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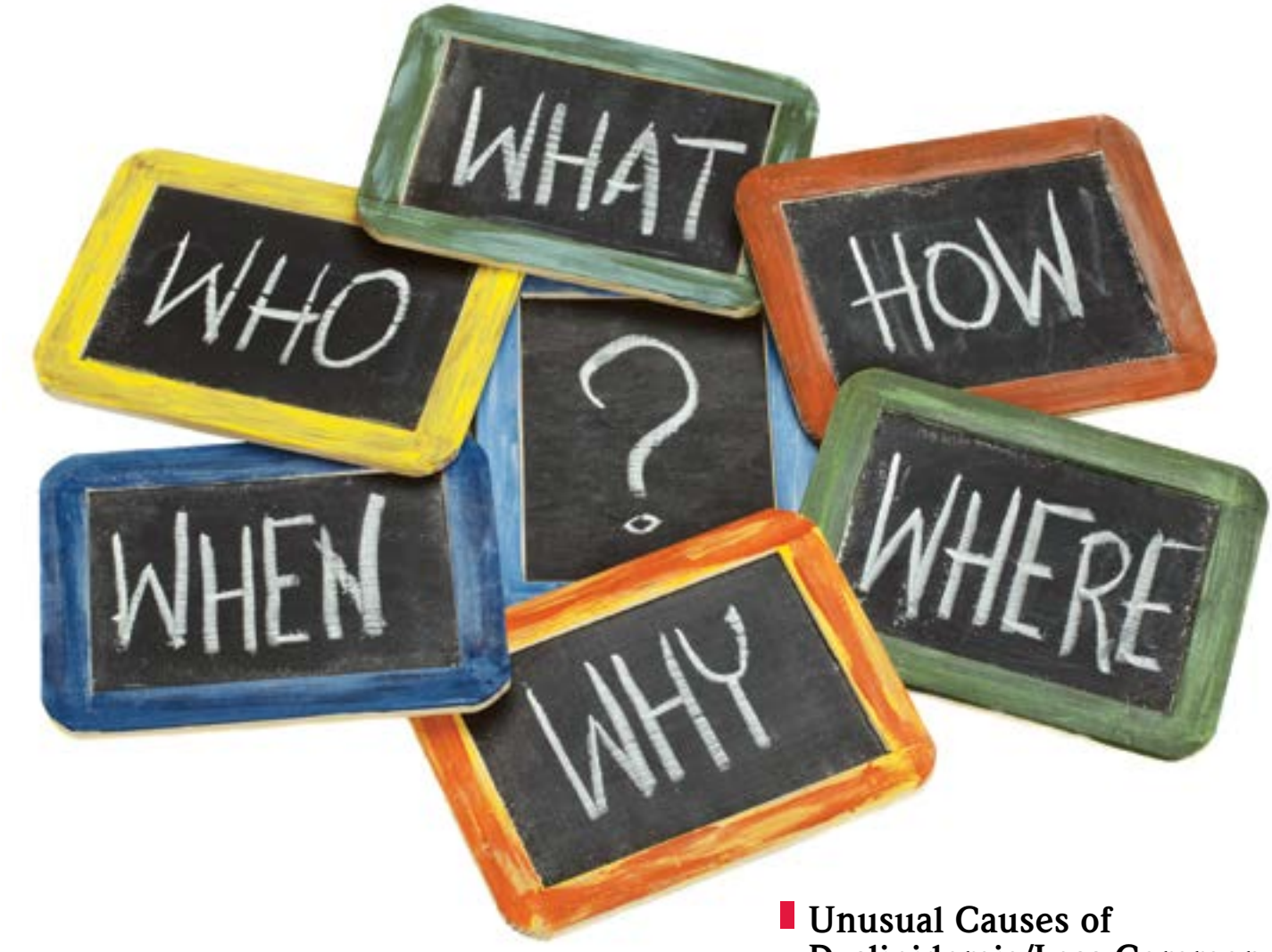

Unusual Causes of Dyslipidemia/Less Common Dyslipidemias

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Dyslipidemia & Antipsychotic Medications: Who is Monitoring the Lipids?

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Also in this issue:

Foundation of the National Lipid Association 2015 Annual Report

From the NLA President:
Non-Statin Therapy for Atherogenic Cholesterol Reduction

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As clinical lipidogists, the major objective of care for most of our patients is to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). All major guideline documents, including the NLA Recommendations for Patient-Centered Management of Dyslipidemia and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol Guideline, advocate lifestyle therapy as the first step in patient care, regardless of whether drug therapy is concomitantly employed. Unfortunately, most providers received little practical training in medical school on how to properly counsel patients to make meaningful lifestyle change. In addition, the time constraints placed on us leave little time to counsel our patients on the changes in diet and exercise that are necessary to achieve the best results. Even worse, most insurance plans do not provide coverage for dietary counseling for lipid disorders by the true experts in dietary change therapy, registered dietitian nutritionists. These forces combine to push providers toward the easier pathway of writing a prescription for lipid-altering drugs. Fortunately, generic, safe, strong statins that provide evidence-based ASCVD risk reduction are widely available and are generally well-tolerated by most patients.

The appropriate use of statin therapy was the focus of the 2013 ACC/AHA Blood Cholesterol Guideline. The identification of statin benefit groups in this document represented their attempt to use randomized controlled trial evidence to guide clinicians toward the use of appropriate-intensity statins in specific clinical scenarios. While the NLA Recommendations focused more on the importance of lowering atherogenic cholesterol, both agreed on the importance of recommending, after a patient-provider discussion, moderate or high-intensity statins for most patients with ASCVD, familial hypercholesterolemia, and diabetes mellitus.

The ACC/AHA Guideline, published prior to the results of IMPROVE-IT and the preliminary data on PCSK9 inhibitors, recommended limited use of non-statin therapy based on sparse randomized controlled trial evidence of additional ASCVD risk reduction and safety concerns. The NLA Recommendations provided the perspective that in those situations in which lifestyle and statin-induced reduction of non-HDL-C and LDL-C are insufficient to achieve lipoprotein goals, the addition of non-statin therapies should be considered for further reduction in atherogenic cholesterol, based on the premise that greater reduction in non-HDL-C and LDL-C is generally associated with more favorable outcomes.

Many patients on high-intensity statin therapy have persistently elevated LDL-C. A meta-analysis of eight RCT employing high-intensity statin therapy in 38,253 subjects showed that more than 40 percent of the statin treated subjects did not achieve an LDL-C <70 mg/dL. IMPROVE-IT showed that in pateints who had a recent acute coronary syndrome, combination therapy with ezetimibe and simvastatin

was associated with greater ASCVD risk reduction than simvastatin monotherapy. Pre-specified subgroup analysis showed that the beneficial effects were limited to those with diabetes mellitus or those age 75 years or older. Whether one limits use of this agent to only those groups, or applies the broader perspective that "lower is better" is a matter of clinical judgment, but it is increasingly clear that additional reduction in atherogenic cholesterol using non-statin therapy may provide additive ASCVD risk reduction in selected patients, after considering cost, potential side effects and patient preference.

We await with great anticipation the ASCVD outcomes data in the ongoing PCSK9 trials. In the meantime, we should continue to advocate lifestyle change therapy and appropriate-intensity statins, reserving consideration of non-statin drugs for those whose atherogenic levels remain elevated, despite these measures. ■

From the SELA President:
Horses, Zebras, and Unicorns — Oh My!

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The theme of this issue of Lipid*Spin* is "Unusual Causes of Dyslipidemia/Less Common Dyslipidemias." Topics range from sitosterolemia, to lysosomal acid lipase deficiency, to myositis due to red yeast rice. Although not necessarily rare for many lipidologists, other topics include potential worsening of lipoproteins with a low-carb diet, issues regarding dyslipidemia and antipsychotic medications, and use of niacin-statin combination in lipid management. Finally, this issue includes a well-earned spotlight on Dr. Pamela Morris.

Much of the National Lipid Association's (NLA) efforts in the past few years have focused on "patient-centered" recommendations and guidance regarding general evaluation and management of dyslipidemia. The NLA's viewpoint on basic principles of evaluation and treatment of dyslipidemia were, and are included in the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 and 2. They are also summarized in the National Lipid Association Annual Summary (which was updated in 2016 to include National Lipid Association Recommendations Part 2). While the prevalence of dyslipidemia in patients who are at risk for clinical atherosclerotic cardiovascular disease is certainly not rare, educational efforts addressing the more common challenges in evaluating and treating dyslipidemia are important, because many clinicians look toward their local lipidologist for guidance in regard to treating the countless dyslipidemic patients at risk for clinical atherosclerotic cardiovascular disease.

> "It is also equally important that the NLA not lose sight of the importance of educating its members on the more rare causes of dyslipidemia."

Having said this, it is also equally important that the NLA not lose sight of the importance of educating its members on the more rare causes of dyslipidemia. That is because clinicians also look toward their local lipidologist for help in the evaluation and management of the more rare causes of dyslipidemia, as well as the more nuanced issues that may arise with secondary causes of dyslipidemia, or use of combination lipid-altering drug therapies.

It is with this largely in mind that this issue of Lipid*Spin* is intended to focus on the more unusual or less common dyslipidemias, as well as challenges regarding nutritional interventions, lipid effects of certain concomitant drug use, and insights into what is now the less common use of certain lipid-altering drug combination therapies. ■

Letter From the Lipid*Spin* Editor:
There is Never a Dull Moment In the World of Clinical Lipidology

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This edition of the Lipid*Spin* is an outstanding representation of how there is never a dull moment in the world of clinical lipidology. This SELA edition of Lipid*Spin* has many outstanding lessons and insights nested within the various articles. As I read through this edition, two things stand out to me as highly noteworthy: collaboration and quality.

A collaborative multidisciplinary approach is commonplace among the National Lipid Association (NLA). Seeing two sections co-authored by professionals from different disciplines is very encouraging. Team-based care is promoted as a key component of high quality patient care. It seems to me that this edition supports that assertion. The Lipid Luminations column is written by a physician and a clinical pharmacy specialist and demonstrates to me a great example of collaborative approach to investigating patients presenting with an interesting case of severe myositis that utilizes evidence.

The Clinical Feature focuses on monitoring for metabolic side effects of antipsychotic medications and is authored by both a doctor of nursing practice (DNP) and a doctor of pharmacy (PharmD). I will use this information in my clinical practice. I have always practiced in a clinical setting where clinical pharmacists work side-by-side with medical providers, and am convinced that this is the optimal model to provide patient care for those with chronic diseases. This is especially important when using medications with elevated risk for long-term harm or when medication use is challenging, either from an ease-of-use perspective or need for patients to be highly engaged with managing their disease. This is the case with clinical lipidology.

Within this edition of Lipid*Spin,* many contemporary and timely issues are addressed in an evidence-based manner. I am confident that the information about a low-carb diet, lysosomal acid lipase (LAL) deficiency, and niacin-statin combination therapy will be useful in your clinical practice and help you manage patients optimally. I personally will consider the possibility of LAL deficiency in certain patients based on the Specialty Corner column. And without a doubt, the EBM Tools for Practice and the Tear Sheet will also be useful. The Chapter Update, Member Spotlight, Foundation Annual Report, and the news and notes section were also helpful in continuing to keep me informed and in the loop as it pertains to the NLA.

I hope you enjoy this edition of Lipid*Spin* as much as I have. ■

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Clinical Feature:
Dyslipidemia & Antipsychotic Medications: Who is Monitoring the Lipids?

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Introduction

Patients diagnosed with serious mental illness prescribed antipsychotic medications present unique challenges to healthcare providers. The use of second-generation, or atypical, antipsychotics is associated with significant adverse metabolic effects. These include weight gain, glucose intolerance, and dyslipidemia. Furthermore, cardiovascular disease (CVD) is the leading cause of death among patients on antipsychotic therapy.[1-5] Patients are 1.5 to 3 times more likely to suffer a cardiovascular event such as myocardial infarction or stroke when prescribed medications.[3] The monitoring and management of these adverse metabolic effects should be a focal point for healthcare professionals managing patients receiving these medications.

Access to psychiatric care often is limited, in part because of the shortage of psychiatrists and the high cost of specialist care for under-insured and uninsured patients.[6] As a result, the responsibility of medication management often falls to the primary care provider, who may not have adequate knowledge of the metabolic effects associated with antipsychotics.[7] Considering primary care providers manage 31 percent of patients with severe mental illness,[7] it is essential for these clinicians to assist in ensuring that patients who are taking antipsychotics receive the appropriate monitoring to identify any adverse effects early. Primary care providers routinely screen and treat patients with lipid disorders and research shows they can be more effective than psychiatrists at screening and treating

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patients receiving antipsychotic therapy when they are the prescribers.[1] Providers must be alert for patient populations at increased risk, such as the elderly and socioeconomically disadvantaged, because these groups have a higher death rate when taking antipsychotics.[1,2,6]

Effects of Antipsychotic Drugs on Lipoproteins

Both first- (typical) and second-generation (atypical) antipsychotic drugs induce lipid abnormalities, albeit more so with second-generation agents. The most commonly observed abnormality is an increase of 20 to 50 percent in triglycerides (TG), which is unsurprising given these drugs also are associated with weight gain and elevated glucose levels. A decrease in high-density lipoprotein cholesterol (HDL-C) and increase in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) also have been observed, but these lipoprotein changes tend to be minor in comparison to the increases in TG.[8]

There are several proposed mechanisms that may explain how antipsychotics increase TG levels, including enhanced TG metabolism by stimulating hepatic production or inhibiting lipoprotein lipase-mediated TG hydrolysis, or indirectly via weight gain and obesity.[9] The weight gain observed in patients receiving antipsychotics is primarily driven by appetite stimulation due to the effects these medications have on important serotonergic, dopaminergic, and histmaminergic neurotransmitters. Additionally, the sterol-regulatory element-binding proteins (SREBPs), which affect lipid biosynthesis, also plays a major role in increasing TG.[8] SREBP-1 regulates fatty acid and TG metabolism, while SREBP-2 regulates cholesterol metabolism. Antipsychotics increase SREBP activity, which may explain the observed increases in TG and cholesterol levels.

HIGH Risk			
•	Clozapine	•	Quetiapine
•	Olanzapine	•	Chlorpromazine*
MILD Risk			
•	Risperidone	•	Iloperidone*
•	Paliperidone		
LOW Risk			
•	Aripiprazole	•	Lurasidone*
•	Ziprasidone	•	Haliperidol
•	Asenapine*	•	Perphenazine

* limited data available
Adapted from: *Am J Manag Care* 2014;20:S166-S173.[12]

Table 1. Relative Risk of Dyslipidemia with Antipsychotics.

While dyslipidemia appears to be a "class effect," it is important to note there are key differences regarding the significance of dyslipidemia observed with antipsychotics (Table 1). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial[10] compared the effectiveness and safety of olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone. During the 18-month study, olanzapine was associated with more weight gain and greater increases in blood glucose and lipids compared to the other medications. Olanzapine and clozapine are considered to have the highest risk of metabolic adverse effects, but there is limited data on the metabolic impact of this class of medicine. Despite that, the Food and Drug Administration (FDA) required all atypical antipsychotics to carry a warning about the metabolic risks associated with this class of agents.[11] As such, monitoring is recommended.

Guidelines for Surveillance and Testing

In 2003, the American Diabetes

Parameters	Baseline	4 Weeks	8 Weeks	3 Months	6 months (Biannual)	Yearly
Medical/Family history	X			X		X
Smoking, diet & exercise	X	X	X	X	X	X
Blood Pressure	X	X	X	X	X	X
Weight (BMI)	X	X	X	X	X	X
Waist circumference	X			X	X	X
Fasting glucose & A1C	X			X		X
Fasting lipid profile*	X			X	If LDL>130	X

Baseline pregnancy test in females before initiating medication and if history indicates. Some European guidelines recommend lipid testing at 6 weeks but effectiveness of earlier evaluation has not been established.[14]
Adapted from: Br J Psychiatry. 2011;199(2):99-105.[2]

Table 2: Recommended baseline and long-term monitoring for patients prescribed antipsychotic medications.

Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists (AACE), and North American Association for the Study of Obesity developed consensus guidelines on monitoring and treating patients who are prescribed antipsychotics.[13] Research indicates that, despite these guidelines and the known adverse metabolic effects of antipsychotics, adherence to surveillance guidelines is suboptimal.[1,5,14] In a three-state study of 109,451 Medicaid patients, despite the published warnings of the FDA, less than 12 percent of the patients undergo lipid testing.[6] An updated consensus recommendation has not been formally published since 2003. However, there have been updates to the recommendations based on current research and surveillance. Table 2 contains the current monitoring recommendations.[1,5] While these are the minimal recommendations for adult patients, more frequent monitoring may be indicated in pediatric and high-risk populations.[4,5] ASCVD risk assessment tools could underestimate the risk of ASCVD in these patients.[1] Decisions regarding testing and treatment should include history, cardiovascular risk factors, and the antipsychotic medication prescribed.[1] Clinical trials assessing coordination of metabolic monitoring and treatment between psychiatry and primary care have not been identified.

Barriers to Testing

The psychiatric comorbidities of patients taking antipsychotics may make them less likely to take advantage of screening and preventive medical care in comparison with the general patient population, presenting a major barrier to identifying and treating lipid abnormalities.[14] Additionally, there is limited research into the barriers of lipid profile screening in patients with serious mental illnesses. Contributing factors to testing barriers may stem from the patient, the provider, and/or system factors (Table 3).[1,15] Prescribers of antipsychotics should evaluate barriers specific to their patients and practices.

Patient Factors	Lack of understanding of adverse effects of medication and need for testing
	Refusal of the test
	Missed appointments
	Inability to fast
	Inconvenient location of testing facility
	Cost of tests are prohibitive
	Younger patients or those without comorbidities may not have a primary care practitioner
Health Care Practitioner Factors	Health care practitioners are unaware of the risk of the metabolic impact and monitoring
	Mental health prescribers defer testing to the patient's primary care practitioner
	Time constraints
System Factors	Lack of coordination of care between mental health care and primary care
	Absence of process to alert provider to perform test
	Mental health records are afforded special protection under the Health Insurance Portability and Accountability Act and access is limited[1,16]

Adapted from *Clinical Lipidology*. 2012;7(5):509-523.[1,17]

Table 3. Barriers to testing.

Conclusions

In recent years, ASCVD-related mortality has declined, in part because of collaboration between organizations that have developed guidelines to improve surveillance and treatment of patients at risk of ASCVD. However, cardiovascular events in patients receiving antipsychotics remain high. Recognizing at-risk patients is essential for appropriate treatment and to improve the quality of life in this population. It seems feasible that ASCVD risk among patients receiving antipsychotics could be reduced with proper screening and management, especially in the primary care setting. The patient would benefit from education on the metabolic effects of antipsychotics and early adoption of lifestyle modifications to reduce their ASCVD. Systems and quality initiatives should be implemented to improve monitoring and treatment.[1] Future quality initiatives suggested by the authors include convening a task force to update the consensus recommendations, reviewing the most current research, and designing a method to improve clinicians' access and adherence to the findings of the panel. ■

Disclosure statement: Dr. Croy has no disclosures to report. Dr. Dixon has received honoraria from Novartis and Sanofi. Lindsey Kennedy has no disclosures to report.

References are listed on page 31.

Guest Editorial:
Worsening Lipoproteins on a Low-Carb Diet

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An exciting new approach to treating obesity and insulin resistance involves significant carbohydrate restriction with the goal of achieving a ketogenic state that results in weight loss and improved insulin sensitivity. Many lipidologists, however, have seen frequent cases of worsening lipid and lipoprotein parameters with such carbohydrate-restricted diets. What's going on here, what are the associated risks of this increased atherogenic lipoprotein burden for cardiovascular disease (CVD), what's the mechanism, and what should be done with these patients? Here's a typical case scenario:[1]

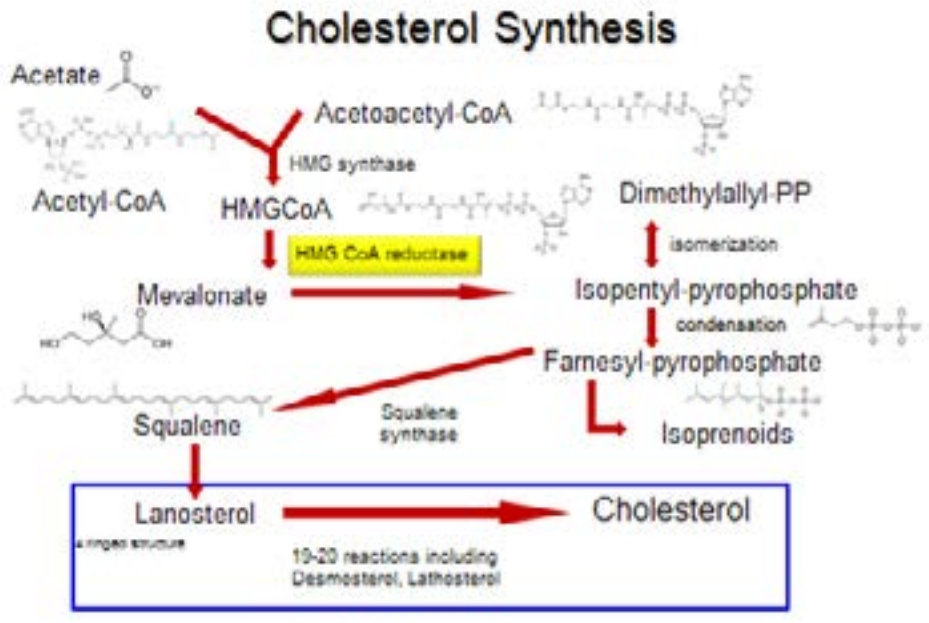
A healthy, 55-year-old menopausal female, who is 5'4", 154 pounds, and has no cardiovascular disease history struggles with weight loss, decides to follow a low-carb/Paleo diet. Her baseline lipid panel is: total cholesterol = 196, low-density lipoprotein cholesterol (LDL-C) = 105, high-density lipoprotein cholesterol (HDL-C) = 75, triglycerides (TG) = 78, and non-HDL-C = 121 (all in mg/dL). She loses 30 pounds in three months on this diet and her new lipid panel is: **TC = 323, LDL-C = 230**, HDL-C 83, TG 49, and **non-HDL-C= 240** (all in mg/dL). **Total low-density lipoprotein particle number (LDL-P) (by NMR) = 2643 nmol/L** (99th percentile population cut point). Is this presumed increase in atherogenic lipoproteins (no baseline lipoprotein values other than that inferred by unremarkable non-HDL-C) dangerous?

Patients commonly go on a low-carb ketogenic diet (LCKD) (defined by many at less than 50 grams of carbohydrate or <10 percent of calories/day) to lose weight, with the secondary goal of improving insulin sensitivity and decreasing cardiometabolic risk. The Paleo diet[2] is another variation of a LCKD, often but not necessarily with a major increase in saturated fat intake. It should be noted that many popular variations of LCKD exist, including Atkins, South Beach, Paleo, Dukkan, and others, and that these diets may vary substantially in fat and other macronutrient composition. There is a substantial body of evidence that a LCKD is at least as effective at weight loss as low-fat diets, and changes in the triglyceride/HDL axis and markers of insulin resistance are usually more beneficial with low-carbohydrate diets. It is tempting to conclude that these favorable changes would be associated with a reduction in cardiovascular disease but, as of yet, we have no randomized clinical trial data with CVD outcomes to support this.[3]

The most consistent and predictable lipid change on LCKD is a decrease in triglycerides. Changes in other lipid parameters have been variable, but an increase in LDL-C often has been noted (anecdotally, about 30 percent of the time) in clinical practice and is thought to be related to the increased saturated fat composition of the LCKD. A 2009 meta-analysis comparing low-carbohydrate diets (defined as < 45 percent of calories from carbohydrates) vs. low-fat diets (<30 percent of calories from fat) for six months or more, showed that "compared

with participants on low-fat diets, persons on low-carbohydrate diets experienced a slightly but statistically significantly lower reduction in total cholesterol and low-density lipoprotein cholesterol, but a greater increase in high-density lipoprotein cholesterol and a greater decrease in triglycerides.[4]" Data on lipoprotein changes with LCKD are more sparse and variable. A six-month study in children placed on a ketogenic diet for epilepsy showed a significant and persistent increase in Apolipoprotein B (ApoB).[5] Other studies have shown reductions in ApoB; for example, this study of lipid and lipoprotein changes in overweight men with atherogenic dyslipidemia.[6] Volek, et al., discuss improvements in the ApoB/ ApoA-1 ratio in adult subjects on a LCKD vs. a low-fat diet.[7] However, it is difficult to draw conclusions from all of these studies because of the heterogeneity of the subjects and composition of the diets studied.

What is the etiology of the increase in LDL-C/ApoB/LDL-P in our patient? The expected drop in triglycerides in such a diet would obviously change the composition of LDL lipoproteins, causing an increase in their size and cholesterol composition and a shift from small dense "pattern B" to large and buoyant "pattern A." The magnitude of this change is dependent on the starting triglyceride level and genetic factors. Most LCKD followers also increase their dietary saturated fat (SF) intake, which is a recognized cause for an increase in LDL-C levels. The explanation for the ApoB/LDL-P increase from carbohydrate restriction is more complex.[8] When dietary carbohydrate restriction occurs, the body switches to fatty acid (FA) catabolism for energy. Intracellularly, these FA are activated to form acyl-CoA, and then acetyl-CoA, which eventually is utilized for fuel production via the Krebs cycle. Acetyl-CoA may be converted into



Adapted from Dayspring T in Chap 14 Davidson, Toth, Maki Therapeutic Lipidology 2008

ketone bodies, which can be measured in the urine as a simple index of the degree of ketosis the dieter has achieved on a LCKD. (For a further discussion of the safety and clinical utility of ketogenic diets, see Peter Attia's excellent discussion,[9] "Ketosis – advantaged or misunderstood state? [Part I])." Two acetyl-CoA may combine to form acetoacetyl-CoA, which can be utilized to form mevalonic acid and, ultimately, increase cholesterol synthesis through the 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) pathway. Also, when ketone bodies are in excess, there is an increased production of HMG-CoA, again driving the cholesterol synthetic pathway. Anecdotally, it has been observed that many on LCKD with increased LDL-C/ ApoB/ LDL-P have increased desmosterol levels, a marker for increased cholesterol synthesis. Diabetic ketoacidosis and anorexia nervosa patients have elevated LDL-C/ApoB/LDL-P, in part via similar mechanisms. Excessive hepatic cholesterol synthesis will drive the formation of more ApoB particles, and the increased synthesis in the liver will decrease the expression of the LDL-receptor (modulated through the nuclear transcription factor "sterol toxicity sensor" Liver X Receptor [LXR]), prolonging LDL clearance, and adding to the increased LDL-P concentration in circulation.

One might wonder if the accompanying increase in exogenous cholesterol intake occurring in many LCKD diets — increased eggs, shellfish, meats, etc. — might drive increases in LDL-C, but it now is well established that absorption of endogenous cholesterol (of hepatobiliary origin) plays a much greater role in determining LDL-C levels than cholesterol from exogenous sources.

So what is our patient's risk from her increased LDL-C/ApoB/LDL-P and what should we do about it? Certainly we can speculate that, in a typical overweight and insulin-resistant patient, improvements in her insulin selectivity and "vascular biology" from the LCKD and its associated weight loss would help reduce her cardiometabolic risk. We don't know this patient's metabolic status, but the low-TGHDL-C ratio argues against much insulin resistance. No one knows what

the CVD risk of increased LDL-C/ApoB/LDL-P is in LCKD states, and the evidence for the long-term safety of this dietary approach is lacking. Many patients with increased ApoB/LDL-P (for example, familial hypercholesterolemia patients) never get cardiovascular disease, and the explanations for this are all speculative. Sarah Hallberg, DO, of Indiana University

> "It is tempting to conclude that these favorable changes would be associated with a reduction in cardiovascular disease but, as of yet, we have no randomized clinical trial data with CVD outcomes to support this."

is the principal investigator for a large study comparing patients with type 2 diabetes or prediabetes who are being treated with a ketogenic diet vs. patients being treated using the standard American Diabetes Association (ADA) dietary guidelines, looking at NMR LDL-P, metabolic markers, and carotid intima-media thickness (cIMT) over two years. She said, "Atherogenic dyslipidemia so dramatically improves and diabetes resolution occurs so frequently that we have to be asking, even in the patients who have a rise in LDL-C, are we not still improving their health? For those patients with a rise, is there a perfect blend with statin therapy?" However, it is difficult to ignore the massive epidemiologic and clinical trial data that increased ApoB/LDL-P is associated with increased CVD risk and that lowering these parameters with statin therapy reduces risk in proportion to the lowering of atherogenic lipoproteins. It also has been consistently shown that, when discordance exists between LDL-C and ApoB/LDL-P, the risk of disease/events is always more closely associated with the lipoprotein parameters, both in drug-naïve and drug-treated patients. The following algorithm would seem to be a prudent approach to these patients:

Step 1: When faced with an increase in LDL-C in a LCKD patient, assess lipoprotein status with ApoB or NMR-derived LDL-P (to my knowledge, no other form of LDL-P has been validated in clinical disease/outcomes trials as superior to LDL-C in predicting CVD risk). Those without increased ApoB/LDL-P can be reassured that their LDL-C increases are benign.

Step 2 (optional for primary prevention patients ONLY): Imaging studies could be helpful to assess CVD status. Coronary artery calcium and cIMT studies are regularly available, and some are using CT angiogram studies. The presence (or absence) of subclinical atherosclerosis could be used to modify one's approach as to the intensity of treatment of those with elevated increased LDL-C/ApoB/LDL-P. It should be remembered, though, that no imaging study has ever been clinically validated as a way to judge the efficacy of any therapy and no guidelines have recommended follow-up or serial imaging studies as a way to evaluate the efficacy of any therapy.

Step 3: For those with increased ApoB/LDL-P, the following measures can be taken:

- **Decrease saturated fat** intake, especially saturated fat known to increase LDL-C the most, (e.g. dairy products and coconut oils). Increase poly- and mono-unsaturated fats without increasing total carbohydrates.
- **Increase protein** intake as a proportion of daily calories.
- **Liberalize carbohydrate intake**.
- **Re-assess ApoB/LDL-P status**. (Some have suggested that the atherogenic particle increases are the result of the anorexic effect of these diets and may normalize after six months.)

Step 4: Treat those with persistently increased non-HDL-C/ApoB /LDL-P levels per the National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia, usually with statin therapy, to achieve recommended target levels. ■

Disclosure statement: Dr. Pokrywka has received consultant and speaker honoraria from AstraZeneca, Amarin, Regeneron, and Amgen. He has received speaker honoraria from Kowa Pharmaceuticals America and Health Diagnostic Laboratory Inc.

References are listed on page 31.

EBM Tools for Practice:
An Evidence-Based Approach to Sitosterolemia

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Diplomate, Accreditation Council of Clinical Lipidology

Sitosterolemia is a rare, autosomal, recessively inherited sterol storage disease caused by homozygous or compound heterozygous gene mutations of adenosine triphosphate-binding cassette (ABC) genes G5 or G8, in which markedly increased tissue and plasma plant sterol concentrations. The condition can lead to premature atherosclerosis and has also been described as phytosterolemia and Beta-Sitosterolemia.[1-4]

It was first described in 1974 by Bhatacharyya.[5] ABCG5/G8 are membrane based sterol transporters expressed in the enterocytes of the small intestines and hepatocytes and function to rapidly excrete cholesterol, plant sterols, and their saturated derivatives (stanols) from the body and defects in the function of these transporters can lead to pathologic accumulation of phytosterols/stanols.[2] An average of 500mg of cholesterol and 300mg of plant sterols — predominantly campesterol and sitosterol — are consumed in the typical Western diet each day; however, only 50 percent of the cholesterol, <20 percent of campesterol, and less than 7 percent of sitosterol are absorbed.[1] The normal body is able to differentiate between cholesterol and non-cholesterol sterols. The mechanism that allows the body to make this discrimination is not fully understood,[6] but the use of ezetimibe has elucidated some of the processes.

Sitosterolemia is characterized by elevated plasma levels of sitosterol and campesterol with normal or moderately elevated plasma cholesterol levels.[7] The clinical consequences of elevated sterol levels may include premature atherosclerosis, tendon xanthomas, xanthelasma, hemolytic anemia, thrombocytopenia, abnormal liver function tests and, occasionally, arthritis and arthralgia.[1,4,8-10] It can be encountered at any age.[10] The clinical presentation of sitosterolemia may vary widely, depending on the level of plant sterol retention in tissues. Familial hypercholesterolemia and cerebrotendinous xanthomatosis share clinical features with sitosterolemia, primarily xanthomas, and premature cardiovascular disease, but are usually differentiated by normal or moderately elevated cholesterol levels and the absence of cataracts and neurological symptoms.[10]

Although there have only been 100 reported cases diagnosed worldwide,[4] the prevalence of sitosterolemia is expected to be much higher secondary to the variable clinical presentation.

Plant sterols may be transferred by ABCA1 and become part of apolipoprotein A-1, containing high-density lipoprotein (HDL) particles. Once in HDL, plant sterols are esterified by lecithin: cholesterol acyltransferase and can be taken up from HDL in a manner similar to cholesterol ester.[4] The normal function of ABCG5/G8 is to promote excretion and/or limit absorption of non-cholesterol sterols.[6] ABCG5/G8 dysfunction leads to a 50- to 200-fold increase in plasma plant sterol concentrations[10] and varying degrees of hypercholesterolemia.[11] Patients with sitosterolemia have plasma plant sterol

levels ranging from 10 to 65 mg/dL.[9] Standard laboratory enzymes are unable to differentiate between cholesterol and plant sterols and the diagnosis requires the use of gas chromatography or high-performance liquid chromatography to detect plasma plant sterols.[7]

> "While statins are considered the cornerstone of pharmacologic therapy for many lipid disorders, its use in sitosterolemic patients is minimal."

The Niemann-Pick C1-like 1 (NPC1L1) transporter has a significant role in the absorption of plant sterols. NPC1L1 preferentially transports cholesterol over plant sterols.[9] Ezetimibe inhibits NPC1L1,[9] which limits the intestinal absorption of plant sterols;[4,9,12] and has emerged as the primary therapy for sitosterolemia. Although ezetimibe has not demonstrated the ability to improve all of sitosterolemia's negative clinical effects, xanthomas, anemia, thrombocytopenia, and hematological abnormalities all improved on therapy.[9] Ezetimibe has been shown to be ineffective in treating sitosterolemia in children under age 2.[13]

While statins are considered the cornerstone of pharmacologic therapy for many lipid disorders, its use in sitosterolemic patients is minimal, because *de novo* cholesterol synthesis is already depressed.[4,9] Although occasionally ineffective, bile acid sequestrants disrupt the enterohepatic circulation of bile acid, preventing reabsorption in the ileum, and have been shown to decrease plasma plant sterol levels by 50 percent in sitosterolemic patients.[4,9] Their long-term use may be limited by side effects and a late plateau effect.[14] As with bile acid sequestrants, ileal bypass surgery decreases bile acid reabsorption and secondarily decreases plant sterol levels.[7] Sitostanol has been used as a therapeutic alternative to reduce plasma sitosterol and campesterol levels; however, some sitosterolemic patients demonstrated a paradoxical response to therapy.[15]

Although the Mediterranean diet is recognized as protective against coronary heart disease, it is potentially harmful for patients with sitosterolemia. Instead, a low-plant-sterol diet is recommended for these patients and all plant-based foods with a large amount of fat — such as olive oil, nuts, avocados, margarine, and chocolate — should be avoided.[10] All plant-based foods contain some amount of plant sterols, leading to decreased adherence because of the poor palatability of a low-plant-sterol diet.[16] Intake of shellfish also should be limited secondary to the high amounts of the algae-derived plant sterol brassicasterol.[9] Restricted sterol intake is necessary to help ameliorate symptoms and prevent progression of disease, but it will not sufficiently normalize plasma sterol levels.[10]

Establishing a clinical diagnosis of sitosterolemia is difficult because of the rarity of the disease. However, when unexplained premature atherosclerosis and/or hemolytic anemia and abnormal liver function tests are present, providers should consider sitosterolemia in the differential. ■

Disclosure statement: Dr. Elkins has no disclosures to report.

References are listed on page 31.

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Lipid Luminations:
A Case of Covert Use of Red Yeast Rice Resulting in Severe Myositis

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This is the case of a 68-year-old white female who was being seen in her home in August 2014 as part of a health evaluation for her insurance company. She had a history of hyperlipidemia, hypertension, and diabetes mellitus. She had been placed on atorvastatin five years prior to this visit and developed significant myalgia with an elevation in her creatine phosphokinase (CPK) level to 250 mg/dL per patient. In addition to having myalgia at that time, she also complained of severe muscle weakness. After discontinuing atorvastatin, there was no improvement in either her myalgia or muscle weakness over the course of the next three months.

She underwent a complete evaluation at a local hospital and, eventually, a muscle biopsy at a university hospital showed nonspecific findings of type II muscle fiber atrophy. There was no evidence of myonecrosis, polymyositis, or inflammatory myopathy. The patient was told by a consulting physician that she had statin-induced myopathy, "which can sometimes be permanent." She was placed on a variety of medications for her muscle pain and weakness, including pregabalin, cyclobenzaprine, and oxycodone.

At the time of her evaluation in August 2014, she was ambulating with a four-prong walker. Her muscular symptoms were progressive and debilitating, thus requiring hired medical assistance. She had mild, diffuse muscular tenderness in both her proximal and distal extremity muscle groups and weakness in the flexors and extensors of her extremities. There was no evidence of muscle wasting and she appeared to be neurologically intact. Her CPKs continued to run from 300 mg/dL to 500 mg/dL, even after the discontinuation of atorvastatin.

Her medications at the time, in addition to those mentioned above, included metformin, amlodipine, and cholestyramine. Prior to conclusion of the evaluation she mentioned she was taking a variety of nutraceuticals, one of which was red yeast rice (RYR).

Discussion:
Statin-associated muscle adverse events — myalgia, myopathy, myositis, and myonecrosis, with or without myoglobinuria or acute renal failure — have been reported in the literature, occurring at a rate of 1 to 5 percent in clinical trials and 11 to 29 percent of observational cohorts.[1] These symptoms generally resolve upon discontinuation of the offending agent.[2] Autoimmune myopathies, including

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Our Mission

The Foundation supports patient and clinician educational, research, and community outreach activities that enhance and support the initiatives of the National Lipid Association in its efforts to reduce cardiovascular events and deaths related to abnormalities of cholesterol metabolism.

President's Message

The Foundation of the National Lipid Association achieves its mission through raising funds to support the initiatives of the NLA. The Foundation continually seeks funding to support programs that raise awareness about dyslipidemia for healthcare providers and patients through research, education, and community outreach grants.

Foundation donors in 2015 can say that they have helped us work toward this goal as shown by the impact that several of our initiatives had last year on a national level. I am pleased to give you an update on several successful initiatives by the Foundation of the National Lipid Association in the past calendar year.

- In keeping with the Foundation's mission to educate the lay public, the Foundation collaborated with Sanofi US and Regeneron Pharmaceuticals Inc. in their launching of an unbranded cholesterol awareness campaign, "Cholesterol Counts" during 2015. The campaign consisted of polling patients on their knowledge of cholesterol, lipid disorders, and their own risk associated with LDL-C. Dr. Ralph Vicari, Foundation president-elect, served as the program spokesperson in this effort. This collaboration focused on helping to address the unmet needs of cardiovascular health and the role cholesterol plays. It is our hope to provide resources to help patients better understand and take control of their heart health. The Foundation assisted with marketing efforts via media interviews, publications, the Foundation's social media accounts, and LearnYourLipids.com. It is a goal of Dr. Vicari and the Foundation to do a final report and publish a paper in 2016 focusing on the results and outcomes of this project.

- In honor of Donald Hunninghake, MD, a pioneer in lipid research, the Foundation continues to offer the Hunninghake Familial Hypercholesterolemia Abstract Award for the best submitted abstract at the NLA Scientific Sessions, specifically in the area of familial hypercholesterolemia (FH) research. The 2015 recipient of the Hunninghake FH Abstract Award was Amy L. H. Peterson, MD, for her abstract, "Universal vs. Selective Pediatric Lipid Screening in the Diagnosis of Familial Hypercholesterolemia." Dr. Peterson presented her abstract at the 2015 NLA Scientific Sessions in Chicago. With funding secured for a five-year awards program, the Foundation is moving into its second year of offering this award and will be selecting the 2016 winner in time to be honored and to present the research at the upcoming 2016 NLA Scientific Sessions in New Orleans.

- Starting in 2015, the Foundation, along with the NLA, began offering the Akira Endo Award for Achievements in the Development of Treatments to Prevent Atherosclerosis. This award was presented by W. Virgil Brown, MD, and presented at at the 2015 International Symposium on Atherosclerosis (ISA) in Amsterdam in May 2015. This award is to honor the scientific achievements of Dr. Akira Endo of Tokyo, Japan, the discoverer of statins. The recipient of the 2015 Endo Award was Harry R. "Chip" Davis, Jr., PhD, for his tremendous involvement in advancing the therapy of lipid disorders. This award will continue to be presented at future ISA meetings, which occur every three years, to a scientist who has made major contributions in the development of treatments to prevent atherosclerosis — the leading cause of death of developed countries throughout the world.

2015 Scientific Sessions Foundation Event

2015 Scientific Sessions Foundation Event

2015 Fall CLU Foundation Event

- Starting in 2015 in conjunction with the NLA Scientific Sessions, the Foundation began sponsoring a memorial wall posthumously honoring past leaders and pioneers in the field of lipidology. These banner "walls" were placed in the Poster Hall and were meant to recognize the tremendous contributions that have been made in areas relating to the causes, prevention, and treatment of cardiovascular disease and lipids. The Foundation will continue to present the Memorial Wall each year at the NLA Scientific Sessions.

Honorees for 2015 included:

E.H. "Pete" Ahrens, Jr., MD
Edwin Bierman, MD
John Brunzell, MD
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Robert Levy, MD
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Daniel Steinberg, MD, PhD
Roger Williams, MD
Donald Zilversmit, PhD

- The Foundation hosted three successful events to coincide with the NLA's Annual and Clinical Lipid Update meetings: A social gathering and beer tasting at a local brewery in Denver; a night of dinner, dancing, and good times at the House of Blues in Chicago; and a cooking class and tasting in Pittsburgh. These Foundation events continue to be successful at each of the NLA's meetings and are a great opportunity for people to have fun and enjoy time with peers while supporting a great cause.

As always, thank you for your support of the Foundation, and I look forward to building on this success in the coming year!

Anne C. Goldberg, MD, FNLA
President
Foundation of the National Lipid Association

Outreach

100 Questions & Answers about Managing Your Cholesterol

The Foundation continues to offer this valuable patient resource, produced in partnership with the NLA. The book features frequently asked questions with answers that are provided in lay language. To order a copy for your office, visit amazon.com. The book is also available on Kindle and Nook e-readers.

LearnYourLipids.com

As a patient resource, the Foundation maintains **learnyourlipids.com**. Throughout the year, the site continues to be updated with new materials focusing on cholesterol management and lipid disorders.

Looking Ahead into 2016

The Foundation already has big plans for 2016 and we look forward to sharing them with you. A few of those plans include the following projects and initiatives:

Rare Lipid Disease Campaign

In conjunction with Cholesterol Awareness Month in September 2016, the Foundation will launch an awareness campaign with an objective to establish a national patient outreach program that will enable the Foundation to address the medical community and to educate healthcare professionals and patients about the latest knowledge and information regarding rare lipid disorders. These disorders have a major impact on individuals and their families. We believe that we can improve the physician-patient relationship by helping patients become better informed about rare lipid disorders and by creating information and education that also increases physician awareness of disorders such as familial chlyomicronemia syndrome (FCS), lysosomal acid lipase deficiency (LAL-D), lipodystrophy, and both heterozygous and homozygous familial hypercholesterolemia (HeFH and HoFH, respectively).

This national education program intends to inform patients and healthcare professionals about the opportunities available to improve the identification and management of these rare lipid disorders in order to better the overall quality of care delivered to patients who might be identified as having a rare lipid disorder. Ultimately, the best level of healthcare is achieved when consumers are better educated and have a deeper grasp of the essential issues regarding their health and plans of treatment.

Please stay tuned to **learnyourlipids.com** and **lipid.org** throughout the coming months to see what we have in store for this campaign!

W. Virgil Brown Distinguished Achievement Award

Beginning in 2016, the Foundation, along with the NLA, will begin offering the W. Virgil Brown Distinguished Achievement Award, established by the Dyslipidemia Foundation of Boston, and the Foundation of the National Lipid Association. The award will be given annually at the 2016 NLA Scientific Sessions to honor an individual, who like Dr. W. Virgil Brown, has made significant contributions to our understanding of lipoprotein metabolism, the diagnosis and treatment of lipid disorders for cardiovascular disease prevention, and the education of healthcare providers in this important field. The recipient of this award will be selected by a committee of the Foundation of the NLA.

W. Virgil Brown, MD, FNLA

Fundraising

The Foundation recognizes two contribution levels: Sustaining and Contributing. Sustaining donors make a gift of $1,000 or more throughout the course of the year. All other private donations are considered Contributing donors. Every donation is greatly appreciated and helps make the Foundation projects and outreach possible.

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Scan for Lipids

2015 was the fifth year the Foundation benefited from the NLA's "Scan for Lipids" program at its scientific meetings. Participating exhibitors agreed to donate $1 for every attendee name badge scanned.

Thank you to our "Scan for Lipids" Donors in 2015:

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polymyositis,[3-10] dermatomyositis,[11-20] and immune-mediated necrotizing myopathy[21,22] also have been reported with statin therapy. These myopathies would not be expected to resolve on their own following discontinuation of statin therapy.[2] Even fewer cases of myopathy have been reported with RYR.[23-26] The discontinuation rate of RYR (5 percent) because of myalgia has been comparable to that of pravastatin 20 mg twice daily (9 percent) ($p = 0.99$).[27]

Nutritional supplements and complementary or alternative products can be collectively referred to as "nutraceuticals." While the overall prevalence of nutraceutical use in the U.S. is not known, some small data collection studies have estimated that from 49 to 73 percent of the U.S. population take nutraceuticals.[28,29] Estimating the rate of nutraceutical-related adverse events is an even more daunting task. A recent study in the *New England Journal of Medicine* estimated that 18,134 visits to U.S. emergency departments annually have been attributed to nutraceutical-related adverse events.[30]

RYR is produced from fermentation of *Monoscus purpureus* on rice, yielding a red coloration. It has been used for centuries as a food colorant and taste enhancer in Asian countries and for various health benefits in Chinese medicine.[31] RYR has been marketed for several decades as a "natural" alternative to statin therapy in the U.S. Preparations of RYR can contain up to 10 monacolins, specifically *monacolin K* (MK), which is structurally identical to lovastatin, a commercial HMG-CoA reductase inhibitor.[32] It has been proposed that all 10 monacolins could have 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitory effects.[33-35]

The Dietary Supplement Health and Education Act of 1994 provides that any product marketed as a dietary supplement cannot contain an article that is approved as a new drug unless the product was marketed before the drug's approval.[36] In 1998, the Food and Drug Administration (FDA) determined that cholestin, which contained RYR, was not a dietary supplement but an unapproved drug and recommended it be removed from the U.S. market. Cholestin and other RYR products temporarily disappeared from the U.S. market. However, laboratory testing in 2007 confirmed that higher-than-trace amounts of MK were present in RYR products available in America.[37] The Food and Drug Administration (FDA) issued a warning letter to manufacturers, telling them to stop promoting and selling the illegal products. However, studies in 2010 and 2011 revealed that many commercial products still contained substantial amounts of MK, despite the regulatory status of RYR.[38,39] It is not clear how tightly RYR products are actively surveilled by the FDA.[40]

The content of MK has been shown to differ substantially across products.[32,39,41] In 2014, Avula and colleagues used mass spectrometry to analyze 14 RYR supplements available in America.[32] Their analysis showed a 20- to 40-fold variation in concentration that would yield a 10-fold variation in MK dose delivered daily, based on the label's recommended number of servings (from 0.12 mg/day to 10.46 mg/day). Gordon and colleagues analyzed 12 RYR products labeled as 600 mg capsules.[39] They found a 100-fold variation in MK per capsule, with concentrations of MK up to 1.7 percent and total monacolins up to 1.9 percent. Since reported dose ranges of RYR can be as high as 4,800 mg per day,[27] a patient could receive 82 mg/day of MK (equivalent to lovastatin) and 90 mg/day of total monacolins based on these findings. Drug interactions can potentiate adverse drug reactions of RYR monacolins, placing consumers at risk for the development of myopathies and other adverse drug reactions.

Poor RYR manufacturing methods also can result in a nephrotoxin byproduct called *citrinin* being present in RYR. Heber, et al., found citrinin in seven of nine of the products they analyzed in 2001.[41] One third of the 12 products tested by Gordon, et al., in 2010 contained citrinin.[39]

Back to the Case:

The patient was informed that RYR can occasionally cause muscle symptoms and sometimes frank myopathy. RYR was discontinued and within one month, the patient was ambulating without a walker. She also no longer required cyclobenzaprine and opioid therapy. Her CPK level normalized. As of March 2015 she continued to do well, with no signs nor symptoms of myopathy. It was apparent on historical review that she never mentioned to any prior physicians that she was taking RYR.

Conclusion:

We have reported a muscle-related adverse event including myalgia and myositis in a patient covertly taking RYR. There are a host of dietary supplements presently sold on the U.S. market, including RYR, which could place patients at risk for significant adverse reactions and multiple drug interactions. Regulatory requirements for these drugs should be intensified.

RYR is a potential cause of muscle-related adverse events. Questioning a patient who has muscle symptoms about the use of RYR and other potentially harmful nutraceuticals should be part of a thorough medical evaluation. ■

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References are listed on page 31.

Specialty Corner:
Lysosomal Acid Lipase Deficiency (LAL-D)

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When treating our lipid patients it is important to always consider unusual causes of dyslipidemia in our differential diagnosis. Although rare, lysosomal acid lipase deficiency (LAL-D) is often misdiagnosed as an autosomal dominant lipid disorder and/or fatty liver disease.[1] LAL-D is caused by genetic mutations that result in a marked decrease or loss in LAL enzyme activity in the lysosomes across multiple body tissues resulting in multi-organ damage and premature death.[2,3] With enzyme replacement therapy now available for LAL-D, the outcomes related to this devastating disease are more hopeful.

Lysosomes are membrane-enclosed organelles that contain an arrangement of enzymes capable of breaking down proteins, nucleic acids, carbohydrates, and lipids. Lysosomal Storage Disorders (LSDs) are inherited conditions in which one or more of the enzymes in lysosomes are deficient or not functioning effectively. When this occurs, materials that would normally be hydrolyzed by the lysosome accumulate causing disturbances in normal cell function.[2] The Lysosomal acid lipase (LAL) enzyme plays an important role in metabolizing cholesteryl esters (CE) and triglycerides (TG) in the liver, spleen, blood vessel walls, and other organs.[2,3] When this enzyme is absent or deficient, the accumulation of CE and TG in the hepatocytes can lead to steatosis, which can progress to cirrhosis.[4,5] Lipoprotein cholesterol is primarily in the form of CE and any malfunction or deficiency in this pathway can affect lipid metabolism and the formation of atherosclerosis (Figure 1).[6]

LAL-D is a rare autosomal recessive lysosomal storage disease caused by mutations in the lipase A, lysosomal acid, cholesterol esterase (LIPA) gene.[1-5] These gene mutations can manifest in infancy, known as Wolman Disease, and is fatal soon after birth without enzyme replacement. A more common non-fatal expression occurs in children and adults and is known as Cholesteryl Ester Storage Disease (CESD).[2,3,5] The age-related difference in the progression of the disease is thought to be associated with the nature of the mutations and the degree of residual enzyme activity.[2] Dyslipidemia is a common finding in patients with LAL-D and is often linked to the early development of atherosclerosis, cardiovascular disease, and premature mortality.[1-5] This condition often goes unrecognized or is misdiagnosed as heterozygous familial hypercholesterolemia (HeFH) due to the similarities in the lipid profile. In addition, the physical characteristics of the disorder are non-specific and can overlap with other diseases.[1,2,3]

A timely, accurate diagnosis is essential for treatment of LAL-D to lessen the cardiovascular and hepatocellular sequelae of the disease. The clinical evaluation of these patients demonstrates a type IIa or type IIb hyperlipidemia with high total cholesterol, elevated LDL-C, elevated ApoB, and decreased HDL-C levels.[2] In addition, elevated levels of serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) are observed

LAL-D: Mechanism of Disease[6]

Figure 1.

with varying levels of liver damage.[2,3] Hepatomegaly and splenomegaly are seen in nearly all children and adults with LAL-D. A characteristic feature is the presence of markedly hypertrophic Kupffer cells and portal macrophages on liver biopsy.[2]

The clinical findings in LAL-D would lead to differential diagnosis including; HeFH, familial defective ApoB, familial combined hypercholesterol (FCH), metabolic syndrome, as well as non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and Wilson's disease.[1-5] The astute clinician will get a thorough family history to help differentiate between autosomal dominant disorders (e.g. HeFH, FCH, and polygenic hypercholesterolemia) from autosomal recessive disorders (e.g. LAL-D and sitosterolaemia).[2] A complete viral/immunological profile is important to rule out other etiologies such as hepatitis and autoimmune liver disease. A clinical pearl when reviewing the lipid panel of a patient with LAL-D; the total cholesterol and LDL-C are often not as high as seen with HeFH. Also, the HDL-C is usually lower in LAL-D then in HeFH. Another differential clue is that LAL-D patients with dyslipidemia, fatty liver disease, and elevated LFTs are usually not obese as is commonly seen in our metabolic syndrome patients (Table 1).[1-5]

Screening for LAL-D involves both clinical knowledge and, if indicated, measurement of LAL activity and genetic testing. Z Reiner has recommended a clinical algorithm for deciding upon genetic screening test for LAL-D.

Initially, when evaluating a patient with dyslipidemia, it is important to determine the absence or presence of family history of hyperlipidemia. The absence of family history is more indicative of an autosomal recessive trait such as LAL-D, particularly if the patient has also tested negative for autosomal dominant genetic causes such as HeFH and FCH.[2] The next step in the algorithm is to assess the patient utilizing the following criteria:

- ALT $>$ 1.5 X upper limit of normal
- Hepatomegaly present (may be mild)
- HDL-C $<$ 50mg/dL
- BMI $\leq$ 30 kg/m
- Liver biopsy (if carried out) findings suggestive of microvesicular steatosis

The patient only needs to meet three of the criteria to warrant further genetic

Differential Diagnosis for LAL-D[1-5]

	Heterozygous FH	LAL-D	Metabolic Syndrome	NAFLD/NASH
Etiology	Autosomal dominant Genetic disease	Autosomal recessive genetic disease	Disorder of energy utilization and storage	Accumulation of fat deposits in the liver not caused by alcohol
Age of onset of manifestations	Childhood to adulthood	Infancy to adulthood	Childhood to adulthood	Childhood to adulthood
Elevated LDL-C	Yes	Yes	Varies	Varies
Decreased HDL-C	No	Yes	Yes	Yes
Elevated Triglycerides	No	Varies	Yes	Yes
Elevated ALT	No	Yes	Yes	Yes
Hepatic Steatosis (imaging)	No	Yes (may be missed by ultrasound)	Yes	Yes
Hepatic Steatosis (biopsy)	No	Yes (predominately microvesicular)	Yes	Yes
Fibrosis/cirrhosis	No	Often present	Varies	Varies
Hepatomegaly	No	Yes (may be mild)	Varies	Often present
BMI Percentile	Obese or not obese	Obese or not obese	Often obese	Often obese

Table 1.

testing of LAL activity or mutations in the LIPA gene.

Previous treatment of LAL-D has been limited to supportive therapy to reduce the burden of disease and the use of HMG-CoA reductase inhibitors (statins) alone or in combination with other lipid-lowering therapies. These medications reduce serum cholesterol and TG numbers; however, this lowering effect has not been consistent with improvements in liver function tests or hepatic CE or TG content.[4] Several studies have demonstrated that treatment with statins does not change the progression of liver damage in patients with LAL-D.[2,4]

In December 2015, the Food and Drug Administration approved sebelipase alfa as the first treatment for patients with lysosomal acid lipase (LAL) deficiency. Treatment is provided via intravenous infusion once weekly in patients with rapidly progressive LAL deficiency presenting in the first six months of life, and once every other week in all other patients.[6] Sebelipase alfa is an innovative enzyme replacement therapy that addresses the underlying cause of lysosomal acid lipase deficiency by reducing substrate accumulation in the lysosomes of cells throughout the body.[6] In the multicenter, randomized, placebo-controlled ARISE (Acid Lipase Replacement Investigating Safety and Efficacy) study of children and adults with LAL-D, treatment with sebelipase alfa improved survival in infants with LAL-D and led to significant reductions in ALT and liver fat content, as well as significant improvements in lipid parameters, in children and adults with LAL-D.[6]

Lysosomal acid lipase deficiency should be included in the differential diagnosis for all patients with increased serum total and LDL cholesterol with a marginally low HDL, elevated AST/ALT and hepatomegaly. Although LAL-D is an ultra-rare disease, affecting two to 25 lives per million depending on the time of onset, increased awareness of this condition and the evidence based enzyme replacement therapy now available is important in reducing the devastating effects of this disease. ■

Disclosure statement: Dr. Friedrich has no disclosures to report.

References are listed on page 32.

Case Study:
Specialized Use of a Niacin-Statin Combination in Lipid Management

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Case:

We report on a 77-year-old Caucasian male with coronary disease and hereditary dyslipidemia requiring intervention. He was treated with rosuvastatin 10 mg daily. This resulted in remarkable improvement of his low-density lipoprotein (LDL-C) to < 70 mg/dL and triglycerides (TG) to < 150 mg/dL, however, he continued to have elevated lipoprotein(a) [Lp(a)] with small, dense LDL — pattern B. A few years later, he required a carotid endarterectomy (CEA) for progressive symptomatic carotid artery disease; he also had angiography evidence that his coronary disease was progressing, though not yet requiring intervention. He was referred for specialized lipid therapy, during which he was switched to atorvastatin 40 mg daily and was slowly titrated on extended-release niacin up to 2,000 mg daily. This resulted in a remarkable decrease in his Lp(a) and normalization of his LDL density pattern to large, buoyant LDL — pattern A, as illustrated in Table 1. He had no recurrent events in the few years since this change. This uncommon case of dyslipidemia demonstrates the importance of addressing residual risk, which would require tailored individual therapy — often with combination therapy — despite achieving a seemingly well-controlled, guideline-recommended lipid profile with statin therapy alone (Table 1).

An extensive body of evidence exists supporting the safety[1] and superiority of therapy with 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitors (statins) in the primary[2] and secondary[3] prevention of cardiovascular events. Recent ACC/AHA guidelines on high blood cholesterol have shifted the focus of therapy from the traditional LDL-C and non-high-density lipoprotein (non-HDL-C) targets to the intensity of statin treatment in various primary and secondary prevention categories.[4] This shift in paradigm was heavily evidence-based, taking into consideration the results of major clinical trials impacting the outcomes of tens of thousands of patients. Nevertheless, when it comes to the individual patient who has suffered a coronary event, even high-intensity statin therapy may leave the patient with residual, often fatal cardiovascular risk that is not addressed by the guidelines.[5] We believe that there should be an imperative to adopt more personalized lipid evaluation and treatment strategies to account for both traditional and non-traditional risk factors. The expectation is that a

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	Cholesterol	LDL-C	HDL-C	Triglycerides	ApoB	Lp(a)	LDL density	hsCRP mg/L
	mg/dL							
Pre-therapy	257	129	49	396				0.1
Rosuvastatin 10 mg/d	144	64	57	113	74	22	B	
Atorvastatin 40 mg/d + Niacin ER 2 gms/d	104	35	56	91	44	5	A	0.3

Table 1. Effect of lipid therapy with rosuvastatin alone, versus atorvastatin plus Niacin ER on lipid parameters of the case presented.

personalized approach may result in better individual outcomes.[6]

Our patient had established coronary artery disease and was aggressively treated to a target LDL-cholesterol level of less than 70 mg/dL, which was achieved on rosuvastatin 10 mg daily. Although his HDL-cholesterol and TG levels also showed marked improvement, with a seemingly optimal overall lipid profile, he returned with evidence of progression of his coronary artery disease, in addition to symptomatic carotid artery disease that necessitated intervention. He, therefore, was an ideal candidate for assessment of inflammatory markers and for advanced lipoprotein testing, as recommended by the NLA's 2011 Expert Panel Statement on Biomarkers.[7] A vertical auto profile (VAP) lipid panel was ordered; a normal high-sensitivity C-reactive protein (hsCRP) level was documented pre-therapy. Although levels of traditional risk markers were well controlled, an elevated Lp(a) level and LDL pattern B were identified as important residual risk markers[8,9] and as potential targets for therapy with added niacin to improve this patient's individual atherosclerotic risk.[10,11]

Niacin enjoys a long history as a lipid-lowering drug, with a multitude of mechanisms explaining its various anti-lipidemic effects. It inhibits a key enzyme for TG synthesis, resulting in increased hepatic ApoB degradation and decreased secretion of very-low-density lipoprotein (VLDL-C) and LDL-C particles.[12] Niacin also partially inhibits adipose tissue lipolysis, thereby decreasing free fatty acid flux and hepatic VLDL synthesis. Furthermore, niacin decreases the removal of HDL by the liver, increases cholesterol efflux, and decreases the synthesis of Lp(a) without affecting its catabolism.[13] Niacin, therefore, has been increasingly recognized as a "broad spectrum" lipid drug ever since its lipid-lowering effect was shown 60 years ago.[14] Additional "pleiotropic" anti-inflammatory, antithrombotic, and antioxidant effects of niacin also have been suggested.[15]

Niacin is unique in its ability to significantly reduce plasma Lp(a) levels.[16-18] The atherogenic potential of Lp(a) has been observed in several studies.[8,19,20] Aggressive reduction of Lp(a) with lipoprotein apheresis by 60 to 70 percent, added to a background of optimal lipid therapy, resulted in a significant decrease in the annual rates of major adverse coronary events.[21-23] The reduction of Lp(a) by niacin alone (at dosages of 1,000 mg to 2,000 mg daily) or in combination with a statin, however, is more modest and has ranged between 17 and 36 percent.[13,16,24] Dramatic lowering of Lp(a) by 88 percent with niacin 2,000 mg daily in combination with atorvastatin 40 mg daily has been reported,[10] a treatment similar to our reported case, in which we observed a 77-percent reduction in the Lp(a) level. Therefore, there seems to be a marked variability in the individual response to niacin therapy with respect to Lp(a) lowering. Niacin — alone and in combination with statin therapy — has shown favorable vascular effects, decreasing carotid atherosclerosis[25] and carotid intima media thickness.[26,27] Moreover, it has demonstrated mortality benefit, when given as monotherapy in high-risk men with high cholesterol, in the Coronary Drug Project.[28] It is difficult to tease out the potential benefit of reducing Lp(a) levels, given the multiple salutary effects of niacin on other atherogenic lipid parameters.

Niacin ER did not demonstrate any improvement in major cardiovascular events when added to moderate intensity statin with and without ezetimibe in recent clinical trials. This strategy was tested in the Impact on Global Health Outcomes (AIM-HIGH) study[29] and the Heart Protection Study 2 — Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study.[30] The results have shaken the confidence in niacin in general among those who have used this as add-on therapy, as an HDL-C raising strategy.[31] Despite these negative results, meta-regression derived from available clinical studies still supports the efficacy of niacin therapy in conferring atheroprotection and reducing cardiovascular disease risk.[32] Of interest, the AIM-HIGH study showed that baseline and on-study Lp(a) predicted cardiovascular events in both the control and the niacin treatment arms, suggesting that Lp(a) still contributes to residual cardiovascular risk even after achieving target LDL-C levels with statin therapy.[20] However, niacin treatment

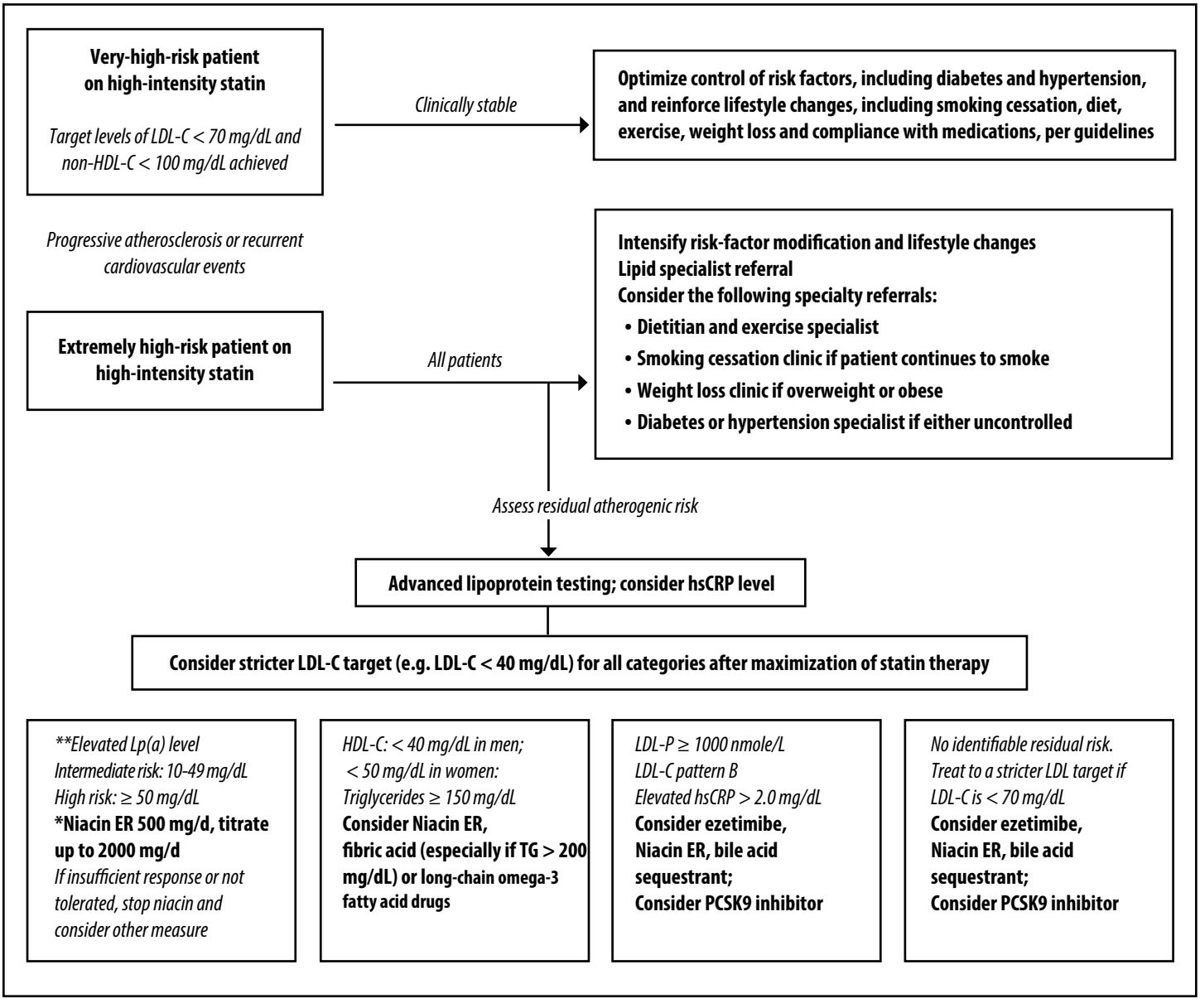

Figure 1: A proposed algorithm for the evaluation and treatment of extremely high-risk patients with progressive atherosclerosis or recurrent cardiovascular events despite optimum guideline-directed medical therapy and the achievement of LDL-C and non-HDL-C targets on maximally tolerated statin therapy.
*Niacin ER is associated with decreased flushing and improved tolerance compared to other formulations such as immediate release niacin.
**Reference range for Lp(a) by the VAP test is < 10 ng/dL.

in the AIM-HIGH study resulted in only a modest 19 percent decrease of Lp(a) levels compared to placebo, which may have blunted the clinical effectiveness of niacin. It is important to point out that the placebo arm in the AIM-HIGH study included 50 mg of immediate-release niacin, to mimic the flushing effect of 1,500 mg to 2,000 mg of Niacin ER in the treatment arm, which resulted in a 4.2 mg/dL (11.8 percent) increase in HDL in the placebo group. Of note, very-low-dose niacin added to statin therapy previously has been reported to result in a modest, but significant, 5 percent (2.1 mg/dL) increase in HDL-C.[33] Taking into consideration the significant 22 percent relative risk reduction in cardiovascular events seen in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study on gemfibrozil,[34] with only 2 mg/dL (6 percent) improvement in HDL-C levels, leaves one to wonder if the AIM-HIGH study was, in reality, a comparison of high- versus low-dose niacin, and whether a portion of the anticipated benefit of niacin has already been realized in the placebo arm. In the HPS2-THRIVE study, 2,000 mg Niacin ER was combined with the anti-flush drug laropiprant, resulting in a 14 percent (6 mg/dL) increase in HDL-C; a similar effect previously was reported with such a combination.[35] This, however, is lower than the 25- to 30-percent improvement in HDL-C observed with high-dose niacin without laropiprant[36] and

also reported in the AIM-HIGH study. Even though the HPS2-THRIVE study showed a nonsignificant improvement in the primary outcome of first major vascular events (nonfatal myocardial infarction, death from coronary causes, stroke or arterial revascularization), subgroup analysis was consistent with a significant 10-percent decrease in any revascularization procedure. The addition of laropiprant to niacin conceivably may have blunted the beneficial effects of niacin on optimally raising HDL-C and, perhaps, on the overall cardioprotective effect of niacin. It seems that neither trial answered the question with regards to the efficacy of adding high-dose, extended-release niacin alone (without laropiprant) to high-intensity statin therapy in improving outcomes compared with high-intensity statin therapy alone (without added low-dose niacin). Nevertheless, both trials do cast doubts on the effectiveness of niacin in reducing cardiovascular events in patients with atherosclerotic cardiovascular disease, despite significant improvements in HDL cholesterol and triglyceride levels, with the potential for increased risk of serious adverse events. Further careful subgroup analysis of both the AIM-HIGH and the HPS2-THRIVE studies may help shed further light on their overall unexpected negative outcomes.

Overall, niacin has a well-delineated side effect profile.[37] Skin manifestations include a flushing sensation, which causes an average discontinuation rate of ≤ 6 percent for niacin ER, in addition to non-allergic skin rashes and dry skin. Patient education, dosage changes and use of moisturizing creams may alleviate many of these side effects and improve compliance. Significant liver toxicity is mostly seen with high-dose, slow-release preparation. Reversible niacin-induced insulin resistance usually has minimal effect on glucose control in diabetic patients and is rarely associated with new-onset diabetes. Except for a few case reports, niacin alone or in combination with statin therapy, in general, does not appear to cause or exacerbate muscle symptoms. Rare reported side effects of niacin include cystoid macular edema — causing blurred vision, nausea, and vomiting — and worsened peptic ulcers. Uncommon laboratory abnormalities include elevated prothrombin time and uric acid, and decreased platelet count and serum phosphorus.

Our patient was gradually titrated on extended-release niacin to 2,000 mg daily, which he tolerated well with only minimal flushing symptoms at the beginning of the therapy. He did not complain of any muscle symptoms, and his laboratory data, including his liver function tests and A1c, remained normal. His initial Lp(a) was moderately elevated at 26 mg/dL and decreased to 22 mg/dL on rosuvastatin alone. However, after the addition of niacin and a change from rosuvastatin to atorvastatin (as a result of formulary considerations), his Lp(a) dramatically decreased to a safer level of 5 mg/dL, and his LDL pattern improved from the highly atherogenic pattern B to a favorable, less atherogenic pattern A. Overall, he has done well, without evidence of progressive atherosclerosis for the three years he has been on this combination therapy. His response to niacin, with regards to the lowering of Lp(a), was more dramatic than previously reported in the major clinical trials discussed earlier, the type of response associated with clinical improvement seen in lipoprotein apheresis studies. It is plausible that our patient's carotid artery disease may have antedated the initial start on statin therapy to where the CEA may have been inevitable. However, the appearance of symptoms related to his carotid artery stenosis and the evidence of progression of his coronary disease while on statin therapy were concerning for untreated residual risk. Overall, this underscores the need for earlier detection and primary preventive treatment efforts to avoid the development of cardiovascular disease.

The NLA Recommendations for Patient-Centered Management of Dyslipidemia[6] provide clearly defined criteria for atherosclerotic cardiovascular disease (ASCVD) risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy in four risk categories: low, intermediate, high, and very high. However, when it comes to treatment of patients with progressive atherosclerosis or recurrent events, despite evidence-based therapy, as in our patient, the NLA Expert Panel consensus' view is that "very aggressive therapy to lower atherogenic cholesterol levels to values well below goal thresholds may be considered for such patients, although it is acknowledged that this approach is not clearly supported by clinical trial evidence." We propose that such patients be categorized as extremely high risk, and undergo specialized patient-centered care by a lipid specialist for detailed analysis and treatment of their residual atherogenic risk, as shown in Figure 1. It is imperative to understand that large, randomized clinical trials, which form the basis of much of our evidence-based medicine, have inherent problems[38] when applied to an individual patient with unique characteristics and residual risk not addressed by such trials. A patient-centered and personalized approach to the interpretation and application of multiple studies as they pertain to a single patient is the crux of individualized medicine, making every patient's unique response essentially a one-patient clinical trial.[39]

In conclusion, when an optimally treated patient with cardiovascular disease has another cardiovascular event, it is

continued on page 26

Chapter Update:
A Transitional Year

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"What a day that was" – David Byrne, Talking Heads, Stop Making Sense

Last year (2015) was a transition year that expanded upon the challenges and changes the National Lipid Association (NLA) had undergone for the prior couple of years. From a national perspective, at the demand of NLA members, the NLA released its NLA Recommendations for Patient-Centered Management of Dyslipidemia Part 1 and 2. These documents laid out NLA principles regarding lipid evaluation and management, and represented a point of view most consistent with the "on the ground" clinical lipidology NLA members.

Concomitant with these clinical documents was the inaugural issue of the NLA Annual Summary of Clinical Lipidology, which was first published in 2015, and which underwent a major upgrade with the 2016 issue. As with the principles inherent within the NLA Recommendations, the upgrades to the NLA Annual Summary reflected the principles of NLA members, as well as the expertise of almost 40 reviewers — with the vast majority being Diplomates of the American Board of Clinical Lipidology or Certified Clinical Lipid Specialists.

During this time of change on the NLA national level, in 2015, the NLA Chapters also underwent change, via restructuring. The intent was to streamline processes, and enhance opportunities for NLA Chapter leaders and members. The Southeast Lipid Association (SELA) was likely no different than the other NLA chapters, in that 2015 was a year of acclamation to a new set of priorities, a new way of doing things, and most of all, a greater flexibility in serving on committees, with greater availability in the creation and completion of tangible "deliverables." Each of these restructuring processes had the intent of helping lipidologist colleagues in the care of their patients with dyslipidemia.

An example of how NLA priorities include the interests of NLA chapter members can be found within the NLA Annual Summary. During this transition year, a commitment was made to better recognize the efforts put forth on the part of NLA chapter members. An "E Link" section was added to the NLA Annual Summary document. This "E Link" section now provides online hyperlinks to NLA podcasts, webcasts, slideshows, websites, applications, and NLA continuing medical education initiatives. Each of these hyperlinks fulfills the intent to assist lipidologists and their patients, by providing better access to the NLA content, which were "deliverables" involving many hours of thought and work by NLA chapter members in crafting these initiatives.

Perhaps the clearest illustrative example within the NLA Annual Summary of recognizing the work of NLA chapter members is the dedicated icon and hyperlink to an aggregated list of "Patient Information" documents, which are practical, clinical documents for which so many NLA chapter members have

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invested so much time and effort. This is but one example of how the NLA structural changes on the national level are intended to better integrate NLA chapter members, chapter leaders, and chapter contributors into national priorities. In short, the transition year of 2015 was a sentinel one for both the national NLA, and the NLA chapters. My anticipation is that 2015 will serve as a springboard to even further opportunities and integration of NLA chapters in 2016 and beyond.

It's past time we started making sense. ■

CASE STUDY continued from page 24

reasonable to consider treatment options which have not been strongly endorsed by any guidelines. Such options, however, are not considered standard of care due to the absence of sufficient evidence, and patients should be counseled accordingly. If dramatic lowering of Lp(a) or other atherogenic particles, beyond what has been demonstrated in the major negative randomized clinical trials, is not achieved with niacin, then the clinician should heed the results of such trials and consider stopping niacin. Addition of ezetemibe to statin therapy may be another option to further lower LDL cholesterol levels and improve cardiovascular outcomes, as demonstrated in the IMPROVE-IT trial.[40] Aggressive LDL-C lowering with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has recently emerged as another lipid-lowering therapeutic option in patients inadequately controlled on maximally tolerated statin therapy; however, outcomes data are pending.[41] Beyond the currently available potent LDL-lowering therapies, which may have reached their maximum potential to reduce risk, there has been interest in raising HDL with cholesteryl ester transfer protein (CETP) inhibitors. However, despite the significant increase in HDL-C with the CETP inhibitor dalcetrapib in patients who had a recent acute coronary syndrome, there was no reduction in the risk of recurrent cardiovascular events.[42] Renewed interest has recently surfaced, however, in this therapy's potential benefit on cardiovascular outcomes in specific pharmacogenetic variants.[43] ■

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References are listed on page 32.

Member Spotlight:
Pamela B. Morris, MD, FNLA

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Pamela Morris, MD, is currently an associate professor at the Medical University of South Carolina where she serves as director of the Seinsheimer Cardiovascular Health Program and co-director of Women's Heart Care. She is also the chair of the American College of Cardiology's Prevention of Cardiovascular Disease Leadership Council and Section.

When asked about the best part of her occupation, Dr. Morris said that she is very fortunate to have a career that is ever-changing and dynamic. "Just when I think I understand my areas of interest, I blink and everything is new again," Morris explains. "Exciting new science to inform my clinical practice; new opportunities for education of my students, residents, and fellows; and informative discussions and challenging debates with my colleagues in prevention and lipidology."

Dr. Morris's interest in lipidology came unexpectedly. She says she was on a path to the animal lab studying angiogenesis factors during her cardiology fellowship, and as she neared the end of her training she was asked to become the medical director of the Duke University Preventive Approach to Cardiology (DUPAC) — Duke's robust cardiac rehabilitation and prevention program. "Perhaps one too many rat infarction procedures made me jump at the offer and the rest is history," said Morris. Together with her endocrinology colleague, Dr. Fred Dunn, Dr. Morris started the first joint lipid clinic at Duke. "We were just beginning to enjoy the benefits of the first statin for cardiovascular risk reduction and it's been a wild ride since then!"

No two days are ever the same for Dr. Morris, which keeps her engaged and enthusiastic to meet each day's challenges. Dr. Morris spends her days in her busy clinical practice in CVD prevention and management of complex dyslipidemias, women's heart care, and some general cardiology. Weekly nuclear cardiology and cardiac CTA reading sessions, ECG interpretation, and cardiac rehabilitation supervision fill some of her non-clinic hours. Dr. Morris is also a Master Clinical Skills Instructor at MUSC, and teaches weekly Physical Diagnosis sessions to enthusiastic second-year students. On top of all that, for three months each year, Dr. Morris supervises the Inpatient Cardiology Consult Service that provides general cardiology consultations for other services throughout the hospital system.

Dr. Morris became involved in the NLA when she relocated from the frigid winters of Minnesota to Charleston, S.C. in the mid-1990s and joined the Southeast Lipid Association. "SELA gave a name (clinical lipidology) to my career passion, gave me a 'professional home' with colleagues who shared my interests, and provided exposure to brilliant minds in the field who have never ceased to amaze me with their insights and discoveries," she says.

Without a moment's hesitation, Dr. Morris says that her favorite part of the NLA is the people that she has met and the relationships she has gained. "The NLA staff works tirelessly and joyfully to promote the mission of the association, to help make the rest of us look good and effectively do our jobs in support of the organization, and to make membership in the NLA truly a 'five-star' experience." Dr. Morris also went on to say that the

professional and personal relationships she has established as an NLA member have shaped and enriched her career and the friendships will be lifelong.

As a cardiologist, Dr. Morris would like to see preventive cardiology/clinical lipidology recognized as a subspecialty. She says that it continues to be somewhat frustrating as her colleagues say things like "I have the patient on a statin, what more do you want?" Dr. Morris believes that there is a gross underestimation of the value of prevention and the expertise of clinical lipidologists in ASCVD risk reduction.

When Dr. Morris is not hard at work in a professional setting, she enjoys spending her time scuba-diving. She says her hobby blends her love of the ocean, wildlife, photography, and remote travel destinations. Dr. Morris says that she can be happy anywhere there is a boat and a tank of Nitrox. Also, if you are in need of a drink, Dr. Morris says she can make a mean cocktail with only the finest ingredients. ■

Written by Membership and Marketing Coordinator Nichole Vanderpool.

Education and Meeting News and Notes

Registration Open for the 2016 Scientific Sessions

Registration is now open for the National Lipid Association's annual Scientific Sessions May 19–22, 2016, at the Hyatt Regency Hotel in New Orleans. Don't miss featured sessions on: "Human Genetics Impact on Clinical Practice in Lipidology," "Pathogenesis and Management of Non-Alcoholic Fatty Liver Disease," "ACC Expert Consensus Panel Recommendations on Non-Statin Therapy to Reduce ASCVD Risk," and many more. For more information, and to register, visit **lipid.org/sessions**.

Don't Miss Out on the Foundation Event at the Scientific Sessions

Join us on the evening of Saturday, May 21 at the National WWII Museum in downtown New Orleans for an eventful evening filled with fun, food, exhibits, and a show! The World War II Museum is the top-rated tourist destination in New Orleans and is considered the No. 3 museum in the country. Designated by Congress as the official WWII museum of the U.S., the museum will become the destination for our private event just for attendees and guests of the NLA Scientific Sessions. For more information, and to register, visit **lipid.org/sessions.**

Enjoy a New Member Reception in New Orleans

Enjoy light cocktails and hors d'oeuvres with new and active members on the evening of Friday, May 20 during the NLA Scientific Sessions in New Orleans. Would you like to learn how the NLA can benefit your career? The New Member Reception is a wonderful opportunity to mingle with leaders in the organization, and ask them any questions you may have about their experience in the association, how they have benefited from the educational opportunities, and the relationships they've created. Build new connections with other members that will enrich your experience as an NLA member and last a lifetime! For more information, visit **lipid.org/sessions.**

Pay Your Dues for 2016

The 2016 NLA dues statements and membership cards have been mailed. In addition to paying your 2016 dues, this is a great opportunity to donate to the Foundation of the NLA. To pay your dues online, visit **lipid.org/dues.** For more information or questions regarding dues, contact Membership Manager Britney Caldwell at **bcaldwell@lipid.org.**

NLA Releases Annual Summary of Clinical Lipidology 2016

The second edition of the Annual Summary of Clinical Lipidology was recently released in the *Journal of Clinical Lipidology*. This annual summary is intended to be a ''living document,'' with future annual updates that will be based on emerging science, clinical considerations, and new NLA position and consensus statements. The goal is to provide clinicians an ongoing resource that translates the latest advances in medical science toward the evaluation and treatment of patients with dyslipidemia. To read the 2016 edition, visit: **lipidjournal.org.**

ICD 10 Reference Sheet Now Available

Ralph La Forge, MSc, CLS, FNLA, chair of the Lipid Clinic Operations Committee, created a quick reference sheet of commonly used lipid-centric ICD-10 codes. The sheet highlights some differences between ICD-10 and the old ICD-9 codes. The sheet is designed to help clinicians at level I or level II lipid clinics with most of the key lipid-centric ICD-10 codes. The sheet can be found on **lipid.org** under the Practice & Policy tab and in the Operations Section.

NLA Online Enduring Educational Activities

The NLA partners with various medical education providers to offer many free, online educational opportunities to its members. These include programs on how to lower CVD risk, how to manage lipids beyond statins, and much more. These activities are free of charge and can be completed at your own pace and from your iPad or Android device. To access these activities, visit **lipid.org/education/online/other.**

Certification in Clinical Lipidology: Spring Testing Window

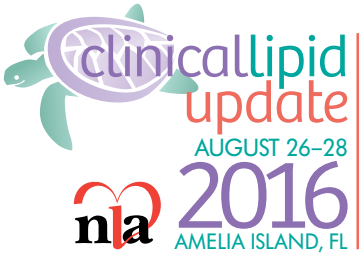
The spring testing window for lipid certification will be April 3, 2016–May 14, 2016. Application materials for the American Board of Clinical Lipidology (ABCL) certification and the Accreditation Council for Clinical Lipidology (ACCL) Clinical Lipid Specialist certification are due Friday, March 25, 2016! For more information regarding the ABCL requirements, please visit **lipidboard.org.** For more information regarding the ACCL-CLS certification, please visit **lipidspecialist.org**.

NLA Events Calendar

2016 National Lipid Association Scientific Sessions

Hosted by the Southwest Chapter

May 19–22, 2016
Hyatt Regency New Orleans
New Orleans, LA
lipid.org/sessions



2016 National Lipid Association Clinical Lipid Update—Fall

Hosted by the Southeast and Northeast Chapters

August 26–28, 2016
Omni Amelia Island Plantation Resort
Amelia Island, FL
lipid.org/fallclu

Lipid Academy
May 18–19, 2016
New Orleans, LA

August 25–26, 2016
Amelia Island, FL

Masters in Lipidology
May 18–19, 2016
New Orleans, LA

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Amelia Island, FL

NLA Coding Course
May 18, 2016
New Orleans, LA

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Clinical Feature

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Guest Editorial

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EBM Tools for Practice

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Lipid Luminations

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Specialty Corner

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The 5-Minute Nutrition Counseling Tool

Advice from the National Lipid Association Clinician Lifestyle Modification Toolbox

How To Engage Patients in Nutrition Counseling

- Step 1. Bring up the specific nutrition topic, e.g., overweight, elevated LDL-C, or triglycerides, in a non-judgmental way.
- Step 2. Assess the patient's current knowledge of the identified nutrition topic.
- Step 3. Ask if the patient is already making diet and lifestyle changes.
  - If so, support and encourage them!
  - Ask the patient to explain what changes he or she is working on.
  - If the patient has not been making lifestyle changes, assess if they are in the contemplative phase.
- Step 4. Ask permission to discuss lifestyle changes with the patient, then share advice and correct misinformation.
  - Ask "Would you like to hear what has worked for some of my other patients?"
  - After sharing advice, ask "What are your thoughts?"
  - At the end of the discussion, ask: "Would you like a referral to a registered dietitian nutritionist (RDN) to help you personalize your nutrition therapy eating plan?"
- Step 5. Assist the patient with goal setting and reinforce that seeing an RDN will promote successful lifestyle changes aimed at improving cardiovascular risk and also help improve quality of life.

Partnering With a Registered Dietitian Nutritionist (RDN)

- Registered Dietitian Nutritionists (RDNs) are:
  - Lifestyle change facilitators skilled in motivational interviewing and behavior modification.
  - Food and nutrition experts who have completed at least a B.S. degree and a supervised internship, passed a national exam, and maintain continuing education requirements.
  - Bearers of the "RDN" credential, a legally protected title beyond that of a "nutritionist."
- How to Find and Partner with an RDN
  - Go to **www.eatright.org** to find an RDN in your area by zip code**,** contact the outpatient nutrition department of your local healthcare system, or check if the patient's healthcare plan maintains a provider list of RDNs.
  - Once located, have your staff contact the RDN to discuss availability, billing, and areas of expertise.
  - Prior to the visit, send a formal referral, along with a clinic note, and relevant lab data.
  - Ask the RDN to share patient goals and progress notes with you.

Update on Insurance Coverage for RDN Services

- Coverage of medical nutrition therapy (MNT) for those with diabetes (DM) or renal disease (CKD) is universal.
- Currently, Medicare Part B does not cover MNT for dyslipidemias without DM or CKD. Since 2011, Medicare has covered intensive behavioral therapy (IBT) for obesity if services are provided by PCPs, who may partner with an RDN. Medicaid coverage of MNT for dyslipidemia or obesity varies by state; check with your program.
- Commercial payer coverage of MNT for dyslipidemia provided by RDNs is good, and continues to expand as a result of the Affordable Care Act (ACA) and stakeholder efforts. In general, most large payers currently cover nutrition counseling for dyslipidemia.

This Information Is Provided Courtesy of the National Lipid Association

NATIONAL LIPID ASSOCIATION
6816 Southpoint Pkwy
Suite 1000
Jacksonville, Florida 32216

A Night at the Museum

National WWII Museum

Private Event

DINNER ▪ DRINKS ▪ LIVE MUSIC
EXCITING EXHIBITS

SATURDAY, MAY 21
7:30-10:30 PM

A Foundation of the NLA Event

Learn more at: **lipid.org/sessions**

FOUNDATION
of the National Lipid Association