include a $1,000 donation to the Foundation of the NLA, which will be set aside to establish training programs and fellowships in Clinical Lipidology. Please visit **www.lipid.org/lifemember** for more information.

Survey of Physicians' Responses to Plaque Imaging on CTA

Please provide insight into the use of plaque information obtained from coronary CTA in managing your patients by participating in "Potential Clinical Applications of Plaque Imaging by CTA: A Survey," conducted by Harvey Hecht, MD, and colleagues from Mount Sinai Medical Center and The University of Erlangen. To participate, please download the survey from the "NLA Updates" section on the NLA homepage at **www.lipid.org**, mark your responses on the answer sheet, and then e-mail your answer sheet to **plaquesurvey@mountsinai.org**.

Early-bird Rate: Register for Annual Scientific Sessions Now and Save!

This 4-day comprehensive learning experience features a wide variety of scientific sessions, symposia, case presentations and poster sessions that provide practical solutions for applying the latest research in your clinical practice. All sessions and educational events are evidence-based and clinically relevant to the practicing lipidologist. Register at **www.lipid.org/sessions** by **March 29** to take advantage of the special Early-bird rate of $525.

New Chapter Bylaws Proposed

At the NLA strategic planning meeting that was held February 9-10, the leaders of the NLA and its Chapter Boards agreed to adopt a uniform set of Bylaws for all five of the NLA's regional Chapters. The proposed bylaws, available at https://www.lipid.org/about/newbylaws, will need to be adopted by each Chapter's Board of Directors and are scheduled to take effect on June 2, 2013, after the NLA 2013 Annual Scientific Sessions end. The NLA plans to hold the vote of the Chapter Boards between April 1-5, 2013. If you have comments on the proposed bylaws change, please contact your Chapter President or **Lindsey (Howard) Mitcham** at lhoward@lipid.org.

HDL CME/CE-certified Newsletter Series

All three installments of the HDL-themed CME/CE-certified interactive newsletter series have launched and are now open for member participation. This series aims to help clinicians successfully manage and treat residual risk in cardiovascular disease (CVD) due to abnormally low or dysfunctional HDL. This interactive newsletter will evaluate HDL-C as a tool to assess an individual's cardiovascular risk and examine the various atheroprotective functions of HDL and their role in determining CHD risk. Please visit **www.cmecorner.com** and choose "Dyslipidemia" among the featured programs to get started.

ABCL Maintenance of Certification

The American Board of Clinical Lipidology (ABCL) recently voted on maintenance of certification requirements in order for diplomates to maintain their certification after 10 years. Applicants must accumulate 500 points in the following areas in order to recertify: Evidence of Professional Standing, Lifelong Learning and Self-Assessment, Cognitive Expertise, Practice Performance Assessment. Stay tuned for more information.

Featured NLA Podcasts on ReachMD

Catch broadcasts of the NLA's latest ReachMD shows featuring Lipid Luminations host **Alan Brown, MD**, on XM Satellite Radio Channel 167. Below are the first air dates for our latest programs. For the broadcast replay schedule and to access the entire catalogue of NLA podcasts, visit the Lipid Luminations website at **www.reachmd.com/lipidluminations**.

- March 25: **Robert Wild, MD, PhD**: "Managing CVD in Women During Childbearing Years"
- April 4: **Kevin Maki, PhD**: "Obesity, Diabetes and the Metabolic Syndrome"
- April 8: **Rebecca Reeves, DrPH, RD**: "Changing Nutritional Needs Throughout the Lifetime"

Lipid Spin Review

Thanks to **Wayne Warren, MD**, for reviewing articles for this issue.

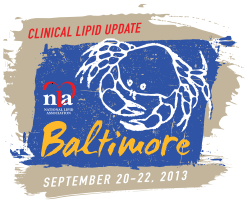
Events Calendar

2013 Scientific Meetings

2013 National Lipid Association Scientific Sessions

Hosted by the Pacific Lipid Association
May 30–June 2, 2013
Red Rock Hotel
Las Vegas, Nevada
www.lipid.org/sessions

2013 National Lipid Association Clinical Lipid Update—Fall



Hosted by the Southeast Lipid Association and the Northeast Lipid Association

September 20–22, 2013
Hyatt Regency Baltimore Hotel
Baltimore, Maryland
www.lipid.org/clu

Other 2013 Meetings

SCAN Annual Meeting
April 26–28, 2013
Westin Michigan Avenue
Chicago, Illinois
www.scandpg.org

PCNA Annual Meeting
May 2–4, 2013
Paris Hotel
Las Vegas, Nevada
www.pcna.net

2014 Scientific Meetings

2014 National Lipid Association Clinical Lipid Update—Spring
Hosted by the Pacific Lipid Association and the Southwest Lipid Association
March 14–16, 2014
Grand Wailea Hotel
Maui, Hawaii

2014 National Lipid Association Scientific Sessions
Hosted by the Southeast Lipid Association
May 1–4, 2014
Hyatt Regency Grand Cypress Hotel
Orlando, Florida

2014 National Lipid Association Clinical Lipid Update—Fall
Hosted by the Midwest Lipid Association and the Northeast Lipid Association
August 22–24, 2014
JW Marriott Hotel
Indianapolis, Indiana

Foundation Update

FOUNDATION
of the National Lipid Association

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Following the Foundation of the NLA's inaugural Familial Hypercholesterolemia Roundtable in New Orleans this past February, I am pleased to report meaningful progress on our important FH initiative. We convened with an outstanding delegation of representatives from the American College of Osteopathic Physicians, American Society for Preventive Cardiology, FH Foundation, International FH Foundation, National Lipid Association, National Society of Genetic Counselors, and the Preventive Cardiovascular Nurses Association, as well as several additional representatives from the Foundation of the NLA. The group discussed our shared commitment to the development and achievement of FH awareness. There are plans for meetings throughout the year to share information and ideas to further awareness of FH.

February also proved to be an important month for planning the Foundation's future. At the NLA's biannual strategic planning session, held February 9-10 in Miami, we reaffirmed the Foundation's desire to focus on FH awareness and educational efforts. We also discussed the need to establish broader financial support for the Foundation. Currently, the best ways to donate are to make individual contributions, to apply for Lifetime Membership through the NLA at **www.lipid.org/lifemember**, or to attend a Foundation event. Supporting the Foundation allows us to provide seed funding for educational and research grants. We are developing a fund to support fellowship programs in Clinical Lipidology, and $1,000 from each Lifetime Membership fee will be set aside for this purpose.

Looking ahead, please join us for an evening poolside to go "Dancing in the Desert" on Saturday, June 1, during the Annual Scientific Sessions in Las Vegas. The Red Rock Hotel's luxurious pools will provide the perfect setting to enjoy a warm summer evening complete with music, a photo booth and premium cocktails. Register at **www.lipid.org/sessions**—it will be a great time for a great cause!

As always, thanks for your support of our Foundation. ■

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FOR YOUR PATIENTS

Have you been told your ApoB or LDL Particle Number is high? Here are some dietary changes that may help lower these numbers.

A diet lower in carbohydrates and higher in protein and monounsaturated fat may decrease ApoB and reduce risk for coronary heart disease.

Diet focus	Tips for getting it done
Go vegetarian one night a week. Include a serving of legumes and whole and high protein grains.	Try beans with corn or whole wheat tortillas; minestrone, split pea or lentil soup with whole grain crackers; vegetarian chili with whole grain bread or top salad with beans and serve with a whole-wheat roll. Try vegetarian meal substitutes such as veggie burgers on a whole grain bun or tofu with brown rice. Serve bulgur or millet as a side dish instead of rice.
Change the way you think about meat.	Decrease intake of animal protein to 4 oz. daily. Consume lean meat, skinless white meat or poultry once daily or less.
Eat fish.	Include tuna, herring, salmon, sardines rich in omega-3 fatty acids and shellfish including mussels, oysters, and clams. Eat fish two times weekly, 4 oz. per serving.
Enjoy fat free or low fat dairy products.	Add a glass of fat-free milk to cereal at breakfast, low fat cottage cheese at lunch and low fat yogurt or low fat string cheese for snacks.
Enjoy one serving of fruit at every meal with an extra serving at breakfast.	Add dried fruits (no added sugar) such as dried raisins, apricots, plums or figs to cold or cooked cereals at breakfast, along with a banana or a serving of berries. You can also think of fruit as dessert.
Eat lots of vegetables. Enjoy 2-3 servings at lunch and dinner.	Choose large salads with a variety of raw vegetables at lunch and dinner. Include lots of raw vegetables and pickles with sandwiches. Include both cooked and raw vegetables with lots of color: brussels sprouts, broccoli, carrots, peppers (green, orange, yellow and red), spinach, tomatoes, etc.
Use good fats. Extra virgin olive oil, nuts, peanuts, sunflower seeds, olives, avocados and unsalted peanut butter.	Use olive oil in cooking, choose nuts and seeds for snacks and add olives and avocado to salads and sandwiches. Choose unsalted, natural peanut butter on sandwiches or toast.
Increase plant sterols and stanols.	Try orange juice, yogurts or margarines fortified with plant sterols or stanols. Choose low sugar options.
Increase soluble fiber.	Aim for 10-25 grams daily. One-half cup of cooked oatmeal has 2 grams, one-half cup of lima beans has 3.5 grams, or three tbsp. of psyllium fiber supplement has 6 grams.
Always eat breakfast.	Eat breakfast to fuel your day from the start.

Name:_____ Date:_____ Health Care Provider:_____

LDL Goals:_____ Weight Loss Goals:_____

Activity/Exercise Goals:_____

Medications Recommended:_____

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