Debunking Common Myths in Clinical Lipidology

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As I near the end of my term as president of the National Lipid Association (NLA), I have so many thoughts about this rewarding experience that I want to share with you. I remember meeting with an ever-smiling Michael Davidson, MD, FNLA, in 2004, who had so much to tell me about this young organization that he thought would be a perfect fit for me. He asked me to come to a Midwest Lipid Association (MWLA) Regional Update, and by the time I left that meeting, I knew that I was hooked for good. As I immersed myself into studying about clinical lipidology, I was first struck with the realization of how little I knew. My lack of knowledge fueled a voracious appetite to read and learn everything I could and to attend every NLA educational session that the organization gave. The NLA Self-Assessment Program was a great place to start, and the Masters in Lipidology course only served to make me want more. When I took the first certifying exam of the American Board of Clinical Lipidology in 2005, I knew that I was on a path that would enrich my skills as a clinical cardiologist.

As a member of MWLA, my dedication to the NLA was particularly fueled by working with MWLA leaders, including Dr. Davidson; Neil Stone, MD, FNLA; Jennifer Robinson, MD, FNLA; Anne Goldberg, MD, FNLA; and Alan Brown, MD, FNLA. I enjoyed serving on the MWLA Board of Directors and was privileged to become president of MWLA from 2009–2010. Participation at the regional level served as a springboard to my service on the NLA Board of Directors beginning in 2008, to the Executive Committee in 2012, and, to my developing close friendships and rewarding working relationships with a number of respected NLA leaders, including Virgil Brown, MD, FNLA; Matthew Ito, PharmD, FNLA; Peter Jones, MD, FNLA; and Terry Jacobson, MD, FNLA.

The past five years have been a time of rapid change and maturity for our organization and our leadership. During that time we evolved in our approaches to education of our membership, created valuable Expert Panel recommendations on familial hypercholesterolemia and biomarkers, and produced updates of our Self-Assessment Programs. The collegial spirit that characterized the creation of the NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 1 and 2 helped further establish our organizational identity and give providers our view on what constitutes evidence-based therapy for the prevention of atherosclerotic cardiovascular disease (ASCVD) and hypertriglyceridemia-induced pancreatitis.

This past year has been a time of evolution for the NLA. A strategic planning meeting, under the outstanding leadership of Dr. Jacobson, set the tone for the high level of performance that characterized the 2015–2016 year. Dr. Jacobson’s work as chair of the Science and Policy Council kept us in the forefront of advocacy issues
that impact clinical lipidologists. The Regional Affairs Council, led by our NLA President-Elect and Council Chair, Joyce Ross, MSN, FNLA, promoted committee involvement that enabled our regional members to become more engaged with the national agenda, helped the national organization better understand the local perspectives of our membership, and facilitated the identification of rising stars who will provide our future leadership. Our presence on social media, championed by Jamie Underberg, MD, FNLA, as Communications Council chair, effectively increased external awareness of the NLA’s activities. The selfless and tireless devotion of Dean Bramlet, MD, FNLA, in his work on the Executive Committee and as chair of the Practice Management Council, helped move forward activities that support clinical lipidologists. Dr. Alan Brown’s thoughtful initiatives as Membership Council chair breathed new life into our membership recruitment and retention strategies and helped our new members understand that the NLA welcomes them and appreciates their involvement. The endless energy and constant striving for excellence of Harold Bays, MD, FNLA, as Education Council chair and creator of the NLA Annual Summary, have served as an inspiration to the rest of us. Finally, I want to recognize the steady leadership of Brian Hart, JD, who, along with the NLA staff, have helped facilitate the multiple agendas that make up the fabric of our organization.

A major theme of this past year has been collaboration. Through the tireless work of Dr. Bays, the NLA collaborated with the American Society for Metabolic and Bariatric Surgery and the Obesity Medicine Association to create a consensus statement on lipids and bariatric procedures. The organizational bridge building efforts of Dr. Alan Brown and Pamela Morris, MD, FNLA, resulted in the NLA being asked to participate in the LDL Think Tank meeting in October 2015, and in an American College of Cardiology Writing Group that produced the 2016 Expert Consensus Decision Pathway on the Role of Non-Statin Therapies in the Management of Atherosclerotic Cardiovascular Disease Risk, a document that was endorsed by the NLA Board of Directors and published online in the *Journal of the American College of Cardiology* in April 2016. In recognition of our key role as thought leaders in the field of clinical lipidology, the NLA was invited to become a partner with the American College of Cardiology and the American Heart Association in the creation of the next update of the Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults.

I thank you all for the privilege of serving the NLA during my year of presidency in 2015–2016. Your new President, Joyce Ross, has inherited a healthy, optimistic organization with almost endless potential to move forward our important agenda in 2016–2017.
From the NELA President:
Myth Busters

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We hope you enjoy this issue of the LipidSpin, and hope that it helps in the future management of your patients. After all, isn’t that what we’re all about?

“...We all are regaled from time to time by well-meaning patients who have believed misinformation/disinformation.”

Welcome to the Scientific Sessions issue of the LipidSpin — this year sponsored by the Northeast Lipid Association (NELA). We have had a lot of fun putting this issue together, and hope that you will enjoy reading this issue just as much.

The theme for this issue is “Debunking Common Myths in Clinical Lipidology.” The thought behind this theme was that we all (nurses, MDs, RDs, pharmacists, etc.) are regaled from time to time by well-meaning patients who have believed misinformation/disinformation, which they have picked up from various media sources. This may involve a dubious therapy, like chelation (see the EBM Tools for Practice article by Erik Kelly, MD, on page 14), or the unnecessary maligning of a proven therapy, like statins (see the Patient Tear Sheet by Merle Myerson, MD, FNLA, on page 37). In addition, Julie Bolick, RD, FNLA (Lipid Luminations – Page 16); Wahida Karmally, RD, FNLA (Specialty Corner – Page 18); and Frances Burke, RD (Practical Pearls – Page 21), help to clear up some nutritional confusion.

There are also topics more closely related to the field of lipidology that are in need of having a little light shed on them. These articles include the Clinical Feature by Scott Altmann, PhD, on Page 7; the Guest Editorial by Om Ganda, MD, on Page 11; and the Guest Review by Kenneth Kellick, PharmD, FNLA, on Page 25).

Discuss this article at www.lipid.org/lipidspin

Update Your NLA Member Profile
We have added some exciting new features to our NLA member profile area on lipid.org. To update your profile, log in to the NLA website and then click on the “My Account” option at the top of the page.

The “Find a Member” feature is the most used tool on the NLA website. If your profile is not updated, you might miss out on referrals or collaborations. The new profile gives you the ability to let other members know if you accept referrals or new patients, what your specialty areas are, and much more.

Are you in New Orleans? If so, stop by the NLA booth in the exhibit hall. While there, update your member profile for a chance to win a $25 Starbucks gift card.
“He who thinks he knows, doesn’t know. He who knows that he doesn’t know, knows. For in this context, to know is not to know. And not to know is to know.” – Joseph Campbell, The Power of Myth

I provide printed instructions to my patients after office visits that read: “As we discussed, you have significant atherosclerosis and risk for serious cardiovascular events and I strongly recommend a heart-healthy diet, regular activity/exercise, no smoking, aspirin 81 mg daily, excellent BP control, and statin therapy at doses shown to reduce risk.”

These are the things I know will help my patients. There are many other interventions that have less strong evidence for benefit, others with evidence of both benefit and harm, and others with no evidence at all. Of course, it is the clinician’s job to sort through an ever-growing body of medical literature, weigh the evidence, put it in the context of the patient’s needs, and then offer advice for all of the available intervention. Clinicians should be able to discuss, but not necessarily have answers to, difficult questions, including: What about CoQ10? Should I eat low carb? What about eggs? Does chelation help? Clinicians need to prioritize recommendations based on need, evidence, risks, cost, availability, and our patients’ belief systems.

All clinicians struggle with the best way to answer these questions/concerns. If you’ve been well trained in evidence-based medicine (EBM), then it is almost a reflex to dismiss all of these queries as not valid of serious discussion. However, a dismissive response is a disservice to our patients. Our patients ask us for advice on all matters and, while it is reasonable to not know an answer, they certainly expect us to have considered some of the quandaries being reviewed in popular press, TV shows, social media, and in social settings (the “cocktail party” discussions) and to be able to help them weigh the available evidence.

Supplemental and complementary care tends to fail when held up to the EBM light. These therapies often lack physiologic plausibility, rigorous scientific testing, clinical trial validation, and/or uniformity of production/delivery and oversight. However, not all supplements or complementary care is the same. Some interventions do have some of the combination of attributes we look for in proven therapy while others are pure snake oil and others yet, flat out harmful. For example, I don’t typically contradict my patients who take daily vitamin C supplements with their glass of orange juice in the morning, expecting this to prevent cancers and other maladies when the only disease I am sure they won’t get on this regimen is scurvy. I remain more skeptical about the potential benefits/risks of vitamin D supplementation since, if this truly has potent impact on physiology, then I expect some potential for hazard as well. We should all know a lot more on this topic in the next few years as long-term studies are underway. I doubt we will
learn the same for other supplements that lack the background science to pique the interest of the Centers for Disease Control and Prevention (CDC), National Institutes of Health, and other major stakeholders.

Despite the gaps in information, the American supplement industry is enormous (estimated at between $12–37 billion last year), complementary medical programs are starting to appear in U.S. medical schools and hospitals, and the “healthy diet” discussion is part of everyday and political discussion.

It is critical to understand the context for all therapies, but particularly for complementary therapies. The mainstream, less skeptical patient may be looking for validation from his doctor confirming the touted supplement in question is not necessary. Another patient may be more desperately looking for any glimmer of hope for a difficult to treat condition and a more open minded approach can be extremely helpful in solidifying a relationship and trust between the doctor and patient.

While you read through this issue on myths in our field, keep in mind that the things we “know” today, may be viewed very differently in the next generation. An appreciation of the fleeting knowledge of our profession mandates a humility that is necessary for the compassionate healer. I make it clear to my patients that I value the knowledge in our profession, but also embrace those safe interventions that provide a source of strength and healing even when we don’t know whether they will be helpful or why our patients value them. The clinician who can balance these issues can be a truly valuable healer.

The NLA partners with various medical education providers to offer many free, online educational opportunities, including programs on how to lower CVD risk and how to manage lipids beyond statins.

Learn more at lipid.org/education/partners.
Clinical Feature:
The Continuing Saga of HDL: Truth, Fallacy, or Something in Between?

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William Hazlitt, an 18th century literary critic and philosopher, once said, “When a thing ceases to be a subject of controversy, it ceases to be a subject of interest.”1 If one accepts his premise, then interest in high-density lipoprotein (HDL) shall endure for some time. As far as contemporary medical controversies go, the HDL story is definitely in contention.

Without question, our evolving understanding of the structure and metabolism of lipoproteins has led to important insights into treatment and prevention of coronary heart disease (CHD). Results from these efforts are reflected in favorable trends in national lipid and lipoprotein levels.2 Indeed, due in part to improved nutritional and clinical guidelines, increased public awareness of risk factors and new lipid-lowering therapies, CHD mortality has leveled off and even declined since the late 1960s.3 These achievements, along with a growing number of promising therapies that lower low-density lipoprotein (LDL), elicit a sense of optimism that more advances will follow.4 However, CHD stubbornly persists in the U.S. as a leading cause of death in both men and women — a sobering reminder that this medical success story is still a work in progress. Thus, the goal of curtailing CHD remains paramount and still seems far off.

Interventional clinical trials are considered the ultimate test and final arbiter for the validity of scientific theory in medicine. Conducting a clinical trial exemplifies a conviction that one has arrived at a fundamental understanding concerning the pathophysiology of a disease and a confidence that a deliberate action taken will favorably change the outcome. Thus, it was widely anticipated that therapeutic increases in HDL-cholesterol (HDL-C) would translate into coronary artery disease (CAD) protection to augment the already successful approach of lowering LDL-cholesterol (LDL-C). However, the failures of HDL-C-raising therapies — including three cholesteryl ester transfer protein (CETP) inhibitors5 and extended-release niacin6 — have struck at the very core of a favored scientific philosophy.7 Some scientists, clinicians, and policy makers have begun to write off HDL as a therapeutic target or biomarker. Still, there are many who passionately argue that the pendulum has swung too far in the opposite direction and insist that HDL still holds great promise. HDL has indeed become controversial — and more interesting than ever.
Did the clinical trials mentioned above really kill HDL or did they simply kill the myth that HDL-C is a good marker for HDL? A more sobering assessment of these clinical trials reveals that they were never designed to assess the health benefit of HDL or even test whether modulating HDL would improve CHD outcomes. Instead, they were a referendum on the ability of HDL-C to reflect improved functionality of all HDL particle populations. The notion that HDL and HDL-C are one in the same — or even biologically equivalent — has been impugned. It is becoming clear that viewing HDL biology through a cholesterol lens and the fallacy of a “one-component-represents-all” approach have reached the end of their usefulness.

Moving away from a reductionist model and toward a high-definition systems approach to particle population monitoring is inevitable. This is a key tenet of precision medicine (PM), and translating this approach to atherosclerotic cardiovascular disease brings with it the most viable means to advance diagnosis and treatment. This may appear obvious to some, but there is scant evidence that this strategy has been broadly adopted. Of the ~13,000 articles identified using the search term “personalized or precision medicine,” only 0.6 percent can be linked to “atherosclerosis or heart disease.” This is in stark deference to the cancer field, which accounts for ~36 percent of these publications, and is not unexpected given that oncology researchers engaged the PM model early on. The similarities between cardiovascular disease and cancer are evident, including an underlying genetic susceptibility influenced by non-modifiable and modifiable risk factors. Perhaps some valuable lessons may be gleaned given the dramatic increase in approved cancer drugs in the past decade.

The limitations of the cholesterol-centric focus have been glaringly revealed by recent advances in mass spectrometry that have uncovered an expanded lipoproteome and lipidome unforeseen just a few years ago. As a lipoprotein class, HDL has the most extensive particle diversity and population heterogeneity, with more than 100 proteins and ~200 lipid species in an undetermined number of combinations. Particle constituents exist in distribution disequilibrium with each other and to the particle population as a whole, which can be observed across multiple separation methods. Figure 1 illustrates this model from the perspective of the HDL proteome, but this also is true for specific lipid species, as well.

“We offer the belief that HDL is a nexus that mediates a tremendous amount of unknown biology.”

There is an intrinsic relationship between particle constituents, physicochemical properties, and functionality. Each particle is a macromolecular assemblage of molecular species that produces a related set of physicochemical properties such as density, size, or electrophoretic mobility. However, consider the idea that each particle is a collection of constituents that are selectively combined to generate a self-contained set of “operating instructions” that dictate the particle’s activities. Although separating particles based on physicochemical properties has allowed one to apportion activity to particle subfractions, one needs to look beyond defining HDL subpopulations based on their physicochemical attributes. Instead, it is the protein constituents themselves that should serve as surrogate markers to classify HDL particles and provide the basis for assigning functionality.

The most essential facet of a healthy HDL profile is the capacity of the particle populations to perform their biological function(s) as effectively and efficiently as possible. This notion of HDL functionality is embodied in the term “HDL quality,” which encapsulates the atheroprotective properties of HDL. Those properties include reverse cholesterol transport and its antioxidant, anti-inflammatory, and antiapoptotic activities, among others. HDL functions also can become impaired or “dysfunctional,” thus complicating the picture. Particle alterations that reshape functionality are a result of genetic and metabolic factors that directly modify the lipoproteome and lipidome as well as influence particle population dynamics. It is no surprise that HDL exhibits a range of activities outside the traditionally viewed roles in cardiovascular disease. These disease/function associations are mirrored in the proteome, with numerous constituents playing known roles in various other diseases. Figure 2 summarizes a variety of diseases in which alterations in lipoprotein distribution profiles or changes in HDL particle constituent levels have been observed in humans.
Additionally, genetic association studies in diseased individuals have identified single-nucleotide polymorphisms in specific HDL proteome members, although confirmatory studies with independent cohorts are still required to validate some of these associations. Yet the model of subparticle functional heterogeneity predicts a role for HDL in distinct biological processes. Some of these involve important roles in cardioprotection — others may not. It also follows that, if we can identify these subspecies or markers of these subspecies and relate them to disease protection or progression, we will have a much better biomarker with which to track disease and stratify risk in individuals.

We contend that the current HDL measurements are fundamentally insufficient to address the challenge posed by particle diversity and heterogeneity. A simple analogy is presented in Figure 3 to make the point. An illustration of HDL particle diversity and population heterogeneity is shown (Figure 3, left image). Each is a symbolic rendering of the proteome and lipidome. No two particles are identical, but some molecular similarities can be discerned. For example, the cholesterol:triglyceride ratio is reflected as a color gradient from red to orange and at the center of each particle is a proteomic core comprising apolipoprotein combinations. Juxtaposed to the particle population is an aerial view of a neighborhood (Figure 3, center image). Even without closer inspection, one knows that each home has distinct characteristics that make it unlike another. It is obvious that the combination of features that make a home unique also contributes to its resale value. However, one could probably should not buy a home simply based on total square footage, one should avoid relying on HDL-C when considering the health benefits of HDL.

It has been suggested that “advanced lipid testing” techniques, which measure particle number or distinguish particle subpopulations using physicochemical attributes such as density, size, or electrophoretic mobility, bring diagnostic improvements. HDL subtypes classified in this manner result in a highly constrained particle nomenclature. Defining HDL subtypes may offer incremental insight, but we argue that these still are inadequate to address the problem at hand. Particle modeling based on combinations of distinct protein and lipid constituents are predicted to be significantly larger.

The age of Omics Research is now offering a glimpse at the horizon of lipoprotein characterization and, perhaps, a truer understanding of the requirements for HDL molecular profiling. In an ideal world, it would be best to develop a phenotyping strategy that is capable of measuring large numbers of particles and all of their associated constituents. As this likely involves tens of thousands of particles in a drop of plasma, this technologically is out of reach. However, next-generation HDL measurements will need to strike a balance between clinical assay practicality and a breadth of particle coverage that allows one to monitor numerous particle subpopulations, or at least their surrogate

Figure 2. There is much more to HDL than cardioprotective and transport activities. A summary of human disease states in which alterations in lipoprotein profiles or changes in particle constituent levels have been observed. Reported linkage of single-nucleotide polymorphisms to specific HDL proteome members are indicated in red font.
markers, that are relevant to a particular disease state. Entry points to this area are emerging as, for example, Sacks and colleagues have begun to fractionate HDL using immunoaffinity separation techniques and relate these to disease risk.\cite{Sacks2016} While such candidate particle approaches have promise, one ultimately would like to develop technologies that track the entire HDL “interactome”\cite{Altmann2016} in an unbiased way. Once translated into clinically feasible assays, such measures would be applicable to contemporary concepts such as precision medicine.

Sophisticated molecular phenotypes derived from HDL diagnostic tests that rely on integrated biomarker panels will go hand-in-hand with the genomic sequencing efforts. The lack of molecular context and granularity that connects physiological consequence to the sequence variants identified\cite{Davidson2016} remains a crucial element to designing future interventional strategies. Most excitingly, their use to advance the study of the progression of HDL-related diseases such as CHD, assess efficacy of experimental therapeutics, and stratify patients into groups that may respond better to certain treatments should not be opportunities missed. Given the stunning compositional complexity of HDL and the widely varying known functionalities of the proteins that associate with the particles, we offer the belief that HDL is a nexus that mediates a tremendous amount of unknown biology. Staggering resources have been poured into raising HDL-C. Shouldn’t we invest a bit more to better track the protein combinations that likely mediate these beneficial activities and enable assessment strategies that guide treatment for individuals rather than the population?

**Disclosure statement:** Dr. Altmann owns HDL Apomics LLC. Dr. Davidson has received speaker and consulting honoraria from Eli Lilly, and he is on the advisory board of HDL Apomics.

**References** are listed on page 35.
The global epidemic of type 2 diabetes (T2DM) continues unabated. Atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF) are the most common causes of T2DM-related mortality. More than 90 percent of patients with T2DM are overweight or obese. The pathogenesis of this disorder is heterogenous, but insulin resistance and relative β-cell dysfunction are its key characteristics.

Insulin resistance is a major contributor to cardiometabolic syndrome, comprising the characteristic atherogenic dyslipidemia — triglyceride-rich lipoproteins, elevated apolipoprotein B (apo B), and low high-density lipoprotein cholesterol (HDL-C) — hypertension and increased thrombogenicity. Over the course of years, β-cell loss progresses, partly because of increased insulin demand resulting from ongoing insulin resistance, which worsens by a net caloric excess and failure to achieve appreciable weight loss, thus creating a vicious circle. Not surprisingly, while lifestyle changes such as diet and exercise may initially control hyperglycemia, most patients over the years will require various drugs designed to improve insulin resistance or β-cell function, often in combination as double or triple therapy and, ultimately, as insulin replacement.

Metabolic and Vascular Effects of Insulin
Insulin has both metabolic and mitotic effects at the cellular level. Under physiological circumstances, insulin — via phosphoinositide 3-kinase (PI-3 kinase) and mitogen-activated protein kinase (MAP-kinase) pathways, respectively — has both anti-atherosclerotic and anti-inflammatory actions, e.g. increased nitric oxide synthase, reduced nuclear factor — kappa B NF-κB, reduced platelet aggregation, etc., as well as pro-atherosclerotic/pro-inflammatory actions (e.g., increased plasminogen activator inhibitor 1 [PAI-1], increased endothelin-1 [ET-1] receptor activity, increased cell proliferation, etc.) in the vessel wall. The former effects likely predominate in the absence of insulin resistance.1-3 Because of variable degrees of insulin resistance, some patients will require a progressively increasing insulin dosage to overcome the underlying defects in insulin action. However, at the clinical level, it is not clear if a subset of such patients requiring a very high insulin dosage to overcome their insulin resistance may actually have deleterious effects, particularly from the cardiovascular viewpoint.

Potential “insulin-induced harm” was the theme of the recent provocative perspective articles by Nolan, et al.4,5 They propose that, in T2DM patients with unremitting obesity primarily the result of caloric surplus and a lack of physical activity, the worsening insulin resistance may actually reflect an adaptive defense mechanism against “insulin-induced metabolic stress.” They also propose that the induction of insulin resistance serves as a “safeguard” against insulin-induced glucolipotoxicity at the level of myocardium, in particular (Figure 1). They discuss the deleterious role of intensive insulin regimens in driving excessive entry...
Potential mechanisms for adverse cardiovascular effects of intensive insulin treatment in Type 2 Diabetes with insulin resistance and “refractory hyperglycemia”

1. High intracellular glucose and FFA promote mitochondrial dysfunction and increased reactive oxygen species (ROS) production in insulin sensitive tissues e.g. myocardium, endothelial cells, liver, and muscle.

2. Increased malonyl CoA/AMPK ratio leading to increased intracellular lipid synthesis > increased ER stress and steatosis.

3. Increased FFA levels > inhibition of pyruvate dehydrogenase (PDH) > increased flux via glycogen synthesis, hexosamine pathway, and polyol pathway > advance glycosylation end products (AGEs).

4. Increased ATP/AMP ratio + Decreased AMPK + toxic lipids and ceramide + elevated ROS > increased inflammasomes > cardiomyopathy.

5. Nutrient excess > inhibition of PI3K/AKT pathway > uninhibited MAPK pathway > prothrombotic effects.

6. Loss of cardiac protection by ischemia-induced pre-conditioning.

7. Adverse consequences of further weight gain in overweight obese patients with type 2 diabetes.

8. Intermittent episodic hypoglycemia.

Table 1.

of glucose and free fatty acids (FFA) in the myocardium, thus overloading the electron transfer chain and leading to mitochondrial dysfunction, excessive reactive oxygen species (ROS) production, and oxidative stress. These phenomena and failure to oxidize FFA result in the accumulation of toxic lipids (e.g., ceramide) and reduced Adenosine Monophosphate Kinase (AMPK) activity, leading to the activation of inflammasomes and further myocardial injury. The increased prevalence of cardiomyopathy in patients with T2DM has been recognized since the Framingham Heart Study. It is likely that such patients account for the increased risk of heart failure in patients with diabetes.

Table 1 summarizes the various mechanisms for adverse cardiovascular effects of intensive insulin therapy in patients with refractory hyperglycemia.

Interpreting Insulin Effects in Clinical Trials

The benefits of intensive glycemic control, with or without insulin therapy, on microvascular complications of both types 1 and 2 diabetes are well established in landmark trials such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), respectively. However, none of the clinical trials with intensive insulin therapy in obese T2DM patients thus far has shown a reduction in CVD mortality. The UKPDS trial is the only primary prevention trial that provided evidence of significant but modest benefits from “intensive” glucose control (with insulin, with or without sulfonylurea therapy). However, CVD outcomes and mortality benefits were seen only after 10 additional post-trial years of follow-up. Of note, these patients were relatively younger, newly diagnosed and, on average, overweight but not obese at baseline (mean age 53 years, BMI 28), and the mean insulin dose was only 22–36 units daily.

In contrast, three large cardiovascular randomized controlled trials (RCTs) compared intensive and conventional glycemic treatment. These included Action to Control Cardiovascular Risk in Diabetes (ACCORD),10 Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),11 and the Veteran Affairs Diabetes Trial (VADT).12 The trials involved >23,000 older patients with a mean age between the three trials of 60 to 66 years, a mean BMI of 28 to 32, and a mean duration of diabetes from 8.0 to 11.5 years. Of those, between 32 and 40 percent had pre-existing CVD. A particular concern was an unexplained 22 percent increase in total deaths and a 35 percent increase in CV deaths in ACCORD, despite a reduction in ischemic coronary events. In VADT,12,14 a significant decline was reported for major CV events, but not total deaths, after a median of 9.8 years of observational follow-up. In ADVANCE,11 a reduction in total deaths or CV events was not seen even after 5.4 years of additional follow-up. In both ACCORD and VADT, intensive insulin therapy was associated with considerable weight gain and increased rates of severe hypoglycemia. During both trials there was a significant increase of 35 and 32 percent in CV mortality, respectively.10,12 Thus, in these pivotal trials, intensive insulin therapy in relatively older patients with a long duration of pre-existing disease, including pre-existing CVD in many, was shown to adversely affect cardiovascular mortality and total mortality, despite a reduction in ischemic events.

A few other trials have investigated the long-term effects of insulin compared to conventional therapy in patients with T2DM and CVD. The Diabetes Insulin-Glucose in Acute Myocardial Infarction study (DIGAMI-1) was a RCT in which 620 patients with acute myocardial infarction (MI) were randomized to short-term intensive insulin or conventional therapy. There was an 11 percent decrease in mortality at 3.4 years. However, none of these patients was on statin therapy at baseline; thus, the implications of
the results are unclear. DIGAMI-2 (N=1,253),17 and the Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) study (N=240),18 showed no significant effects of intensive insulin on mortality in post-MI patients after mean periods of three years and six months, respectively. However, in an observational follow-up of DIGAMI-2, there was a marked increase in the composite of re-infarction, stroke, and total mortality (HR 1.78, 95-percent confidence interval, CI [1.14-2.40]).19

In the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (HEART2D) trial, a prandial insulin regimen was compared to basal insulin.20 During a mean follow up of 2.7 years, there were no differences in CVD outcomes or glycemic control. Finally, the Outcome Reduction with an Initial Glargine Intervention trial (ORIGIN trial) — in >12,000 patients at high risk for CVD with recent onset of T2DM or pre-diabetes — compared basal insulin glargine or noninsulin treatments.21 The baseline hemoglobin A1c (HbA1c) was relatively low at 6.4 percent, and the mean daily insulin dose was only 28 units. There was no effect on CVD outcomes (HR, 1.02; 95 percent CI, 0.94-1.11) after a median follow-up of 6.2 years.

The Implications in Type 2 Diabetes Management

Nolan, et al., present a persuasive scientific rationale for the detrimental cardiovascular effects of long-term treatment with an increasing insulin dosage in a subset of obese patients with T2DM, where insulin resistance may protect the heart and other organs. Their hypothesis may explain the lack of expected cardiovascular benefits in such patients where insulin-induced metabolic stress may dampen the effects of attempted intensive glycemic control with an increasing insulin dosage. They make a critical distinction between overriding insulin resistance via increased insulin availability versus nutrient off-loading.

For example, in the long-term Action for Health in Diabetes (Look AHEAD) trial, the lifestyle program in subjects with mean BMI of 36 resulted in a significant weight loss, and appreciable trends in reductions in mortality (HR 0.85, 95 percent CI 0.69-1.04), as well as fatal and non-fatal MI, and HF (22). Furthermore, in the recent CVD outcome EMPA-REG trial, with the sodium glucose-cotransporter-2 (SGLT-2) inhibitor empagliflozin, in >7,000 T2DM patients there was a 14-percent reduction in the primary endpoint (CV deaths, nonfatal MI, or nonfatal stroke) (P=.04), a 32-percent reduction in all-cause deaths (P<.001) and a 35-percent reduction in hospitalization for heart failure (P=.002).23 These benefits were accompanied by modest reductions in HbA1c levels, body weight (~2 kg), waist circumference (~2 cm), and systolic blood pressure (~4 mm) in the absence of hypoglycemia, in contrast to the intensive insulin trials discussed above. Recurrent hypoglycemia is both mechanistically and epidemiologically linked with increased CV mortality in recent studies.24,25

Unfortunately, there currently are no pharmaceutical agents that would effectively and safely improve insulin sensitivity without causing further weight gain. Thus, testing the Nolan hypothesis, at least in patients with severe obesity and poor control despite increasing insulin dose (e. g >1-2 units/Kg body weight) would be of much interest. Therefore, a clinical trial comparing an insulin regimen with a combination of strategies that reduce insulin resistance, reduce weight, and avoid hypoglycemia such as intensive lifestyle changes + SGLT2 inhibitor + GLP-1 agonists and perhaps an alpha-glucosidase inhibitor is needed to assess the CVD outcomes. Bariatric surgery is another alternative,26 but the cost and long-term adverse effects need consideration.

Disclosure statement: Dr. Ganda has received research support from Amarin Pharmaceuticals and consulting fees and speaker honoraria from Merck, Sanofi, and Amgen.

References are listed on page 35.
Cardiovascular disease (CVD) is the leading cause of death in the U.S.\(^1\) There have been many important advances in the treatment of CVD in recent decades. However, not all touted therapies carry the same quality of evidence supporting their use. Chelation therapy is one such treatment that has been controversial since its inception more than half a century ago. Is its use as a treatment for CVD proven or a myth?

Chelation therapy, the intravenous infusion of ethylenediaminetetraacetic acid (EDTA), was first recognized as a treatment for lead toxicity in the 1950s.\(^2\) Later that decade, Clarke and colleagues made the association between EDTA and the dissolution of metastatic calcium when a patient with nephrocalcinosis treated with EDTA had radiographic improvement in kidney stone burden.\(^3\) This observation, coupled with observations that calcium and cholesterol are components of atherosclerotic plaques, led investigators to hypothesize that EDTA chelation therapy could dissolve calcium-forming plaques and, therefore, treat cardiovascular disease.\(^4,5\)

In subsequent years, two controlled clinical trials were conducted to look at this question, but each found no difference between placebo and EDTA therapy for the treatment of CVD.\(^6,7\) This is in contrast to many case reports and three open-label studies, which described improvement in the signs and symptoms of CVD.\(^5,8,9\) In addition, there was one meta-analysis of uncontrolled trials and unpublished data that concluded chelation therapy was effective at improving CVD symptoms in more than 80 percent of cases.\(^10\) These positive studies were criticized for their small sample sizes, open-label designs, and the use of qualitative, rather than quantitative, endpoints.\(^5\)

More recently, there have been multiple systematic reviews of the literature on this topic. A literature review by Grier and Meyers looked at 16 case reports or case series, two longitudinal studies, three clinical trials, and 19 book testimonials.\(^11\) The authors concluded that there was little valid scientific evidence to support the use of chelation therapy for the treatment of CVD. Moreover, they believed that the best evidence showed it to be ineffective.\(^11\) A systematic review by Villarruz and
colleagues analyzed five randomized, controlled trials of EDTA chelation therapy in patients with atherosclerotic CVD. The authors found that four of the five studies showed no significant difference in direct or indirect measurement of disease severity and subjective measures of improvement. They concluded that there was insufficient evidence to decide on the effectiveness of chelation therapy based on the available evidence. Three other systematic reviews of clinical trials concluded that chelation therapy is not supported by evidence.

Despite the paucity of evidence for EDTA therapy and its as yet undefined risks, chelation therapy grew in popularity, from 66,000 treatments in 2002 to 110,000 in 2007. Treatments cost between $75 and $125 per session, and most patients undergo dozens of treatments over several months. Therefore, one complete treatment course can cost in excess of $5,000. Most often, patients incur the full cost of treatment, as health insurance typically does not cover EDTA therapy. Nationally, the estimated out-of-pocket costs for EDTA to treat CVD ranges from $400 million to $3 billion.

For these reasons, in 2003, the National Heart, Lung and Blood Institute and the National Center for Complementary and Alternative Medicine sponsored the Trial to Assess Chelation Therapy (TACT). This multicenter clinical trial of 1,708 patients with previous myocardial infarction (MI) were randomized to receive 40 infusions of chelation solution or placebo. After a median follow up of 55 months, the primary endpoint (total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina) occurred in 222 (26 percent) patients in the chelation group and 261 (30 percent) patients in the placebo group with a P value of 0.035. The most significant between-group difference involved fewer coronary revascularizations in the chelation group (15 percent) than in the placebo group (18 percent). The authors conclude that, among patients with a history of MI, the use of chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They go on to say that the results are not sufficient to support the routine use of chelation therapy for this patient population.

From the outset, this study was met with controversy. There were concerns over the credentials and capabilities of the study clinical sites. Many were described as complementary and alternative medicine clinics known to offer a variety of unproven therapies to patients, perhaps undermining their ability to perform a high-quality study. Ethical issues also arose around the informed consent process for study participants, resulting in an investigation by the Office for Human Research Protections. Additionally, there were multiple concerns with the fundamental study design and implementation. For example, 18 percent of the original study population was lost to follow-up, with significantly more patients withdrawing from the placebo group than the chelation group. This unexpected finding has led some to believe that there was unmasking of treatment assignments. Another frequently cited limitation of the trial was its use of two less objective and reliable endpoints — coronary revascularization and hospitalization from angina — in the primary composite outcome.

Taken together, the evidence for chelation therapy as a treatment for CVD, from the 1950s through present day, is inconclusive at best. The majority of studies conducted with scientific rigor have concluded that chelation therapy is not supported by evidence and many of the studies supporting the treatment are fraught with criticisms. Indeed, the Journal of the American Medical Association editors conclude that the TACT trial findings do not support the routine use of chelation therapy as secondary prevention for patients with MI. Chelation therapy has long been controversial, but given the current state of the evidence, the myth is busted that chelation therapy is a proven treatment for CVD.

Disclosure statement: Dr. Kelly has no disclosures to report. Dr. Hemphill received a clinical research grant as a principal investigator from Regeneron/Sanofi and Ionis Pharmaceuticals. She received honorarium from Aegerion.

References are listed on page 35.
Coconut oil consumption is rapidly increasing. This increase is in part because of supposed health benefits, including relieving mental fatigue and depression, altering risk factors of cardiovascular disease, and modifying cognition. Despite limited evidence for these purported benefits, consumption and therefore demand in the food industry is rising.

To better delineate the potential for coconut oil to modify cardiovascular disease (CVD) risk factors, including serum cholesterol, it is important to understand coconut oil composition. Coconut oil is primarily composed of saturated fat (92 percent) and, therefore, is solid at room temperature. Because of its high saturated fat content, coconut oil has a long shelf life. This makes coconut oil attractive in food processing and the baking industry.

While it is tempting to classify fats by saturation status (e.g. saturated fat, monounsaturated fat), fatty acid chain length also is important. Saturated fatty acids in coconut oil is mostly lauric acid (12:0) at 45 to 56 percent, myristic acid (14:0) at 16 to 21 percent, and palmitic acid (16:0) at 7.5 to 10.2 percent. Because the saturated fat in coconut oil is largely composed of the medium-chain triglyceride (MCT) 12:0, this differentiates coconut oil from other saturated fat food sources, such as lard and beef tallow. These MCTs, which are made up of fatty acids that are six, eight, 10, or 12 carbons in length (6:0, 8:0, 10:0, and 12:0, respectively), are transported directly from the intestinal tract through the portal vein to the liver and primarily are used as an immediate source of energy. This is considered beneficial as a higher rate of fatty acid oxidation in the liver is thought to reduce the accumulation of lipid in adipocytes.

When delineating the impact of coconut oil consumption on cardiovascular health, one also must consider how coconut oil is extracted and processed. Coconut oil can be largely unprocessed (virgin coconut oil) or processed (refined coconut oil). The Asian and Pacific Coconut Community (APCC) sets standards for virgin coconut oil (VCO). VCO must come from fresh, mature coconuts, and must not have undergone chemical refining, bleaching, or deodorizing. On the contrary, conventional or refined coconut oil widely used in the food and supplement industry is made from dried coconut — otherwise known as “copra” — that is cooked, bleached, and has had chemicals added. It is possible...
that the polyphenol/antioxidant content in virgin coconut oil may provide health benefits not seen in refined coconut oil; the specific type of coconut oil used in trials must be considered when determining the impact of coconut oil on cardiovascular health.

Evidence that coconut oil is beneficial in treating or preventing CVD is limited. In 2014, the Academy of Nutrition and Dietetics position paper on dietary fatty acids concluded that coconut oil is not currently recommended for consumption and that additional peer-reviewed literature is needed before any statements about its health benefits are made. In a recent comprehensive review of 15 randomized controlled trials (RCTs) in humans, the authors concluded that coconut oil consumption increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), and that removing coconut oil from the diet reduced total cholesterol and LDL-C with variable effects on HDL-C. The specific type of coconut oil used in these trials is not known.

As coconut oil is primarily saturated fat, research delineating the impact of saturated fat on risk factors for CVD is relevant. A recent Cochrane Review of 15 RCTs of 59,000 participants reported that decreased saturated fatty acid intake led to a 17-percent reduction in CVD risk. The 2015 Dietary Guideline Advisory Committee reported saturated fat as a “nutrient of concern” in the U.S. and recommends an intake of less than 10 percent of total daily calories. The NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 2 supports a cardioprotective eating pattern that includes <7% energy from saturated fat, with minimal intake of trans fatty acids to lower atherogenic cholesterol (LDL-C and non-HDL-C).” Strength A, Moderate Quality Evidence. Unsaturated fats can be used to partially replace saturated fats and proteins, as long as the goal of getting <7 percent of energy from saturated fat is met.

It is important to note that some extrapolate the health benefits of MCTs to coconut oil itself. However, most studies that have reported the impact of MCTs on health outcomes have used or reported on the benefits of 8:0 and 10:0. Therefore, the results of these studies cannot be extrapolated to consumption of coconut oil itself, because a majority of its MCTs are 12:0.

With a majority of the population over-consuming saturated fats and the evidence linking saturated fats and heart disease, it is prudent to consider avoiding the addition of food products, including coconut oil, that add saturated fat to the diet. Additional research is needed to identify whether particular fatty acids or other components in coconut oil may provide beneficial effects on serum cholesterol levels and cardiovascular health.

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References are listed on page 36.
Specialty Corner:
Nutrition Recommendations and Disorders of Lipid Metabolism: Untangling the Confusion among Consumers and Healthcare Providers

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There is an impressive portfolio of evidence-based dietary recommendations for cardiovascular disease (CVD) risk reduction, including those from the American Heart Association/American College of Cardiology (AHA/ACC)¹ and the National Lipid Association (NLA),² and for health promotion (2015–2020 Dietary Guidelines for Americans – DGAs).³ Despite evidence-based recommendations, there are ongoing controversies about diet and disease that pervade both the popular media and scientific literature. This reflects some combination of a lack of understanding, bias, political agendas, and different interpretations of the evidence. At the core of this confusion is the question of what foods and nutrients are cardioprotective and which ones increase CVD risk. This article will discuss some of the more controversial and confusing dietary recommendations and research that relate to the treatment of lipid metabolism disorders. As NLA members are well aware, it is important that these controversies be quelled for optimal management of patients with dyslipidemia.

The benefits of good nutritional practices across all stages of life are indisputable. They are especially important for about half of all American adults — 117 million people who have at least one preventable, chronic disease related to poor dietary patterns and physical inactivity.

The 2015–2020 DGAs (Table 1) issued recommendations, including healthy eating patterns and regular physical activity, to help people achieve and maintain good health and reduce the risk of chronic disease at any age.

Justification for and Controversy about the Nutrients to Limit

Added Sugars and CVD Risk
Sugars are either added during food processing or are packaged as such. They include monosaccharides disaccharides, syrups, naturally occurring sugars isolated from a whole food and concentrated so sugar is the primary component (e.g., fruit juice concentrates), and other caloric sweeteners.

A majority of intervention and observational studies reviewed by the Dietary Guidelines Advisory Committee (DGAC), the
committee that provided recommendations for the DGAs (Scientific Report 2015) reported evidence among adults of an association between the higher intake of added sugars — especially in the form of sugar-sweetened beverages — and an increased risk of CVD — including hypertension, stroke, and CHD mortality — or increased CVD risk factors, including triglycerides and high blood pressure.

The 2015–2020 DGAs recommend that people get less than 10 percent of their calories from added sugars. The World Health Organization (WHO) issued a similar recommendation that both adults and children consume less than 10 percent of calories from added sugars. It is clear that consuming the added sugars found in nutrient-poor foods and beverages (i.e., sugar-sweetened beverages) is not advised. Research is needed, however, to evaluate the effects of added sugar intake on CVD risk factors, including body weight changes with varying nutrient profiles and food matrices for added sugars. One question that remains to be answered is whether added sugars promote consumption of nutrient-dense foods that otherwise would not be consumed (e.g., flavored non-fat or low-fat milk and yogurt for children to increase calcium consumption), and, if so, is this better than not consuming the healthy foods without sugar?

**Saturated Fat and Risk of CVD**

There is strong evidence that the intake of saturated fatty acids is positively associated with intermediate and end-point health outcomes for: 1) increased total cholesterol, increased low-density lipoprotein cholesterol (LDL-C), and increased risk of CVD; and 2) increased markers of insulin resistance (IR) and increased risk of type 2 diabetes. The DGA, AHA/ACC, NLA, and Cochrane Review all recommend decreasing saturated fat to decrease both LDL-C and the risk of CVD. Controversy has arisen from some epidemiologic studies that concluded that saturated fat and dietary carbohydrates have similar associations for CVD risk. These studies have led to the conclusion that saturated fat does not increase CVD risk. In contrast, based on a large evidence base, when saturated fat is replaced with unsaturated fat (especially polyunsaturated fat), the risk of CVD decreases. One recent analysis of both the Nurses’ Health Study and Health Professionals Follow-up Study reported that substituting unsaturated fats — both polyunsaturated and monounsaturated fats from plant sources — as well as high-quality carbohydrates (from whole grains) for saturated fat lowered CHD risk. Thus, current epidemiologic evidence shows the benefits of replacing saturated fat with unsaturated fat and carbohydrates from whole grains. Moreover, there is strong evidence that saturated fat should be reduced to lower LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C), both of which are atherogenic lipoprotein particles. The AHA/ACC recommends that a person get from 5 to 6 percent of calories from saturated fat and the NLA recommends that less than 7 percent of calories come from saturated fat.

**Dietary Cholesterol and Risk of CVD**

The DGAs and the Institute of Medicine recommend that people eat as little dietary cholesterol as possible while following a healthy eating pattern. There is evidence (rated Grade B, moderate level of evidence) to support the NLA’s recommendation to limit dietary cholesterol to less than 200mg a day to lower LDL-C and non-HDL-C.

The AHA/ACC Lifestyle Guideline did not recommend limiting dietary cholesterol. The DGAs conclude this does not mean that dietary cholesterol is not important for building a healthy eating pattern.

A recent systematic review and meta-analysis of studies on dietary cholesterol...
and CVD concluded that the effects of dietary cholesterol on incident coronary artery disease (CAD) and serum cholesterol outcomes remain unclear. However, the review states intervention trials have shown a significant increase in TC, LDL-C, and HDL-C when comparing doses of dietary cholesterol (500–900 mg/d). In an American Journal of Clinical Nutrition editorial titled “Eggs and beyond: Is dietary cholesterol no longer important?” Robert Eckel, MD, writes that an “increase in HDL-cholesterol with increases in dietary cholesterol is very similar to the effect of saturated fat on HDL-cholesterol and should not be inferred as neutralizing. In general, we live in an age wherein increases in HDL-cholesterol should be interpreted cautiously in comparison to changes in LDL-cholesterol.

In summary, the lack of a dietary cholesterol recommendation in the recently released guidelines is controversial. This should not be interrupted as an affirmation to ignore dietary cholesterol because there is clear evidence that it does increase LDL-C and non-HDL-C, especially in hyper-responders, who represent about 30 percent of the U.S. population.

Sodium and Cardiovascular Disease Risk
There is consistent agreement that adults who would benefit from lowering their blood pressure should decrease sodium intake. DGAC 2015 concurred with AHA/ACC that adults who would benefit from lowering their blood pressure should “lower sodium intake.”

The 2015 DGAC also agreed there is strong evidence that adults who would benefit from lowering their blood pressure should “consume no more than 2,400 mg of sodium/day.” The question is whether lowering sodium intake also decreases CVD events. In summary, the evidence that sodium increases blood pressure is strong. One question that remains to be addressed is: If sodium is reduced to less than 2,300 mg/day or less than 1,500 mg/day, is there an adverse outcome?

Conclusions
As long as dietary guidelines are issued, there likely will be controversy over some of the recommendations or lack thereof. It behooves the scientific community to support current guidelines based on robust evidence and to implement them in practice to reduce patients’ risk of CVD. Failure to do this, especially because of the criticisms of a “vocal few,” is a disservice to science, evidence analysis and patient care.

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References are listed on page 36.
Structure, Function, Dietary Sources

Trans fatty acids (TFAs) are industrially produced during the partial hydrogenation of vegetable oils and they contain at least one double bond in the trans configuration. Smaller amounts are found naturally in meat and dairy products as a result of bacterial fermentation in ruminant animals. Partial hydrogenation of vegetable oil increases its stability for commercial deep-frying, prolongs product shelf life, and improves the mouth feel, palatability, and texture for many fried and baked foods. Increased risk of cardiovascular disease (CVD) associated with saturated fat — the predominant fat in butter — and increased cholesterol levels, and food manufacturers sought to find healthier alternatives. In the following decade, studies began to demonstrate a negative relationship between TFAs and coronary heart disease (CHD). Evidence Regarding Health Implications

A growing body of research has provided substantial evidence that consumption of industrially produced TFAs is associated with increased CHD risk and adverse changes in several cardiometabolic markers. Although the negative effects of TFAs tend to be most prominent when TFAs are compared to cis-unsaturated fats, analogous effects have been observed when compared with saturated fatty acids (SFAs). The question of whether CHD risk related to industrial TFA consumption extends to ruminant sources of TFAs is unresolved. However, several studies note that the amount of ruminant TFA consumed in most diets is too low to have detectable effects.

Studies evaluating the relationship between TFA consumption and CHD risk have been considerable. The Nurses’ Health Study, which follows more than 85,000 women, noted a relative risk (RR) of 1.33 for CHD between the highest and lowest quintiles of TFA intake (a 1.5 percent energy difference), which was
especially pronounced in younger women. Likewise, a meta-analysis of approximately 140,000 people found a 23-percent increase in CHD incidence when TFAs were substituted for 2 percent energy from carbohydrates.

A key meta-analysis of controlled trials showed that, when TFAs replace carbohydrates as an energy source, low-density lipoprotein cholesterol (LDL-C) rises while high-density lipoprotein cholesterol (HDL-C) does not. That, in turn, increases the serum total cholesterol to HDL-C ratio (Figure). Subsequent research demonstrated similar findings and further showed that TFAs increased apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)] levels while lowering LDL-C and apolipoprotein A-1 (apo A-1) levels even when compared to SFAs. Other studies have suggested TFAs can be pro-inflammatory and associated with endothelial dysfunction when compared with SFAs. Controlled and observational studies also have linked TFAs to worsened insulin resistance, especially in predisposed individuals. Indeed, one study of about 84,000 women followed over 16 years reported a 40-percent increased risk of diabetes — after adjustment for other risk factors — for women who consumed the most compared to the least TFAs. Nonetheless, further research is needed before definitive, or cause-and-effect, relationships can be concluded.

Regulations

The U.S. Food and Drug Administration (FDA) required in January 2006 that manufacturers list the amount of TFAs per serving on the Nutrition Facts panel of packaged foods. Products containing <0.5 grams trans fat per serving could be labeled as 0 grams trans fat, despite the fact that the words “partially hydrogenated” may appear in the list of ingredients. A decline in the consumption of TFAs resulted as food manufacturers worked to reformulate products, however, evidence on current levels of trans fats in foods is limited. A recent analysis of more than 4,000 packaged foods showed that almost 1 in 10 products contained PHOs and 84 percent of those labeled as containing 0 grams per serving contained TFAs. In June 2015, the FDA determined that TFAs are not “generally recognized as safe” for consumption and gave manufacturers a three-year period in which to remove them from all commercially prepared foods.

Recommendations and Conclusions

The American Heart Association (AHA) recommends limiting trans fats to <1 percent and saturated fat between 5 to 6 percent of total calories; based on a 2,000-calorie diet that is equivalent to a daily intake of about 2 grams and 12 grams, respectively. Trans fats became more widely used as a strategy for replacing saturated fat in the diet. Studies have shown, however, that trans fats are far more detrimental compared to saturated fat in regard to cardiovascular health. Using butter as a substitute for margarine is not advised because butter is almost 70 percent saturated and contains 7.5 grams saturated fat per tablespoon.

The following are recommended dietary strategies to reduce TFAs:

- Use any unsaturated vegetable oil such as canola, safflower, sunflower, or olive oil most often; dip a pastry brush in oil and use as a spread;
- Choose a liquid or soft, reformulated tub of margarine over harder stick forms (Table);
- Look for “0 grams trans fat” on the nutrition label and the absence of hydrogenated oils in the ingredient list;
- Limit consumption of commercially fried and baked goods.

Although the average dietary intake of industrially produced TFAs in the U.S. has declined, many people are likely eating amounts in excess of the recommendations because of current labeling laws. Since
the FDA has ruled that trans fats are not “generally recognized as safe” they should be eliminated from the food supply in the coming years. Individuals with dyslipidemia should not go back to using stick butter since it is higher in saturated fat than many tub margarine spreads or vegetable oils in today’s market. The use of even a small amount of butter is unlikely to fit into a dietary pattern that meets the current AHA guidelines for saturated fat.

Disclosure statement: Frances Burke has no disclosures to report. Lauren Kelley-Chew has no disclosures to report.

References are listed on page 36.

Table: Examples of Tub Spreads containing < 2 grams of saturated fat and no partially hydrogenated oils per tablespoon

<table>
<thead>
<tr>
<th>Tubs</th>
<th>Calories</th>
<th>Saturated fat (g)</th>
<th>Trans fat (g)</th>
</tr>
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<tr>
<td>I Can’t Believe It’s Not Butter Light</td>
<td>40</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>I Can’t Believe It’s Not Butter Original</td>
<td>60</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Country Crock Original</td>
<td>50</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Brummel &amp; Brown</td>
<td>45</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Promise</td>
<td>80</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Promise Light</td>
<td>45</td>
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</tr>
<tr>
<td>Olivio</td>
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<td>1.5</td>
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<tr>
<td>Olivio Light</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Smart Balance Light</td>
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<td>0</td>
</tr>
<tr>
<td>Land O Lakes Light Butter with Canola Oil</td>
<td>50</td>
<td>2.0</td>
<td>0</td>
</tr>
</tbody>
</table>

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The intent of this article is to review the over-the-counter (OTC) products and dietary supplements that have proven effective on cholesterol levels. There is little direct evidence of how these supplements affect cardiovascular outcomes. Additionally, the dosage forms, recommended daily dosage, and content of these products often vary among manufacturers.

OTC medications differ from dietary supplements in terms of their U.S. Food and Drug Administration (FDA) regulatory requirements. The FDA review of all available OTC drugs is completed by the Center for Drug Evaluation’s Office of Drug Evaluation IV. OTC medications are developed under the OTC Monograph Process or through the New Drug Application (NDA) Process. Any company or sponsor seeking to market or produce their product for OTC sale applies to the Division of Nonprescription Drug Products (DNDP) in the Office of Drug Evaluation IV. The DNDP reviews consumer studies and post-marketing safety data, as well as original efficacy data, drug development, labeling, and any regulatory issues. The DNDP also is responsible for the development of OTC drug monographs. Any other supplementary information or reviews needed may be acquired from additional disciplines or divisions within the Office of New Drugs.1

Many products are considered dietary supplements and, unlike OTC medications, the FDA does not regulate them. They also aren’t required to go through any type of drug approval process. Any company or sponsor, prior to marketing a dietary supplement, is required to confirm that their product — whether manufactured or distributed — is safe, any claims made about the product are not false or misleading, and the product complies with the Federal Food, Drug and Cosmetic Act and FDA regulations in all other respects.2

The focus of this review will be limited to some of the available OTC products and dietary supplements that have proven beneficial in lowering serum cholesterol levels. The following products may be considered as an adjunct or, in some cases, a supplement to conventional pharmacotherapy.

Artichoke Leaf Extract
Artichoke leaf extract (ALE) has key active components, including caffeoylquinic acids, flavonoids, and bitters that have been studied and proposed to have both
hypocholesterolemic and antioxidant properties. The proposed mechanism of action is similar to statins. The mechanism of action is suggestive of a reduction in intrinsic cholesterol synthesis through HMG CoA reductase inhibition, LDL-C oxidation inhibition, and increased elimination of cholesterol through bile secretions. A study conducted in Germany in the 1990s consisted of 143 patients with LDL-C levels greater than 280 mg/dL who were randomized into two groups taking either 1,800 mg of dry artichoke extract daily or a placebo. After a six-week treatment period, they found that patients taking artichoke extract had significant reduction in total cholesterol (18.5 percent) compared to the placebo group (8.6 percent) and LDL-C reduction in patients taking artichoke extract (22.9 percent) compared to the placebo group (6.3 percent). Other recent studies have had conflicting data and do not reproduce results. There is weak supporting information to make a recommendation for use or against use of artichoke leaf extract for the use of hyperlipidemia.

Coenzyme Q10
Coenzyme Q10, also known as CoQ10 and ubiquinone, is a naturally synthesized compound found in the body, concentrated in mitochondria. CoQ10 synthesis is inhibited by statins. Its proposed mechanism includes antioxidant properties on LDL-C as well as energy generation as a player in the electron transport chain within the mitochondria. It is often taken in conjunction with statins to reduce CoQ10 deficiency and decrease risk of myalgia. Few studies have been conducted with CoQ10 as monotherapy for cholesterol reduction. A 2003 study compared the effects of CoQ10 120 mg daily vs. vitamin B in 144 subjects post-MI and found no difference in reductions in total cholesterol or LDL-C. In addition, the CoQ10 treatment group had a statistically significant increase in HDL-C levels.

Another study examined the effects of adding CoQ10 100 mg daily or placebo to atorvastatin 10 mg daily — and there are no differences in total cholesterol, LDL-C, HDL-C, or TGs after 12 weeks. There was a statistically significant difference in mean level of plasma total CoQ10 with the CoQ10 treatment group (+127 percent) compared to 42 percent reduction in the placebo group.

There have been several additional studies that have tried to demonstrate supplementation effects of CoQ10 but have been unsubstantial due to insufficient doses of CoQ10, short treatment periods, as well as a small number of study participants. Although there are disputable results of previous studies for monotherapy of CoQ10, there is a role for CoQ10 supplementation to enable better tolerability of statin therapy.

Fiber
Fiber can be classified as insoluble and soluble. The proposed mechanism of soluble fiber for reduction in LDL-C and total cholesterol is thought to be through a reduced glycemic response that produces reduced insulin stimulation of hepatic cholesterol synthesis and prevents the resorption of bile salts from the small intestine, resulting in increased excretion of bile salts. Soluble fibers include psyllium, oats, flaxseed, and barley. Fenugreek is a spice, naturally found in seed form, which is used as a source of soluble fiber supplementation. There are a number of studies demonstrating the effects of fenugreek, but some have shown total cholesterol reduction of 14 percent, LDL-C reduction of 15 percent, TG reduction of 15 percent, and HDL-C increase of 10 percent.

A 1999 meta-analysis included 67 clinical trials concluded that diets with a high intake of soluble fiber were associated with a 60 to 70 percent reduction in total cholesterol, as well as a reduction in LDL-C levels, though no percentage was provided for the LDL-C reduction. Practical application of these results is limited because of the amount of soluble fiber ingested per patient. The analysis suggested that the daily intake of 3 gram of soluble fiber would decrease total cholesterol approximately 2 percent. The U.S. Department of Agriculture recommends a daily intake of approximately 25 grams to 35 grams of soluble fiber.

In a recent review of dietary supplements, a pooled analysis of 10 cohort studies observed that each 10 gram per day increase in dietary fiber correlated with a 12 percent reduction in the risk of coronary events and a 19 percent reduction in the risk of coronary deaths. An additional meta-analysis found a small but significant 7 percent reduction in LDL-C with the daily ingestion of 2 grams to 10 grams of soluble fiber. While a range of LDL-C and total cholesterol reductions and CV morbidity/mortality response has been reported, it is recommended by the U.S. Department of Health and Human Sciences that patients should have a daily intake of at least 5 grams to 10 grams of soluble fiber either incorporated into foods or taken as an additional supplement.

Flaxseed
Flaxseed has been identified as a plant-source alternative to omega-3 polyunsaturated fatty acids (PUFAs), better known as fish oil. Flaxseed oil is largely composed of acid alpha-linolenic acid (ALA), which can be converted to docosahexanoic acid (DHA) and eicosapentanoic acid (EPA). Flaxseed oil’s mechanism of cholesterol reduction is not well understood but may include the inhibition of acyl coenzyme A (CoA)-1,2 diacylglycerol acyltransferase (DGAT), enhanced plasma lipoprotein lipase activity, decreased lipogenesis in the liver,
and increased beta-oxidation activity in mitochondria and peroxisomes in the liver.\textsuperscript{10} In a study of 62 patients published by the \textit{Journal of the American College of Nutrition},\textsuperscript{13} they enrolled patients with LDL-C levels between 130mg/dL and 200mg/dL that received either 40 grams of flaxseed-containing baked products daily or matching wheat bran products for 10 weeks in addition to a low-fat, low-cholesterol diet. There was a significant decrease (13 percent) in LDL-C levels of the flaxseed treatment group at five weeks but not significant (7 percent) at 10 weeks. They also found that HDL-C levels were significantly reduced at both five weeks (16 percent) and 10 weeks (9 percent).

There are inconsistent results from other similar studies\textsuperscript{15} that raise questions about the supplement’s ability to lower serum cholesterol. Flaxseed is considered a source of soluble fiber and a supplement with at least 5 grams to 10 grams daily is recommended for risk reduction in coronary events and modest reductions in cholesterol levels.

### Fish Oil/Omega-3 Fatty Acids

Fish oil, or omega-3 fatty acid, has been studied for its triglyceride-reduction ability. Omega-3 fatty acids are largely composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There are several prescription products and multiple OTC supplements available. The mechanism of action is believed to include the inhibition of acyl coenzyme A (CoA)-1,2 diacylglycerol acyltransferase (DGAT), enhanced plasma lipoprotein lipase activity, decreased lipogenesis in the liver, and increased beta-oxidation activity in mitochondria and peroxisomes in the liver.\textsuperscript{16} It has also been hypothesized to have antiplatelet and anti-inflammatory properties.\textsuperscript{17} There have been many studies demonstrating fish oil’s effect on cholesterol levels. A review of 65 studies was published in the \textit{American Journal of Clinical Nutrition},\textsuperscript{18} concluding that approximately 4 grams of omega-3 fatty acids results in triglyceride reduction of 25 to 30 percent, HDL-C increase of 1 to 3 percent, no change in total cholesterol levels, and an LDL-C increase of 5 to 10 percent.

There is a wide variety of quality and EPA/DHA content between OTC fish oil supplements. Individual patients should have a clear indication for intended use and expectations when selecting their product. Omega-3 fatty acid supplementation is generally recommended as a treatment option for the subset of patients with hypertriglyceridemia, as results have shown a maximum benefit in triglyceride reduction. In patients with mixed dyslipidemia, omega-3 fatty acids may be used in addition to other therapy or supplements that have superior effects of other lipid panel values, such as total cholesterol, HDL-C, and LDL-C.

### Garlic

Garlic has often been considered an herbal treatment for high blood pressure, but also has been studied for its cholesterol reduction. It is believed to reduce cholesterol by inhibiting enzymes involved in lipid synthesis, increasing antioxidant properties within the body, decreasing platelet aggregation, and preventing lipid peroxidation of LDL and erythrocytes.\textsuperscript{16,19} In 2010, the U.S. Department of Health and Human Services released a report\textsuperscript{20} stating garlic produced small, short-term (approximately three months) reductions in both LDL-C and total cholesterol. A study\textsuperscript{21} of 192 patients with LDL-C levels ranging from 130mg/dL to 190mg/dL. Participants were assigned to one of four possible treatment groups receiving: raw garlic, a powdered garlic supplement, an aged garlic extract supplement, or a placebo. They concluded that none of the garlic supplements had any significant effect on LDL-C, HDL-C, total cholesterol, or triglycerides after six months. There is concern regarding the bioavailability of garlic, the potency of its active ingredient, and the variety of dosage forms available. Based on the lack of any significant evidence, it appears that garlic has little to no effect on cholesterol levels and should not be recommended for use.

### Ginseng

Ginseng is available in a variety of dosage forms, depending on the ginseng plant used. A majority of clinical studies involve the \textit{Panax} species; this species contains ginsenosides or glycosides, which are thought to be the main active cholesterol-lowering component in ginseng. Studies have shown more than 30 ginsenosides exist in ginseng, along with fatty acids, peptides, and polysaccharides. It is believed to reduce cholesterol by inhibiting carbohydrate absorption in the intestines and results in proliferation of peroxisome-activated receptors. Buettner, et al\textsuperscript{22} reviewed six clinical trials of ginseng’s effects on cholesterol levels and found the results were inconsistent, with total cholesterol levels ranging from a 29-percent reduction to a 7-percent increase, LDL-C levels ranging from a 45-percent reduction to an 11-percent increase, and triglyceride levels ranging from a 24-percent reduction to a 10.5-percent increase. The authors concluded that there were insufficient well-designed, randomized, controlled studies to make any recommendations for the use of ginseng in cholesterol reduction.

### Guggul

Guggul is an extract collected from mukul myrrh tree (\textit{Commiphora mukul}) resin. It has been postulated that E-guggulsterone and Z-guggulsterone are present within the extract. Research has shown that guggulsterones have inhibitive activity against the bile acid receptor and farnesoid X receptor (FXR) involved with cholesterol metabolism and bile acid regulation.\textsuperscript{10} Szapary, et al\textsuperscript{23} demonstrated that
Standard- and high-dose guggul resulted in a 4- and 5-percent increase in LDL-C levels, respectively, with no significant changes in total cholesterol, HDL-C, or TG levels after eight weeks. It appears that guggul has no benefit in lowering cholesterol and should not be recommended for use.

Availability
All of the dietary supplements discussed above can be found in various dosage formulations, produced from numerous manufacturers, and available from quite a few drug stores or herbal/dietary market stores. Using the database Natural Medicines, Table 1 represents some of the various dosage forms available and the common daily-dosing regimens.

<table>
<thead>
<tr>
<th>Product</th>
<th>Available Dosage Forms</th>
<th>Common Daily Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artichoke Leaf Extract</td>
<td>Dried leaves, liquid extract</td>
<td>320 mg – 1,800 mg daily</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Soft gel capsule, tablet</td>
<td>100 mg daily – twice daily</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Powder, capsule, liquid extract</td>
<td>2.5 gm – 25 gm daily</td>
</tr>
<tr>
<td>Fiber</td>
<td>Powder, capsule, tablet</td>
<td>Recommended oral intake including diet: 20 gm – 35 gm daily</td>
</tr>
<tr>
<td>Flaxseed</td>
<td>Crushed seeds/ powder, capsule, liquid extract</td>
<td>Recommended oral intake including diet: 20 gm – 50 gm daily</td>
</tr>
<tr>
<td>Garlic</td>
<td>Powder, tablet, liquid extract</td>
<td>1 gm – 4 gm daily</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Dried root, capsule, tablet, liquid extract</td>
<td>200 mg – 9,000 mg daily</td>
</tr>
<tr>
<td>Guggul</td>
<td>Tablet, liquid extract</td>
<td>50 mg – 1,500 mg daily</td>
</tr>
<tr>
<td>Omega-3 fatty acids (fish oil)</td>
<td>Gel capsule</td>
<td>1 gm – 6 gm daily</td>
</tr>
</tbody>
</table>

Table 1.

Conclusion
There are a number of OTC dietary supplements studied for their cholesterol-lowering effects. Artichoke leaf extract, fenugreek, and ginseng supplements have inadequate data supporting efficacy. Both garlic and guggul supplements have been shown to have no beneficial effect on cholesterol-lowering. Coenzyme Q10, fiber, flaxseed, omega-3 fatty acids, and red yeast rice products all have data that support their use as dietary supplements. Consumers should thoroughly review the available ingredients and contents and inform their healthcare provider before using any of these supplements.

Acknowledgement: Dr. Kellick would like to acknowledge the tremendous work of co-author Erin Conway for putting together this article.

Disclosure statement: Dr. Kellick has no disclosures to report. Dr. Conway has no disclosures to report.

References are listed on page 36.
It is a real privilege to serve as the president of the Northeast Lipid Association (NELA). Part of that privilege is having a bird’s eye view of all of the wonderful things the NELA membership is doing. As the president, I feel that my main contributions have been to provide a word of encouragement here or a suggestion there. Overall, however, the success of the NELA chapter is really a testament to the amazing NELA membership — which is not only constantly brimming with new ideas, but also the energy to accomplish them.

One new idea that the NELA chapter is implementing this year is the NELA Travel Reimbursement Scholarship. This scholarship is designed to help provide financial assistance to NELA members that want to attend a National Lipid Association meeting but are unable to attend due to travel cost. Applications for the scholarship are submitted online for the NELA Board of Directors to approve. The goal is for these NELA members to attend the meeting and become involved with the NELA chapter. Two successful applications have already been approved by the NELA Board. The NELA chapter is always looking for opportunities and new ways to help its members get involved.

Kenneth Kellick, PharmD, FNLA, is currently working with the NLA staff to develop a NELA webinar program. This will allow members who cannot attend meetings the ability to receive the same high quality information and CME credit remotely. This is all about seeing and meeting the needs of our membership.

In addition, you can read about Wenliang Song, MD’s, very successful efforts to reach out to trainees in the Member Spotlight on Page 30. He conceived and executed this project, with the blessing of leadership, all on his own. This outreach is all about extending our impact and building for the future.

NELA is happy to endorse educational programs developed by our members for their peers. These include the NYU Langone Cardiovascular Risk Courses (“Dietary Strategies for Cardiovascular Risk Reduction” and “Advances in Cardiovascular Risk Reduction”) that will be offered this May, as well as Merle Myerson, MD, FNLA’s, New York Clinical Lipid Forum. Finally, on the local lipid club front, the Philadelphia Lipid Atherosclerosis Club (PLAC) has merged with the Cardiovascular Institute and will broaden its scope to include primary care cardiometabolic meetings as well as the “hard core” lipid meetings.

I am sure I echo the feelings of my predecessors in this position in saying this year is going by way too fast and there are no people like lipid people!
Wenliang Song, MD, is a third-year internal medicine resident at Bridgeport Hospital of Yale University. He has been a very active young member of the National Lipid Association (NLA). He is on the NELA Membership Committee and the Early Career Development Committee. Dr. Song recently took the initiative to promote awareness of the NLA through a “bottom up” strategy. He introduced the NLA to his residency program and received an extraordinary response. Inspired by that, he built an email database of program directors and coordinators from internal medicine residencies and endocrinology and cardiology fellowship programs of NELA. On behalf of NELA and the Early Career Development Committee, he sent trainees information on NLA activities and various resources available to them. This enabled enrollment of many trainees at the 2015 Fall Lipid Academy in Pittsburgh, Pa. He has been working to replicate that success at the national level and is now actively involved in activities of the national Early Career Development Committee.

Dr. Song has an atypical professional path. He was born, raised, and educated in China. He followed the footsteps of his two elder brothers — both renowned biomedical researchers — to the U.S., and has long decided to commit himself to a career in academic medicine. After graduating from Shandong University Medical School in China, he joined Garret A. FitzGerald, MD’s, group at the University of Pennsylvania as a postdoctoral fellow. Dr. FitzGerald’s group is one of the leading programs in cardiovascular (Penn) research in the world, where basic and clinical research are intertwined and where trainees and other researchers are encouraged to take a translational approach to address questions of clinical relevance. His training experience in the FitzGerald lab was broad — he performed basic lab research in cardiovascular medicine for a number of years, followed by patient-oriented translational research training through a NIH KL2 physician scientist master degree program. He participated in several general and clinical research center-sponsored clinical studies; some of which he designed and served as the principal investigator. He obtained extramural funding from national organizations, such as the American Heart Association (AHA) as a principal investigator, and authored numerous manuscripts in high-impact journals.

His work on niacin, supported by an AHA award, was published in the Journal of Clinical Investigation. In that article, he elucidated the potential cardiovascular hazard attendant to blockade of the DP1 receptor. That highlighted questions of drug safety and effectiveness of the combination of niacin and DP1 antagonist laropiprant in a large scale outcome trial HPS2-THRIVE. His article suggested that laropiprant might have compromised niacin’s cardiovascular benefits, which led to the negative result of HPS2. Notably, his article was published in 2012, a year before the HPS2 study was concluded.
For his research accomplishments, he was promoted to a research assistant professor position at Penn. While he had the option to continue on a successful research career path, his aspiration of becoming a physician-scientist led him to the decision to refresh and expand his clinical skills through a formal U.S. residency. This decision was enthusiastically supported by Drs. Daniel Rader and Muredach Reilly who had acted as inspirational co-mentors for Dr. Song at Penn. Dr. Song developed great interests in clinical lipidology through his work on niacin and from his interaction and collaborations with Drs. Rader and Reilly. He is in the process of getting NLA lipidology board certification.

Dr. Song is excelling in his last year of residency at Bridgeport Hospital of Yale University. Between his busy clinical responsibilities as a resident, Dr. Song has continued to engage in academic research actively during residency and has generated interesting data on the effect of HDL on platelet function with John Hwa, MD, PhD, at Yale. Based on these results, he submitted a grant application to AHA, which is in revision after very encouraging initial reviews. Dr. Song has matched to and looks forward to starting a cardiology fellowship in July 2016 at Vanderbilt University, where Dr. MacRae Linton is leading a large NIH PPG grant on HDL. He is very excited to join Dr. Linton’s research team on these studies. His ultimate career goal is to become a physician-scientist with a focus on basic research in lipid disorders. Dr. Song’s other professional accomplishments and awards include: a New Investigator Award from the Council on Arteriosclerosis, Thrombosis and Vascular Biology, a travel award from a Keystone Symposium, a resident research grant from Bridgeport Hospital Foundation, the co-inventor of two novel lipid biomarker patent applications, and editorial board membership with several scientific journals.

Dr. Song is happily married to his wife Dr. Weiping Li, whom he met in medical school. They have two lovely young children, Kevin and Charles, aged 5 and 1. In his spare time, Dr. Song enjoys cooking authentic Chinese food. He would have pursued a career as a chef if not a physician.
Attend the NLA’s Fall Clinical Lipid Update
Register now for the National Lipid Association’s (NLA’s) Fall Clinical Update in Amelia Island, Fla. The 2016 Fall CLU will take place Aug. 26–28 at the Omni Amelia Island Plantation Resort. Check lipid.org/fallclu for more information and regular updates as they become available.

Shop the NLA Store and Support the Foundation
Do you want to support vital community outreach, patient education, and research surrounding the reduction of cardiovascular events and deaths related to abnormalities of cholesterol metabolism? If so, make sure to check out the new NLA Store. The NLA will donate all sale proceeds to the Foundation of the NLA in an effort to support their educational mission. The store offers shirts, polos, hats, and much more — all with the NLA logo prominently featured. Visit the store at logosoftwear.com/shareandsell/?store=nlastore.

NLA Endorses ACC Guidance for Non-Statin Therapies

A Gene Therapy Study for HoFH
Doctors at the University of Pennsylvania are conducting a gene therapy research study in adult patients with homozygous familial hypercholesterolemia (HoFH). Gene therapy is an experimental way of treating genetic conditions by placing copies of the healthy gene (in this case, the LDL receptor) into cells that contain the malfunctioning or absent gene. This is an experimental study and results have not been proven, the hope is that the healthy gene will correct the genetic mutation and result in better functioning LDL receptors. Early stage research is essential for progress toward a cure for HoFH, but researchers do not yet know if this gene therapy will work. Participants must meet clinical trial criteria. For more information, contact Dr. Marina Cuchel at mcuchel@mail.med.upenn.edu and refer to the ClinicalTrials.gov posting.

Certification in Clinical Lipidology: Summer Testing Window
The summer testing window for lipid certification will be June 5, 2016–July 16, 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, May 27, 2016! For more information regarding the ABCL requirements, visit lipidboard.org. For more information regarding the ACCL-CLS certification, visit lipidspecialist.org.

Pay Your Dues for 2016
To pay your dues online, visit lipid.org/dues. In addition to paying your 2016 dues, this is a great opportunity to donate to the Foundation of the NLA. For more information or questions regarding dues, contact Membership Manager Britney Caldwell at bcaldwell@lipid.org.

NLA Mentoring Program
The NLA is accepting applications to become mentors for our early career members. The mentoring program was established to help develop the next generation of clinical, academic, and administrative leaders in lipidology. For more information, visit lipid.org/education/trainees/mentoring or contact Amanda East at aeast@lipid.org.

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 devise. To access these activities, visit lipid.org/education/online/other.

Stay Current on NLA News by Following us on Social Media
Are you on Facebook, Twitter, LinkedIn or Instagram? If so, make sure you’re following the National Lipid Association on all of its social media accounts. Doing so will ensure that you’re staying current on all of the NLA’s latest happenings. Like us on Facebook at: facebook.com/nationallipid. Follow us on Twitter at: twitter.com/nationallipid. Follow us on LinkedIn: linkedin.com/company/national-lipid-association. Follow us on Instagram by searching the username: nationallipid.
NLA Events Calendar

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

2017 National Lipid Association
Clinical Lipid Update—Spring
Hosted by the Pacific and Southwest Chapters
February 24–26, 2017
Hyatt Regency Phoenix
Phoenix, AZ

2017 National Lipid Association
Scientific Sessions
Hosted by the Northeast Lipid Association
May 18–21, 2017
Philadelphia Marriott Downtown
Philadelphia, PA

2017 National Lipid Association
Clinical Lipid Update—Fall
Hosted by the Southeast and Midwest Chapters
August 11–13, 2017
JW Marriott Indianapolis
Indianapolis, IN

Lipid Academy
August 25–26, 2016
Amelia Island, FL

February 23–24, 2017
Phoenix, AZ

May 17–18, 2017
Philadelphia, PA

August 10–11, 2017
Indianapolis, IN

Masters in Lipidology
August 25–26, 2016
Amelia Island, FL

February 23–24, 2017
Phoenix, AZ

May 17–18, 2017
Philadelphia, PA

August 10–11, 2017
Indianapolis, IN
As we approach the half year mark of 2016, we are reminded once again of the tremendous support surrounding the Foundation of the NLA and its mission to reduce cardiovascular events and deaths through patient and clinician education. To help reach our goals, the Foundation is constantly finding new ways to get its message out and maintain interest in our charitable organization.

One way to support the Foundation is to shop the newly opened NLA store. All proceeds will be donated to the Foundation. The store offers shirts, polos, and many other items branded with the NLA logo. Show your support of the NLA and visit the store online at logosofwear.com/shareandsell/?store=nlastore.

Fundraising events continue to play a large part in the success of the Foundation. This year’s Foundation Event at the Spring Clinical Lipid Update in San Diego was a huge success with more than 40 people enjoying a murder mystery comedy dinner show designed just for our group.

The annual meeting Foundation Event will be another opportunity for NLA members and meeting attendees to enjoy a wonderful evening with colleagues and friends at the World War II Museum. The night will kick off with cocktails and private access to one of the key exhibits, exploring the Road to Berlin, and will be followed by dinner. The night will wrap up with a live showing of the Johnny Cash Experience. The event takes place Saturday, May 21 from 7:30–10:30 p.m.

The Foundation would also like to congratulate this year’s Foundation of the National Lipid Association Donald Hunninghake Familial Hypercholesterolemia Abstract Award, which is being awarded to Laney K. Jones, PharmD, MPH, for Abstract 154 titled, “Baseline Undertreatment Of Adults With Newly Diagnosed Familial Hypercholesterolemia By Genomic Sequencing Abstract.” Dr. Jones will be presenting her work Friday, May 20 from 2:00–2:10 p.m. If you are at the Scientific Sessions in New Orleans, stop by to hear her presentation.

The Foundation, along with the NLA, will be presenting the first W. Virgil Brown Distinguished Achievement Award to Joseph L. Witztum, MD, on May 21 during the Honors and Awards Ceremony in New Orleans. This award is given to only one recipient per year, and it was established to honor one of the founding fathers of the NLA, Dr. Brown, whose contributions to the field of lipidology and the NLA are unparalleled. This year’s recipient, Dr. Witztum, has worked in the field of lipoprotein metabolism and atherogenesis for almost 40 years, and currently serves as a distinguished professor of medicine at the University of California, San Diego. He has made an immeasurable impact in the field of lipidology by providing an understanding of the role of oxidized LDL and immunological mechanisms in atherogenesis.

We are looking forward to what the rest of 2016 has in store for the Foundation. It’s bound to be another great year.
References

EBM Tools for Practice

1. CDB trials. Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999-2013, as compiled from data provided by the 57 reporting areas through the Vital Statistics Cooperative Program. Accessed Feb 3, 2015.


37 of 3 years of life on edarbepride cholesterol therapy. Am J Cardiol. 2013;112(1)21-23.


SPECIALTY Corner


1.  The Truth You Need to Know About Coconut Oil. PositiveMed. Lipid Luminations


32. Dahn WM, Scanlon KS. Eliminating the use of partially hydrogenated oil in food production and preparation. JAMA. 2010;305(2):143-144.
If you and your healthcare provider have determined that you would benefit from cholesterol-lowering medication, there is a good chance that you will be prescribed a statin medication. This group of medicines, also known as “HMG-CoA reductase inhibitors,” helps prevent your liver from making many forms of cholesterol, in particular the “bad” cholesterol called “low-density lipoprotein cholesterol” or “LDL-C.”

There are currently seven different statin medications used in the U.S. The first statin was approved in 1987 and there has been extensive research to demonstrate their efficacy and safety. But, like most medications, statins can have side effects. The most frequent are muscle soreness and increase in liver function tests. When used appropriately, the benefits of the statin drugs far outweigh any risks.

Here are some common misconceptions about statin drugs and what you should know:

1. **Muscle Soreness:** Muscle soreness is a side effect of statin drugs, although most patients do not experience any problem. It may be difficult to determine if the statin drugs are the cause of the discomfort. Some patients have very mild soreness that is well tolerated. This is generally a benign side effect but it is important to work with your healthcare provider to determine if adjusting the dose, changing the medication, or further evaluation is needed.

2. **Risk of Developing Diabetes:** Some studies have shown that there is an increased risk of developing diabetes for patients who take a statin drug. However, it is not clear if these patients would have become diabetic regardless of statin use. More important is that the patients in these studies had significantly fewer cardiovascular events while taking a statin drug.

3. **Memory Loss:** Post-marketing information on statin drugs shows that memory loss has been reported. This finding has not been fully supported by clinical or observational studies and large and well-designed studies will be needed to determine if there are neurological side effects.

4. **Statins and Liver:** Statin drugs can affect the liver, but serious side effects are rare. Before you begin a statin drug, your healthcare provider will check your liver tests and review your medical history to make sure there are no contraindications to your taking a statin medication. In many cases, there will be no need to check your liver tests routinely; others may have periodic measurements made.

5. **Grapefruit Juice:** Statin drugs, like many other drugs, may interact with other medications or food. While grapefruit juice is one of these, it would take at least a pint of juice per day to have significant interactions with some of the statins. The drugs where this combination should be avoided are atorvastatin, lovastatin, and simvastatin.

6. **“Natural” Cholesterol Medications are Preferable:** Red Yeast Rice is sold as a cholesterol-lowering supplement. This substance is produced when a yeast — Monascus purpureus — is grown on rice and fermented producing several byproducts, including one that is the same as the statin drug lovastatin. Other byproducts produced such as citrin have been shown to be toxic to the liver in animals. Red Yeast Rice does not have FDA approval and should not be considered as a substitute for prescription statin drugs.

It is always important to work with your healthcare provider to discuss use of medications and make a plan for monitoring your progress.

Further information on cholesterol medications can be found at [lipid.org](http://lipid.org).
SAVE THE DATES...

2017 Meetings

Top 5 Reasons to Attend:
1. Enhance your understanding of new therapies and patient treatment.
2. Discuss controversies in the field of Lipidology.
3. Learn about novel methods to increase patient adherence and compliance.
4. Hear from the best educators and researchers in the field of lipidology.
5. Connect with colleagues, discuss new information with your peers, and meet world-renowned speakers.

Hosted by the Pacific and Southwest Chapters

Hosted by the Northeast Lipid Association

Hosted by the Southeast and Midwest Chapters

lipid.org/conferences