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This issue sponsored by the Northeast Lipid Association
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- **Cutting-Edge Sessions** – Each day of the conference, thought leaders will present cases and discuss the latest research, guidelines, controversies and clinical strategies.

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- **Advanced Risk Assessment and Diagnostic Testing Dinner Symposium (Non-CME)** Join your colleagues on Friday, August 26 for this promotional (Non-CME) dinner symposium featuring a series of presentations from lipid testing and diagnostic companies. Presenters will address the advantages of advanced testing and novel biomarkers for screening specific patient populations to get patients to their lipid goals.

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**Terry A. Jacobson, MD, FNLA**  
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**Paul E. Ziajka, MD, PhD, FNLA**  
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For reservations, call 407-597-3600 and ask for the National Lipid Association room block.

Rooms have been reserved for NLA meeting attendees for $159/night (plus tax). The discounted rate is available until **August 1, 2011**.

Visit [www.lipid.org/summerclu](http://www.lipid.org/summerclu) for more information and to register.
From the NLA President:
Turning Over the Gavel

MICHAEL H. DAVIDSON, MD, FACC, FACP, FNLA
National Lipid Association President
Clinical Professor
Director of Preventive Cardiology
University of Chicago
Pritzker School of Medicine
Chicago, IL

Diplomate, American Board of Clinical Lipidology

PENNY KRIS-ETHERTON, PhD, RD, CLS, FNLA
National Lipid Association Incoming President
Distinguished Professor of Nutrition
Penn State University
University Park, PA

My congratulations to Sanford Carimi, MD, that his son, Gabe, was drafted in the first round of the NFL draft by the Chicago Bears. Gabe is the first son of a Lipidologist to play in the NFL. This historic event is one of many that I have been honored to enjoy as President of the NLA. The success of the NLA is due to its fantastic staff and from the leadership that proceeded me. As I turn over the gavel to my good friend, Penny Kris-Etherton, I look back with pride to our accomplishments over the past year. The NLA is now truly an international organization with successful educational initiatives in India and Australia. Poland has established a sister organization, the Polish Lipid Association, and will hold its first meeting in September. We have initiated important collaborations with like-minded organization such as the American Society for Preventive Cardiology, American Society of Hypertension and the Society of Atherosclerosis Imaging, as well as strengthened our commitment to working with the Preventive Cardiovascular Nurses Association. We held two expert consensus conferences, the first on Familial Hypercholesterolemia and the second on Inflammatory Biomarkers and Lipoprotein Testing. Finally, the new HDL Master Class will provide our members with the high standards of state-of-the-art education that has made the NLA a standout organization throughout the world. This will be the first step in a major HDL Education Initiative that the NLA will launch over the next year. My great appreciation goes to the NLA staff who are the unsung heroes behind the scenes and to all of you for your support and advice. Many members asked me how they could get more involved with the NLA and my parting wish is that as we continue to grow we will never lose the passion of the members for greater involvement in an organization that provides professional growth with creative programs that improve patient outcomes.

I am deeply honored to assume the position of President of the National Lipid Association. It has been a privilege to work with a great group of colleagues in NLA over the years who are most committed to excellence in research, teaching and quality healthcare. The breadth of expertise of NLA members is truly remarkable and positions us uniquely to address and conquer the health problems that loom ahead.

As President of NLA for 2011-2012, your leadership team will pursue several key initiatives that will serve our members and their colleagues and patients. Consistent with the mission statement of NLA, which is to enhance the practice of lipid management in clinical medicine, our plans are to develop and deliver a variety of educational programs. A major focus will be to educate NLA members about the new Adult Treatment Panel IV Guidelines and develop strategies for implementation in practice.

Collectively, in the next year, a pivotal plan of NLA will be to translate current guidelines for both treatment and prevention of abnormal blood lipids that meld lifestyle recommendations and pharmacologic therapies into useful strategies that can be adopted in clinical practice. To be successful in this key endeavor, we seek your help and active participation in achieving this shared goal. This is an exciting time for NLA, and I passionately believe that we are poised to grow the visibility of NLA and our membership. To achieve all that we aspire for, we will rely on your active participation in developing NLA programs that utilize your expertise. It is my great pleasure to invite you to contribute importantly to the many opportunities that await.
From the NELA President: Personalizing Prevention

DONALD A. SMITH, MD, MPH, FNLA
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Director, Lipids & Metabolism
Mount Sinai Heart
Associate Professor of Medicine, Community & Preventive Medicine
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*Diplomate, American Board of Clinical Lipidology*

The Northeast Lipid Association is proud to be simultaneously hosting the Annual Scientific Sessions for the National Lipid Association meeting for 2011 and presenting *Lipid Spin*, which complements the meeting’s theme—Personalizing Prevention: Lipids and Atherosclerosis Risk. New York City and Central Park are at their best in May and any Mets/Yankees game is a hoot, so we hope you can schedule time to come to what should be an outstanding program.

I am grateful to Tom Tulenko, PhD, Perry Weinstock, MD, Linda Hemphill, MD, Joyce Ross, MSN, and Jamie Underberg, MD—the major NELA program planners—the NLA staff and the many others regionally and nationally who contributed to planning and producing this meeting. The program explores the latest in genetics, plaque imaging, advanced lipoprotein testing, fatty acid research, high-density lipoprotein (HDL) and the management of lipid disorders in many specific clinical conditions.

This *Lipid Spin* complements the national session with articles by Dan Soffer, MD on HDL and measuring cholesterol efflux, Tom Dayspring, MD, on his view of Lipoprotein(a), Louella Santos, MD, and Jamie Underberg, MD, on the safety of statins, and Ken Kellick, PharmD, Janet Long, MSN, Joyce Ross, MSN, and Mark Cziraky, PharmD, on statin myopathy and its management. Penny Kris-Etherton, PhD, RD, and Jennifer Fleming, MS, RD, try to answer the important clinical question of “What is the best weight-loss diet for me?” Ed Goldenberg, MD, compares hsCRP-stratified analyses in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) and in the Heart Protection Study in predicting statin efficacy, and illustrates how stratified analyses can lead to very different results. Joyce Ross, MSN, is spotlighted and gives an illuminating account of her clinical years with low-density lipoprotein (LDL) apheresis and familial hypercholesterolemia (FH), a history that adds personal warmth to the NLA Foundation’s pediatric recommendations to be presented at the national meeting. Finally, John Guyton, MD, and his son, Morgan, have written a moving editorial on the price homozygotes pay for the survival benefits provided by new genomic mutations in heterozygotes. I greatly appreciate all the writers’ and editors’ help in producing this May issue.

The Northeast Lipid Association has more than 500 members, making it the third largest of the regional associations of the National Lipid Association. The current largest NELA group activity focuses on lipids in children. It was initiated by Sam Gidding, MD, of the Nemours Cardiac Center at A.I. DuPont Hospital for Children in Wilmington, Del., and has grown into a national group of concerned pediatricians with cardiovascular preventive interests. Monthly group telephone meetings are held, with the current most focused activity centering on producing an application for a National Institutes of Health (NIH) grant to study mid-teens with obesity and the dyslipidemia of insulin resistance using pulse-wave velocity and

Discuss this article at [www.lipid.org](http://www.lipid.org)
Go to “Topics/Lipid Spin Spring 2011” and look for “From the NELA President.”
carotid intima media thickness (IMT) measurements at baseline and at two years after lifestyle and statin interventions.

Lisa Hudgins, MD, of the Rogosin Institute at New York-Presbyterian Hospital-Weill Cornell Medical College and a member of the pediatric group has worked with LDL apheresis in children since it was approved and is designing a registry of children with homozygous FH to accumulate a national experience that will have the data to support recommendations concerning management.

Mary McGowan, MD, of Concord, New Hampshire, has been involved in the Foundation of the NLA’s efforts to publicize familial hypercholesterolemia, finding volunteers who have personal experiences they are willing to share.

Many of us in NELA would encourage you to attract more cardiology and endocrine fellows into the lipids field by promoting attendance at one of the three NLA meetings held throughout the year. Qualified Fellows are given $500 expense money if they attend the 1½-day Lipid Management Training Course and are allowed to enjoy the Scientific Updates for free. This benefit is available not only to MDs, but to all health professionals in training who specialize in lipidology, and we hope you will encourage them to take advantage of it. Questions can be addressed to Sandra Goode at sgoode@lipid.org. In addition, the NLA offers a web-based in-service exam on lipid metabolism and dyslipidemia management to teach training guidelines for fellowship programs. Four training programs in the Northeast are involved in this effort: Tufts University, University of Medicine and Dentistry of New Jersey (UMDNJ)-Robert Wood Johnson, University of Connecticut, and the University of Rochester Cardiovascular Disease Training Program. Others interested in joining this program can contact the NLA Office at fellows@lipid.org.

I have been greatly honored to have been President of the Northeast Lipid Association. I look forward as new and inactive members join and begin to contribute actively to keeping this great preventive effort rolling.
This issue of *Lipid Spin* is a special one for me, as it brings together many themes, ideas and principles under the grand tent of “personalized medicine.” We are lucky to be able to release this in concert with our Annual Sessions featuring a similar theme and in the setting of the Foundation’s awareness campaign about familial hypercholesterolemia (FH).

There is a new section for patient education, and we hope to use this section as a way to reach out beyond our members to the patients that we all care for in our daily clinical settings.

Several articles in this issue bring home the focus of personalized medicine. The new FH recommendations summarized in this issue’s patient education section remind us that using Framingham risk scoring algorithms for this population is not appropriate, and that once the diagnosis is made, the recommendations apply to all FH patients. The recommendations also focus on the importance of screening family members of those with FH. What can be more personal than this? There is an excellent review of HDL cholesterol testing, reminding us that while HDL cholesterol levels track with risk for populations, this may not apply to individuals. We feature a summary of recent data from the GREACE trial again supporting prior NLA recommendations regarding liver function testing for statin therapy, reminding us that for many with fatty liver disease, this may be a marker of who will do best on statins, and that avoiding or stopping statins in these patients is ill-advised.

Finally, as part of the Foundation of the NLA agenda, patients are being asked to tell their own stories regarding FH on www.learnyourlips.com. How and when were they diagnosed? How did meeting a lipid specialist change their care and management? How does this disease impact not only their lives, but those of family and friends? Allowing patients to tell their stories reminds us all of why we care about and are interested in the field of Lipidology. The essay by John Guyton, MD, and his son, Morgan, summarizes this in a wonderful way.

We all practice personalized medicine on a daily basis. We translate population-based research data to individualized “across the table” patient care every time we see patients. The Member Spotlight piece on Joyce Ross, MSN, demonstrates how each one of us can be personally impacted by the diseases we treat. At the same time, her message to young women going off to college regarding birth control and statin use highlights the value of the personal relationship between providers and their patients.

For me, however, this even goes beyond patient care. The NLA represents a unique collection of some of the nicest and most caring individuals that anyone could ever know and meet. This spans both the membership and the amazing administrative staff who support our ongoing activities. This May we meet in my hometown, New York City, and I, along with all NELA members, are delighted to share this great town with our good friends and colleagues from the NLA. Just like New York, the NLA it is truly a “small town living in a big city.”

In the words of many famous New Yorkers: “You Talking to Me?”

You bet we are. Each and every one of you. I hope you enjoy this issue as much as we did putting it together.

*James A. Underberg, MD, MS, FACP, FACP, FNLA*

Preventive CV Medicine, Lipidology and Hypertension
Clinical Assistant Professor of Medicine
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*Diplomate, American Board of Clinical Lipidology*
Clinical Feature:
HDL—Quality Trumps Quantity

MLS is a 64-year-old Caucasian vital former smoker who had a recent acute myocardial infarction (MI) requiring deployment of two sequential drug-eluting stents in the right coronary artery. She has had very high levels of high-density lipoprotein cholesterol (HDL-C) as long as she can remember and had never taken any cholesterol-lowering therapy prior to the MI. Her clinical features and metabolic/lipid profile before starting medication follow:

- Former smoker (30-pack years; quit 20 years ago)
- Hypertension, diabetes mellitus, metabolic syndrome: neg
- Family history premature coronary heart disease (CHD): neg
- Early surgical menopause (age 40); on ERT x 20 years

There is an inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular risk noted in clinical and epidemiologic trials including the Framingham Heart Study. A number of epidemiologic studies have demonstrated that the low levels of HDL-C are predictive of high cardiovascular (CV) risk, while the highest HDL-C levels exhibit the lowest risk for coronary artery disease (CAD). Similarly, it has been demonstrated that a 2% to 3% reduction in risk results from every 1 mg/dL increase in HDL-C.

There is significant residual cardiovascular risk in treated people and raising HDL-C levels is an important goal in targeting CAD risk reduction after low-density lipoprotein cholesterol (LDL-C) and non-HDL-C goals are met. However, clinical trial evidence for achieving risk reduction with HDL-raising therapy is lacking and certainly less robust than that for LDL-C levels. As monotherapy, nicotinic and fibric acid derivatives have documented value, but tolerability of niacin and inconsistent benefit from fibrates limit their clinical utility. Results of the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and Atherothrombosis Intervention in Metabolic Syndrome with low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) are eagerly awaited.

HDL is atheroprotective because of its combined ability to limit oxidation, inflammation and thrombosis and because of its role in reverse cholesterol transport (RCT). However, there are exceptional conditions and functional assays that have documented that HDL is not always atheroprotective in the ability to limit oxidation and inflammation. In the wake of the torcetrapib failure, more robust surrogate markers of atherosclerosis and protection are surely needed. Recent work by Khera, et al. presented a novel assay for evaluating the ability of HDL to promote cholesterol efflux from cultured macrophage cells. Their finding that cholesterol efflux capacitance has a strong inverse relationship with atherosclerosis strongly supports the concept that HDL is the main player in reverse cholesterol transport.
transport (RCT) and it is this role that provides the protective property of HDL. Targeting this aspect of HDL functionality may prove to be the most important goal in HDL therapeutics.

CV disease remains the primary cause of death and disease in industrialized nations, despite terrific advances in public health, individual pharmacotherapy and revascularization procedures over the past several decades. Blood pressure control and anti-platelet pharmacotherapy are part of the foundation of therapy for prevention and management of coronary and peripheral arterial disease, but no regimen is complete without therapy for the reduction of apolipoprotein B-containing (apoB-containing) particles, especially LDL-C levels.

While management of apoB-containing particles is well validated and is the cornerstone of therapy, there remains significant residual cardiovascular risk in treated people, especially when there is inadequate LDL-C lowering and/or elevated triglyceride (TG) and suppressed HDL-C levels. This problem strongly suggests the need for better pharmacotherapy for combined dyslipidemia.

Pharmacologic interventions for HDL-C raising are presently limited to nicotinic (primarily) and fibric (secondarily) acid derivatives, though the data documenting the clinical value are, thus far, underwhelming. Ongoing clinical trials will attempt to answer the question about the real value of the addition of niacin and fibrates to statin therapy. As of now, the “measuring stick” for assessing functional response to pharmacotherapy is the lipid profile, which is a quantitative focus on lipoprotein-cholesterol levels. LP particle size and number is an alternative and emerging measure of CV risk, as well. These newer assays, along with apolipoprotein levels, predict CV risk with better accuracy than LP-cholesterol levels and are helpful but not yet widely accepted in clinical management. Similarly, atherosclerosis imaging with carotid intima-medial thickness (CIMT) and coronary artery calcification are potentially attractive tools for assessing atherosclerosis progression, but confirmatory studies are still forthcoming as a tool for monitoring therapy.

HDL is the critical component of endogenous protective measures. The particle limits the inflammatory, oxidative and prothrombotic challenges to the activated macrophage. Most importantly, however, the HDL removes oxysterols and transports them back to the liver for recycling or catabolism—completing RCT.

“The need for better pharmacotherapy for combined dyslipidemia.”

In the wake of the torcetrapib failure, more robust surrogate markers of atherosclerosis and protection are surely needed.”
among subjects in the Honolulu Heart Program, if they had specific genetic mutations in CETP.\textsuperscript{11}

To investigate the relationship between HDL function and CVD, an \textit{ex vivo} method has been developed to assess the ability of HDL to promote cholesterol efflux from macrophages. The assay, which is laborious and time consuming, involves the measurement of cholesterol efflux from the macrophage by incubating apoB-depleted serum with J774 cells (a macrophage cell line) that have been preloaded with radiolabeled free cholesterol and stimulated with cyclic adenosine monophosphate (AMP) to upregulate ABCA1. The amount of radiolabeled cholesterol present in the medium after four hours of incubation with HDL represents the amount of cholesterol flux from the macrophage.

Several studies were completed using this assay, but it is worth highlighting the study published recently in the \textit{New England Journal of Medicine.} Khera, et al. evaluated 203 healthy volunteers who underwent evaluation with CIMT, 442 patients with angiographically confirmed coronary artery disease, and 351 subjects without such disease. They demonstrated that cholesterol efflux capacitance is highly inversely correlated with CIMT and atherosclerotic heart disease. This correlation was independent of the relationship to HDL-C and even apoA1 levels, supporting the hypothesis that function predicts outcome better than mass.

In large populations, it is clear there is an inverse relationship between HDL and cardiovascular risk. However, clinicians regularly encounter paradoxical clinical scenarios, such as MLS. While it is an attractive concept to suggest to our patients that we think their CV risk would be lower if they could just raise their HDL-C, we presently have very few therapeutic options. Surrogate markers of HDL function, such as anti-oxidative, thrombotic and inflammatory response, and now cholesterol efflux, should provide mechanisms for guiding new pharmacotherapy development. These tools may someday be refined for the throughput required for clinical medicine but, for now, remain in the hands of our bench research colleagues.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{cholesterol_efflux_assay.png}
\caption{Cholesterol efflux assay. Step 1: Macrophages are incubated in the presence of radio-labeled free-cholesterol; this causes the accumulation of radio-labeled free cholesterol in the macrophage. Step 2: Macrophages are incubated in the presence of cyclic adenosine monophosphate (cAMP) to upregulate ABCA1, one of the main transporter proteins involved in efflux of cholesterol. Step 3: Macrophages are incubated with HDL obtained from the subjects. Step 4: The amount of radio-labeled cholesterol effluxed from the cells is measured. Cholesterol efflux capacity is measured as percentage of radio-labeled cholesterol effluxed during the four-hour incubation (Courtesy of Dr. Cuchel).}
\end{figure}

\begin{quote}
"They demonstrated that cholesterol efflux capacitance is highly inversely correlated with CIMT and atherosclerotic heart disease...supporting the hypothesis that function predicts outcome better than mass."
\end{quote}

MLS was treated with therapeutic lifestyle counseling, combination anti-platelet therapy including aspirin and clopidogrel, beta blocker and standard dose statin monotherapy. She does not require any HDL-C raising therapy, but it is reasonable to speculate that her HDL is dysfunctional to start and, hopefully, these therapies will stabilize her disease and enable longevity.

Disclosure Statement: Dr. Soffer has received salary support from research grants from Novartis and Pfizer Inc.

References listed on page 33.

*Questions and comments about this article may be directed to the author via e-mail at Daniel.Soffer@uphs.upenn.edu.*
Guest Editorial: 

Ringbearers—A Hobbit’s Look at Genomic Medicine

Life turns on a wheel of genomic roulette. Through evolution the human species wins, while individuals of the species often lose. The new field of genomic medicine, currently featured in this issue of Lipid Spin, opens the toolbox of evolution to improve human health, but it also highlights the harsh role of chance in life. What response can we give to our patients’ unanswerable question, “Why me?”

In J.R.R. Tolkien’s The Lord of the Rings, the pivotal character Frodo Baggins, who bore the ring of doom, similarly asked “Why me?” as he faced a task only he could accomplish. People affected by random genomic events remind us of Frodo. Here we describe four ringbearers in a lipid clinic and explain why their quests are as important to humanity as Frodo’s mission was to Middle Earth.

Maureen has a heterozygous defect in the LDL receptor gene. She maintained a strict diet, exercised, and took a statin. At age 39 she endured severe chest pains for 6 weeks before convincing her physicians to perform angiography, leading to a coronary stent. Her cholesterol-swollen Achilles tendons would respond painfully whenever she exercised too much. With new drugs helping to mobilize tissue cholesterol, the tendons become so inflamed she can barely walk. She perseveres in treatment with help from a devoted spouse. Their daughter will have cholesterol testing soon.

Elizabeth has battled metastatic breast cancer now in remission. Her high cholesterol, perhaps related to a hormone modulator, is readily addressed. Elizabeth’s tumor was submitted to gene expression profiling, hoping to achieve tailored cancer therapy. In cancer cells, evolution moves at hyperspeed. Multiple genomic hits generate the tumor. After treatment, relapse is governed by further mutations among surviving cells. Unlike classic genetic disorders where the course is set from birth, in cancer the patient must replay genomic roulette again and again.

Jacob has schizoaffective disorder currently stabilized on antipsychotic drugs. Diabetes and high triglyceride developed as his weight ballooned. With dietary control, weight and metabolism improve. In the human brain, evolution reaches its apex. Yet this incredible organ of fine-tuned complexity may be especially vulnerable to small genomic interactions. Randomness hits the person with mental illness doubly hard. The defect not only disrupts life, but also undermines the very capacity to understand and adapt. Remarkably Jacob expresses gratitude, as he walks a narrow line between medication and hunger.

Eileen was referred at 15 with severe hypertriglyceridemia. When she was a toddler, a genetic problem unleashed her cellular immune system to attack her joints, muscles, humoral immunity, and fat progenitors, leaving her physically disabled, susceptible to infections, and eventually diabetic. In her mid-twenties came successively cardiomyopathy, bone pain and hypercalcemia, end stage renal disease, then fatal liver failure. But this description of illness hardly characterizes Eileen. She was a vibrant young woman with a quick mind and a ready smile. Eileen never ran or danced, but she loved to sing. Taking her motorized scooter on stage, she joined her peers in a musical revue, adding her part to the harmonies and choreographed movements that spurred an audience to wild ap-
A celebrated hero, but his wounds never healed. The story ends with Frodo’s departure for heaven, after living one-third of a hobbit’s normal lifespan.

How does Frodo’s story match up with those of our patients? Like him, he is selected unexpectedly to bear a life-changing burden. By chance, he inherits the ring, which radiates an evil that intensifies and ultimately shortens his life. But Frodo’s mission, which he freely chooses, is the salvation of his world. Is this also true for our patients?

Humans evolve in a wilderness where natural law confronts untamed chaos. As conscious thought emerges over millennia, humans begin to ask questions: Why do some suffer and others not? Is it all worthwhile? Those with genomic illness often say they just want to live a normal life. This ordinary desire, expressed heroically, overcomes unfairness and affirms for all the value of life.

We usually think of evolution as the healthy surviving and reproducing more successfully than the unhealthy. But Simpson in the last century remarked that in humans evolution becomes “subject to conscious control” and that a “new form of evolution works in the social structure, as the old evolution does in the breeding population structure.”

Think how the paradigm is transformed, if we consider that humanity develops as a family, not as isolated individuals. Consider what we call progress—is it not reflected in how a society interacts with its most vulnerable members? Our hope as a species depends upon the dignity with which we treat people today who might have been left on a hillside by a Neolithic tribe, or confined to institutions 50 years ago.

Our patients do not choose their genomic assignment, but they choose how to bear it with bitterness or grace, with courage or despair. In choosing life to the fullest extent possible, they teach the rest of us how to live. Regardless of how they respond, when we treat them with honor, we evolve as a people.

Like Frodo, our patients are ringbearers. The comparison deepens if we notice that often very few people witness their affliction, much less their courage. Those who are truly close to the patients have their counterpart in Frodo’s friend Sam. Only Sam witnessed the full extent of Frodo’s struggle and bore the brunt of his despair. Sam briefly carried the ring himself. At the end, he carried Frodo, ring and all. So we can also name “ringbearers” the caregivers and companions of the afflicted.

Clinicians have the privilege of walking beside humanity’s ringbearers, supporting them through witness and service. They pay evolution’s price for us all and validate life through their travail. Their gift to those who share their struggle is the opportunity to become better humans.

On a high, wide rampart above a once chaotic plain, the citizens of Middle Earth celebrate victory. Scarcely visible in the crowd are some humble fellows, one bearing deadly wounds. Maureen, Elizabeth, Jacob, Eileen, and Meghan—we wish you our patients? Like them, he is selected unexpectedly to bear a life-changing burden. By chance, he inherits the ring, which radiates an evil that intensifies and ultimately shortens his life. But Frodo’s mission, which he freely chooses, is the salvation of his world. Is this also true for our patients?

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On a high, wide rampart above a once chaotic plain, the citizens of Middle Earth celebrate victory. Scarcely visible in the crowd are some humble fellows, one bearing deadly wounds. Maureen, Elizabeth, Jacob, Eileen, and Meghan—we wish you...
Lipoprotein (a) [Lp(a)], pronounced lipoprotein “little a,” was discovered in the early 1960s and has been independently associated with cardiovascular disease in many—but not all—studies. Although the data associating Lp(a) with cardiovascular (CV) risk has recently become stronger, there is still confusion regarding exactly which patients with elevated Lp(a) are at risk. This confusion is likely related to factors such as ethnicity, other laboratory measures such as low-density lipoprotein (LDL), and the method used for Lp(a) measurement. Lp(a) is an LDL particle to which a glycoprotein, called apoprotein(a) [apo(a)], is covalently bound to apolipoprotein B. The atherogenic nature of apo(a) seems related to its thrombotic properties and its ability to serve as a trafficker of oxidized molecules. Like all LDL particles, the risk linked to Lp(a) is almost certainly related to exactly how many Lp(a) particles exist and enter the intima.

The major dilemma, which confuses clinicians in interpreting both patient and clinical trial data, is understanding the difference between molar concentration in units (nmol/L) and mass concentration in units (mg/dL). The apo(a) molecule does not have a fixed size but rather exists as a variable-sized protein. Specifically, there are smaller, low molecular-weight (MW) isoforms and larger, high MW isoforms. Depending on the size, i.e., the number of amino acids (AA) of the specific apo(a) in a particular patient, its MW ranges from 180 to 800 kD. Ideally, measurement of apo(a) should be reported in molar concentration (nmol/L), not in mass concentration units (mg/dL). However, complex genetic methods or Western blotting are required to determine the molecular weight of a person’s apo(a) and, without knowing the exact molecular weight, the true Lp(a) concentration in nmol/L cannot be determined. Therefore, most labs report Lp(a) values in units of mg/dL. Some then convert the weight in mg/dL to nmol/L using a formula based on an estimated average MW of apo(a). Because the person’s apo(a) MW is unknown, this calculation will not be accurate.

Commercial assays generally use polyclonal antibodies, so they are not isoform-specific and, hence, overestimate Lp(a) in patients with large apo(a) and underestimate those with small apo(a). A few molecules of a large, high MW protein would have the same weight (mg) as several low MW proteins. Accordingly, patients with the large, high MW apo(a) isoform would have many less apo(a) molecules than a person with the smaller, low MW isoform, even though they might have the same weight (mg) per dL. Therefore, a patient with the high MW isoform who has an apo(a) or Lp(a) value of 60 mg/dL would have far fewer apo(a) molecules or Lp(a) particles per dL than a patient with the smaller, low MW isoform who also has a value of 60 mg/dL. The Lp(a) particle count, or Lp(a)-P, would be much higher in the person with the smaller, low MW isoform. Clinical trials clearly demonstrate that patients with the low MW isoform have the highest Lp(a)-related risk. At this time, no lab reports the test we really need, namely Lp(a) particle count [Lp(a)-P or Lp(a)-apoB]. Apo(a) or Lp(a) cannot be measured using nuclear magnetic resonance spectroscopy.

Structurally, apo(a) is related to plasminogen and they both consist of

Practical Pearls: Demystifying the Measurement of Lipoprotein (a)

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Go to “Topics/Lipid Spin Spring 2011” and look for “Practical Pearls.”
a series of looped AA moieties named kringles (after the Danish pastry). Plasminogen has five such kringles (I-V) of which apo(a) has two, (IV and V). Kringle IV (K-IV) has an incredibly variable size because the gene that controls the KIV structure is different among patients. Altogether, the apo(a) gene has 10 types of K-IV domains, referred to as K-IV types 1 through 10. These K-IV types are present as single copies, whereas K-IV type 2 is present as multiple copies, varying in number from three to more than 40 copies. Those with multiple copies of K-IV2 have the high MW isoform and those with few copies will have the lower MW isoform of apo(a). The liver has great difficulty secreting the large isoform; thus, even though plasma apo(a) mass in such patients is high—due to the large MW of the protein—the actual number of apo(a) molecules, which bind to LDL, is small. Conversely, the small isoform has no trouble exiting the liver and the number of apo(a) molecules in plasma will be high. Lp(a) mass (mg/dL) might be the same in patients with high or low MW isoforms, but Lp(a)-P is higher in those with the small isoform. Until labs begin reporting Lp(a)-P, the best surrogate measurement to rely on is Lp(a)-cholesterol [Lp(a)-C]. Because patients with the large, high MW isoform have low Lp(a)-P, they have a very low Lp(a)-C (≤ 3 mg/dL). Those with the small, low MW isoform who typically have high Lp(a)-P have a high Lp(a)-C (> 3 mg/dL). In essence, we would be better off relying on Lp(a)-C measurements than any apo(a) mass measurement currently readily available. One might conjecture, subject to clinical trials, that therapeutically one might simply normalize Lp(a)-C and not worry about Lp(a) mass.

Figure 1. Lp(a) particles. Large apo(a) isoform with high molecular weight (HMW) due to multiple KIV-2 repeats is less atherogenic than the smaller isoform (LMW) which has less KIV-2 repeats.

Disclosure Statement: Dr. Dayspring has received honoraria related to speaking from Abbott Laboratories, GlaxoSmithKline, and LipoScience Inc. Dr. Dayspring has received honoraria related to consulting from Abbott Laboratories, GlaxoSmithKline, Kowa Pharmaceuticals America, Merck & Co., Genentech, Daiichi Sankyo, and Health Diagnostic Labs Inc.

References are listed on page 33.
Deepak Chopra said, “We are all on Death Row...the only uncertainty is the length of the reprieve and the method of execution.” It is our responsibility as healthcare practitioners to identify patients likely to die early of cardiovascular disease, to encourage lifestyle changes in them, and to prescribe pharmacologic therapy when indicated.

Our present approach to identifying at-risk patients is to determine if traditional risk factors—hypertension, advanced age, gender, family history of heart disease, diabetes, tobacco use and/or low high-density lipoprotein (HDL)—are present. From this information, patients are classified as to their risk of developing a coronary heart disease (CHD) event within the next 10 years. We classify them into low-risk (<5%), intermediate-risk (5%-10% and 10%-20%) and high-risk (>20%) categories using widely available risk-scoring systems. The INTERHEART study also identified abdominal obesity, psychosocial factors, diet, inactivity, alcohol and a poor apolipoprotein B (ApoB)/apolipoprotein A (ApoA) ratio as other significant contributors to risk. The risk factors identified in INTERHEART are not included in most global risk-scoring systems. The intensity of risk-factor modification is matched to the 10-year risk. The problem is, however, that 66% of population-attributable risk comes from the low- and intermediate-risk groups, not from the high-risk group. How can we better identify risk?

Traditional global risk-scoring systems, when studied for cardiovascular disease (CVD) outcomes, typically yield receiver-operator curve-derived C statistic values of approximately 0.80. Various new biomarkers and subclinical atherosclerotic imaging techniques have been evaluated to improve traditional risk-factor assessment. High-sensitivity C-reactive protein (hs-CRP) is one such biomarker with which we have a lot of clinical experience. A critical question regarding improvement in risk prediction is whether this newer biomarker helps identify those patients with low and intermediate 10-year risk as assessed by common global scoring systems who might benefit from statin therapy. The odds for incident CHD are 1.45 (95% CI 1.25-1.68) times greater when hs-CRP is elevated. The American Heart Association (AHA) scientific statement calls for a more rigorous assessment of additive predictive information of any new risk factor by evaluating discrimination (C statistic, receiver operating characteristic), calibration, reclassification and net reclassification improvement. Of note, in many studies, the C statistic for hs-CRP provides no or minimal additive predictive information. For hs-CRP, calibration, reclassification and net reclassification improvement have not been extensively evaluated. The 2010 American College of Cardiology Foundation (ACCF)/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, based on the JUPITER trial, recommends (Class IIa – level of evidence B) measuring hs-CRP in men older than 50 and in women older than 60 who have low-density lipoprotein (LDL) of less than 130 mg/dL. The guideline recommends (Class IIb – level of evidence B) measurement of hs-CRP in men younger than 50 and women younger than 60 who have intermediate Framingham Risk (FRS). No specific recommendations are provided.
however, for how to use this information. The Canadian Cardiovascular Society recommends an LDL goal of 80 mg/dL in men older than 50 and women older than 60 who are at moderate Framingham risk and have an elevated hs-CRP (Class IIa – level of evidence A).^1

The JUPITER trial tested the hypothesis that an elevated hs-CRP identifies a group with normal lipids who will benefit from rosuvastatin 20 mg/day. Of note, however, is that this was not really a low-risk group. The median 10-year FRS and Reynolds Risk Score (RRS) was 10%; 50% had an FRS and 43% had an RRS of greater than 10%. Approximately 20% had a 10-year FRS of less than 5% and 25% had a 10-year RRS of less than 5%. The low-risk group did not benefit from rosuvastatin 20 mg/day.^2 My interpretation of this data is that statin therapy is beneficial if you have an elevated CRP, normal lipids and a 10-year risk of a CHD event greater than 5%.^2

The unanswered question is what to do with a middle-age patient with normal lipids and a moderate FRS or RRS with a CRP of less than 2. The primary prevention study, Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), in patients with normal lipids and low HDL showed a benefit from simvastatin 40 mg/day. A retrospective analysis of the group with low LDL and CRP did not show a benefit from statin therapy.^3 This finding was considered hypothesis generating. A prospective randomized trial to prove this hypothesis has not been performed. If the FRS is greater than 10%, Adult Treatment Panel III (ATP III) suggests an LDL goal of less than 100 mg/dL. In the JUPITER trial subgroup with a FRS between 5% and 10%, benefit with treatment was found. So what is more important, the 10-year risk or the elevated CRP? Considering this group’s lifetime risk of developing a CHD event is high, should we wait for an event, which in 50% of cases will be sudden death, before we institute treatment?

The Heart Protection Study of 20,536 high-risk patients with established vascular disease, diabetes, or a male older than 65 with hypertension found a 24% reduction in the incidence of first major vascular event in those allocated to treatment with simvastatin. A retrospective analysis of this study found there was no evidence that the reduction in this end point varied with baseline CRP. Benefit was found in the group with low LDL and CRP.^4

Risk stratification remains an imperfect science and requires clinical judgment to identify intermediate- and low-risk patients who are likely to develop a vascular event. It is estimated that one can add 10 years of life by preventing the development of risk factors through primary prevention. Unfortunately, primary prevention efforts often fall short. We need to identify younger patients with cardiovascular (CV) risk factors whose FRS or RRS, which are age dependent, underestimate the lifetime risk of developing CHD and will benefit from aggressive risk-factor modification. Given the growing burden of obesity, waist measurement needs to become a vital sign, and we need to pay attention to non-HDL cholesterol and/or ApoB to better identify patients with normal LDL levels who still have too many circulating, small dense particles. ■

Disclosure Statement: Dr. Goldenberg has received honoraria related to speaking from Abbott Laboratories, GlaxoSmithKline, Merck & Co., and Boehringer Ingelheim.

References listed on page 33.
Legacy is defined as that which is by or received from a predecessor. Physicians’ practice style and technique are often modeled on predecessors. These are habits that begin during medical school and residency, trickle down into fellowship and are often carried over into clinical practice. One such ritual is the periodic monitoring of liver function tests in patients receiving chronic statin therapy and the knee-jerk discontinuation of treatment based on mild elevations. What evidence supports this?

The post-hoc analysis of patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study assessed the safety and efficacy of long-term statin treatment in patients with coronary heart disease (CHD) and abnormal liver tests.¹ The primary outcome was risk reduction for the first recurrent cardiovascular event in patients on statins with moderately abnormal liver tests compared to patients with abnormal liver functions tests not treated with statin therapy. Secondary endpoints included the effects of statins on liver tests.

Briefly, the GREACE study evaluated 1,600 patients with CHD who were followed for three years.² Patients were randomized to either treatment with atorvastatin (10-80 mg/day) to achieve the National Cholesterol Education Program expert panel (Adult Treatment Panel III) (NCEP ATP III) low-density lipoprotein cholesterol (LDL-C) target (2.6 mmol/l; 100 mg/dL)³ or “usual” care. Usual care included lifestyle changes such as adoption of a low-fat diet, weight loss and exercise, and all necessary drug treatments, including lipid-lowering agents.

During the study, 437 patients with baseline moderately abnormal liver tests—defined as less than three times the upper limit of normal—were followed for three years. Elevations in liver function tests (LFT) were attributed to non-alcoholic fatty liver disease (NAFLD) based on ultrasound findings and after ruling out other causes of LFT elevations, such as alcohol misuse, hepatitis B and C, Wilson’s disease and autoimmune hepatitis. Of these patients, 227 were treated with a statin and 210 were not. Patients who started the trial with abnormal liver function tests and received a statin showed the greatest benefit with a 68% relative risk reduction (3.2 events per 100 patient years) compared with patients who did not receive a statin (10 events per 100 patient years). This benefit was even greater.
1. During routine general evaluation of patients considered for statin and other lipid-lowering therapy, it is advisable to obtain baseline liver transaminase levels. If these tests are found to be abnormal, further investigation should be performed to determine the etiology of the abnormal test results.

2. Until there is a change in the Food and Drug Administration (FDA)-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.

3. The clinician should be alert to patient reports of jaundice, malaise, fatigue, lethargy and related symptoms in patients taking statin therapy as a signal of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level and elevated prothrombin time, rather than simple elevations in liver transaminase levels.

4. The preferred biochemical test to ascertain significant liver injury is fractionated bilirubin, which, in the absence of biliary obstruction, is a more accurate prognosticator of liver injury than isolated aminotransferase levels.

5. Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. The etiology should be sought and, if indicated, the patient referred to a gastroenterologist or hepatologist.

6. If an isolated asymptomatic transaminase level is found to be >3 times the ULN during a routine evaluation of a patient administering a statin, the test should be repeated and, if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.

7. According to the Expert Liver Panel, patients with chronic liver disease, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis may safely receive statin therapy.

8. According to the Expert Liver Panel, patients with chronic liver disease, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis may safely receive statin therapy.

**Summary of changes in liver-test recommendations on U.S. Food and Drug Administration package inserts.**

<table>
<thead>
<tr>
<th>Older statin package insert</th>
<th>Current package insert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>(2009) LFTs before initiation of therapy in those with a history of liver disease or when otherwise clinically indicated</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>(2008) LFTs before treatment and then when clinically indicated</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>(2007) LFTs before initiation of therapy and when otherwise clinically indicated</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>(2009) No change</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>(2009) No change</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>(2009) No change</td>
</tr>
</tbody>
</table>

**Table 2.** Table adapted from the article “The Myth of Statin-Induced Hepatotoxicity” by Bader T. Am J Gastroenterol 2010;105:978-980. Labels available at www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
treatment or after a drug holiday are advised to continue treatment with a statin without harm.

In 2006, the National Lipid Association Statin Safety Task Force was assembled to thoroughly address the safety of statins based on a comprehensive review of available evidence and to summarize the findings on record. The report of the task force states clearly that, for isolated, asymptomatic elevations in transaminase levels less than three times the upper limits of normal (ULN), statins should not be discontinued. For levels more than three times ULN during routine evaluation, closer monitoring of liver function tests is recommended with the intention of identifying other causes of liver function elevations prior to withdrawing statin therapy. The published report also counsels on the safety of administering statin therapy in patients with chronic liver disease, compensated cirrhosis, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis. Final conclusions and recommendations regarding the liver and statin safety are shown in Table 1.

Of late, the U.S. Food and Drug Administration (FDA) package inserts for statins have seen some changes in their recommendations for ALT monitoring for patients on statins (Table 2). Of the generic statins, liver-function monitoring with lovastatin is no longer suggested for asymptomatic patients without a history of liver disease.

Several reports have shown that people with baseline liver enzymes are not at higher risk for hepatotoxicity from statins. Specifically, studies in NAFLD patients have shown histological and liver test improvements while on therapy. Statin use has also been demonstrated to have a low frequency of abnormalities of liver function tests and hepatitis when compared with placebo.

In light of compelling new data, monitoring liver function tests should be customized to individual patients instead of using habitual over-testing of ALT and AST levels on all patients on statins. Greater tolerance should be prompted with a goal to sustain statin treatment, especially in high-risk people. In keeping with the emphasis of personalized medicine tailored to each distinctive patient, we should not be too quick to order liver function tests routinely nor to discontinue statins with escalating levels. Maintenance of statin therapy, especially in indicated people, should be the greatest service we offer patients.

Disclosure Statement: Dr. Santos has no relevant disclosures. Dr. Underberg has received honoraria related to speaking from AstraZeneca, Abbott Laboratories, Forest Laboratories, GlaxoSmithKline, Daiichi Sankyo, Kowa Pharmaceuticals America, Novartis, Pfizer Inc., LipoScience Inc., diaDexus, and Merck & Co. Dr. Underberg has received honoraria related to consulting from Abbott Laboratories, Kowa Pharmaceuticals America, LipoScience Inc., Merck & Co., Genzyme, and News Corporation.

References listed on page 33.
JA is a 66-year-old black male with a history of three coronary artery bypass grafts (CABG) one year ago. His target low-density lipoprotein (LDL) is <70mg/dL, based on multiple risk factors consisting of diabetes, not well controlled hypertension and a strong family history of heart disease.

Pertinent labs at this visit include:
- Cholesterol Total 260mg/dL
- LDL-c (Direct) 180mg/dL
- Triglycerides 325mg/dL
- HDL-c 28mg/dL
- HS-CRP 5mg/dL
- CPK 265mg/dL (21-232mg/dL)
- Fasting Glucose 132mg/dL
- ALT/AST WNL

He currently takes three colsevelam tablets twice daily. His medication history includes a trial of simvastatin 40mg at bedtime and pravastatin 40mg at bedtime. The latter two medications were discontinued by the patient after two weeks of therapy with complaints of severe right leg and arm pain. How should therapy for this patient be approached?

We begin by describing the definitions of myopathy. A literature search reveals several conflicting definitions. Myopathy is often confused with myalgia, and the role of elevated CPK levels within those definitions is not always well defined. Myalgia and/or rhabdomyolysis are very often misused and misdiagnosed terms.

Muscle ache, weakness and pain are not uncommon in the population receiving statins. Clinical trials testing statin safety and efficacy often exclude patients with muscle symptoms, so published rates of trial-associated issues are often lower than in the general population. When the patient presents with muscle ache, weakness and pain and suggests it is related to a statin, certain other disease states that are associated with this disorder should be considered.

Published incidents of rhabdomyolysis are very low when one examines results from randomized clinical trials and retrospective database analyses in “real world” settings.

A published report examining 21 clinical trials with 180,000 person-years of follow-up showed statin myopathy occurred in five patients per 100,000 person-years and rhabdomyolysis occurred in 1.6 patients per 100,000 person-years. The true incidence of clinical myositis is very low. It is also pertinent to consider other factors that may increase the risk of statin myopathy and to consider the differential diagnosis of muscle problems.
The Differential Diagnosis of Myopathy

What are possible mechanisms of statin-induced myopathy? Statins compete for the active hydrophobic binding site on 3-hydroxy-3-methyl-glutaryl (HmG)-CoA reductase. This prevents the binding of HmG-CoA to the site and, hence, blocks endogenous cholesterol production.

There are no well understood mechanisms for statin-induced myopathy. One theory is that the depletion of the isoprenoid ubiquinone (Co-Enzyme Q10) could cause abnormal mitochondrial activity and cell death. This theory is plagued by studies showing varying levels of myocyte co-Q10 levels despite decreasing statin-induced endogenous cholesterol synthesis. By decreasing cholesterol synthesis, others propose altered cell wall function leading to cell malfunction. By bypassing the above cycle and focusing instead on squalene synthetase, in vitro myopathy has not been shown. Of interest is that some people who have inherited disorders of cholesterol metabolism are often devoid of myopathy.

More recent theories involve the process of protein prenylation (Table 3). Protein prenylation involves the transfer of either a farnesyl or a geranyl-geranyl moiety to C-terminal cysteine(s) of the target protein. Apoptosis may occur in the face of increased cytosolic calcium and production of a catalytic enzyme. One could then surmise that the more a statin inhibits the production of prenylated proteins—e.g., high statin levels—the more likely the somatic effects.

Signs and Symptoms of Myopathy

Myopathy occurs for most patients early after starting statin therapy. While the median onset has been reported as one month, symptoms can occur in the first seven to 10 days of statin therapy. Oddly enough, patients may have good tolerability of a given statin for a long period of time and then health or medication changes correlate with signs and symptoms of myopathy.

The presentation is different from patient to patient. The larger muscles in the arms and legs are often the most frequently affected, often bilaterally. However, any muscle group may be subject to the signs and symptoms of myopathy. Muscle weakness, tendon pain, nocturnal muscle cramping, fatigue and generalized muscle aching similar to flu-like symptoms have also been reported by the patient.

Differences in Statins and Relation to Myopathy

Of the seven commercially available statins, differences appear in half-life, bioavailability, lipophilicity and elimination. It does not appear that the pharmacologic properties contribute to one statin being “safer” than any other (Figure 1).

What may be most important is understanding potential interactions that could lead to higher systemic levels of one statin over another. An unfortunate lesson was learned when cerivastatin, combined with gemfibrozil, resulted in a notable number of deaths. Cerivastatin was withdrawn from the market in August 2001. Gemfibrozil most potently inhibits CYP2C9, while gemfibrozil-glucuronide inhibits CYP2C8. The combination of the gemfibrozil-glucuronide markedly inhibited the formation of the cerivastatin M.23 metabolite and, thus, “choked” metabolism leading to high systemic levels.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Drug Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age, family history of myopathy.</td>
<td>Dose and high systemic exposure</td>
</tr>
<tr>
<td>Female gender</td>
<td>Lipophilicity</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>High bioavailability</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>Limited protein binding</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>P-glycoprotein interactions</td>
</tr>
<tr>
<td>Diet (e.g., grapefruit juice)</td>
<td>Hepatic cytochrome interactions</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td></td>
</tr>
<tr>
<td>Complex multi-organ disease</td>
<td></td>
</tr>
<tr>
<td>Status post-op (recent surgery)</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>HmG–CoA</th>
<th>Mevalonate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isopentyl-PP</td>
</tr>
<tr>
<td></td>
<td>Squalene ← Farnesyl-PP</td>
</tr>
<tr>
<td></td>
<td>Cholesterol ← Heme A</td>
</tr>
<tr>
<td></td>
<td>Isoprenylated Proteins</td>
</tr>
<tr>
<td></td>
<td>Dolichol</td>
</tr>
<tr>
<td></td>
<td>Ubiquinone (CoQ10)</td>
</tr>
</tbody>
</table>

Table 3.
Many of the patients using gemfibrozil in 2001 were also receiving concomitant fluvastatin. This combination has been shown to be safe and effective. However, a therapeutic interchange occurred in some clinical settings. Some patients who were previously receiving the fluvastatin-gemfibrozil combination potentially may have received the cerivastatin-gemfibrozil combination and, thus, had subsequent adverse clinical reactions.

It has long been known that the cytochrome p450 3A4 (CYP3A4) system can affect the metabolism of such statins as lovastatin, simvastatin and atorvastatin. CYP3A4 inhibitors such as amiodarone, erythromycin, clarithromycin, itraconazole and ketoconazole appear in the warning section of the various package insert materials. Combinations of these or other inhibitors can decrease statin metabolism and subject the patient to potentially increased levels and a higher incidence of side effects.

P-glycoprotein (P-gp) is a member of the adenosine triphosphate (ATP) binding cassette-subfamily B. P-gp is the 170-kD protein product of the MDR1 gene. Many compounds can alter the function and/or expression of P-glycoprotein. A number of clinically important drug-drug interactions, the mechanisms of which previously were unexplained or attributed solely to inhibition of cytochrome P450 (CYP), are mediated by P-gp or concomitantly through P-gp and CYP modulation. Verapamil, cyclosporine, erythromycin, ketoconazole and tamoxifen are examples of agents that have demonstrated either in vitro or in vivo inhibition of P-gp function. An interesting feature of P-gp is the interaction with drug metabolizing enzymes, specifically CYP3A4. P-glycoprotein and CYP3A4 share many substrates and inhibitors and have a common tissue distribution. A substrate for both P-gp and CYP3A4 entering the enterocyte may be absorbed directly into the systemic circulation, metabolized by CYP3A4 in the enterocyte, or secreted back into the intestinal lumen by P-gp. Drug pumped back into the lumen may be reabsorbed at a distal site and exposed again to any of the three fates previously described. This may create a cycling effect (enteroenteric recycling) and increase the mean residence time in the intestinal lumen and interaction, in the case of statins, with HmgCoA reductase. Fluvastatin and pravastatin consistently demonstrate no significant inhibition of P-gp transport. Rosuvastatin acid and lactone do not appear to be substrates for P-gp. The effect of P-gp largely occurs with lovastatin, simvastatin and atorvastatin. Common P-gp drug interactions are shown in Figure 2.

Recommendations Regarding Statin and Muscle Safety

While changes in CPK levels rarely correlate with myopathic symptoms, we recommend the following. Obtain baseline CPK in high-risk patients (renal dysfunction, liver disease, polypharmacy). Routine CPK level assessment is not recommended in asymptomatic patients.

![Statin Pharmacokinetics](image)

![Statin and P-glycoprotein modulators](image)
You may consider routine CPK levels in patients with muscle-related symptoms. Rule out other etiologies in other symptomatic patients or those with elevated CPK levels (hypothyroidism, trauma, seizures, infection, strenuous physical activity). Exacerbating factors, such as concomitant medications and herbal remedies, should be considered.

Management of Muscle Symptoms

If intolerable muscle symptoms develop, discontinue statin regardless of CPK levels and re-challenge only after the patient becomes asymptomatic. If muscle symptoms are tolerable and CPK elevation is moderate to severe, then discontinue statin therapy and weigh the risks and benefits. For patients in whom muscle symptoms are absent or present and CPK elevation is associated with elevated creatinine or a need for intravenous hydration, then discontinue therapy.

Alternative Statin Regimens

Many alternative regimens have been studied. Pravastatin may be tolerable when lovastatin and simvastatin have proven intolerable. Daily fluvastatin has been studied as an alternative regimen for these patients. While not included in the package insert information or reported in peer-reviewed clinical trials, rosuvastatin has become a popular option with weekly, twice weekly and alternate-day regimens proven to have hypolipidemic properties while remaining tolerable. Atorvastatin in non-conventional dosing has also been studied. Many still use ezetimibe despite a lack of demonstrated clinical outcomes. Ezetimibe 10 mg daily dose offers an additional 18% to 20% reduction in LDL and, for those patients who are intolerant, a 5 mg daily dose can be added. This offers approximately 15% additional reduction in LDL when combined with a statin.

Colesterol alone or in combination with ezetimibe has been used to enhance LDL lowering. Colesevelam also has shown secondary benefits with anti-inflammatory effects on the endothelium. Nicotinic acid and bile acid resins have been extensively studied and may be excellent options in this patient population. Recently increased use of over-the-counter red rice yeast has become popular among patients. The caution is that these products are not standardized and are recommended only as nutritional supplements. Most importantly, recommended daily doses of these products may contain from 5mg to 20mg of lovastatin clinical activity.

Recommendations

There are many options to manage the statin-intolerant patient. Begin with a thorough past medical history and blood tests to rule out other causes of myopathy, such as hypothyroidism as noted in the previous chart. In our case patient, it may also be advisable to perform an ankle-brachial index to rule out leg pain in this setting of known diabetes mellitus (DM). Consider a number of statin and non-statin options, specifically since response from one statin does not indicate failure with another, likely related to lipophilicity and metabolism mechanisms. Most importantly, listen to the patient, evaluate his or her responses and do not be in a rush to greatly lower lipids. The crucial factor is to treat the patient to achieve lipid-lowering effects utilizing whatever regimen the patient can tolerate without causing severe adverse events. Keep in mind this may necessitate the use of low-dose combination therapies to achieve the patient’s individual goal.

Disclosure Statement: Dr. Kellick has no relevant disclosures. Ms. Long has received honoraria related to consulting from Genzyme. Ms. Ross has received honoraria related to speaking from Abbott Laboratories, Bristol-Myers Squibb, Kowa Pharmaceuticals America, Kaneka Pharmaceuticals and Sanofi-Aventis. Ms. Ross has received honoraria related to consulting from Genzyme and Kaneka Pharmaceuticals. Dr. Cziraky has no relevant disclosures.

References are listed on page 33.
Specialty Corner:
What Is the “Best” Weight-Loss Diet?

The ongoing overweight/obesity epidemic coupled with many associated adverse health outcomes has been the impetus for identifying the ideal weight-loss diet. There are never-ending claims for the weight-loss advantages of one diet regimen versus numerous others. Consumers and healthcare professionals are inundated with countless diet books, websites, infomercials and advertisements that feature the latest “sure-fire” simple strategy for losing unrealistic amounts of weight fast. Buried in this avalanche of fad diet books are some reputable weight-loss approaches. The challenge for consumers is sorting fact from fiction in deciding which weight-loss diet to follow. Moreover, healthcare professionals must offer sound advice to their patients about losing weight in a sensible and effective manner. This Specialty Corner summarizes the current evidence-based research about the effectiveness of weight-loss interventions.

The National Weight Control Registry (NWCR) was developed to identify the characteristics of people who have succeeded at long-term weight loss. More than 5,000 people in the NWCR have lost significant amounts of weight and kept it off for long periods of time (On average, they lost 66 pounds and kept it off for 5.5 years.) The key characteristics of this cohort are that they modified food intake by decreasing calories and fat, increased physical activity by walking (an average of 1 hour a day), consumed breakfast, weighed themselves weekly and watched less than 10 hours of TV a week. The results of this ongoing study are useful in clinical practice for providing patients with simple strategies they can implement for weight control.

As valuable as the NWCR evidence is, one of the greatest debates about the best weight-loss diet program pertains to which mix of macronutrients is most effective in promoting weight loss. To date, the evidence on type of diet suggests that any diet regimen can promote weight loss and reduce cardiovascular disease risk factors; however, the challenge is to sustain the weight loss for a lifetime. This is where the problems begin. In a 2005 study conducted by Dansinger et al.¹ and designed to evaluate the effects of Atkins (carbohydrate restricted), Ornish (fat restricted), Weight Watchers (calorie restricted) and Zone (macronutrient balanced) diets, only 25% of the participants sustained a weight loss of more than 5% of initial body weight after one year. In this study, the average weight loss for participants on all the diets was 2.9 kg (6.4 pounds). In addition, only from 50% to 65% of the participants completed the one-year weight loss study.

Numerous studies have been conducted to evaluate the effects of low-carbohydrate (and high-protein) weight-loss diets compared with low-fat weight-loss diets and other diets (i.e., Mediterranean-style diets and higher-fat diets). A Bonow and Eckel review² published in 2003 summarized the early literature on the effects of different diets on weight loss, weight maintenance and lipid/lipoprotein levels (Table 1). In general, the research...
shows that low-carbohydrate diets may produce greater short-term (six months) weight loss than low-fat, calorie-restricted diets.3-7 In contrast, in the longer term (from one to two years), the results are variable; some studies found greater weight loss with low-carbohydrate diets than with low-fat diets,7,8 whereas others found no difference.1,3,9,10 One of the more recent prominent studies is a two-year weight-loss trial conducted in Israel with 322 moderately obese subjects who were randomized to a low-carbohydrate diet, a Mediterranean-style diet, or a low-fat diet.8 The mean weight loss for the low-fat group after two years was 2.9 kg (6.4 pounds). It was 4.4 kg (9.7 pounds) for the Mediterranean diet group and 4.7 kg (10.4 pounds) for the low-carbohydrate group. The greatest weight loss was in the Mediterranean diet group and the low-carbohydrate group versus the low-fat group. Interestingly, the low-carbohydrate group had lost about 6.5 kg (14.3 pounds) at six months but regained almost 2 kg (4.4 pounds) during the next 10 months, after which time subjects maintained a similar weight loss compared the Mediterranean diet group. Subjects on the low-fat diet had a similar weight loss at six months compared with the Mediterranean diet group but gained weight thereafter such that they had the smallest weight loss at the two-year mark. In contrast, the Mediterranean diet group lost weight over about a one-year period and maintained it thereafter.

The POUNDS LOST Study recently evaluated the effects of four weight-loss diets with different macronutrient profiles.11 This study is one of the largest diet comparator studies to date; 811 participants followed weight-loss diets designed to achieve a caloric deficit of 750 kcal a day. The four diets tested were: (1) 20% fat (low fat), 15% protein (average protein) and 65% carbohydrate (high carbohydrate); (2) 20% fat, 25% protein (high protein) and 55% carbohydrate; (3) 40% fat (high fat), 15% protein and 45% carbohydrate; and (4) 40% fat, 25% protein and 35% carbohydrate (low carbohydrate). The patterns of weight loss for all test diets were similar, with an average weight loss of 6 kg (13 pounds) by six months and slow, steady, weight regain thereafter. At the end of the study, participants had lost an average of 4 kg (8.8 pounds). More than 80% of the participants completed the trial. At the end of the trial, from 31% to 37% of the participants had lost at least 5% of their initial body weight; from 14% to 15% had lost at least 10%; only from 2% to 4% had lost 20 kg or more. It is interesting that the POUNDS LOST Study and the Israeli study described above8 report about a 4 kg (8.8 pound) weight loss over two years for participants who remained in the study. This agrees with the 2005 Dansinger study that reported a 3 kg (6.6 pound) weight loss after one year.1

Another study7 evaluated the Atkins, Zone, LEARN (low fat, high carbohydrate) and Ornish diets in overweight/obese premenopausal women (n = 311) for one year. A greater weight loss was observed for the Atkins Diet (4.7 kg/10.4 pounds) compared with the Zone (1.6 kg/3.5 pounds), LEARN (2.6 kg/5.7 pounds) and Ornish (2.2 kg/4.9 pounds) diets. The important point of this study and the ones above, in general, is that the weight loss achieved over a one- to two-year period was from 2 kg to 4 kg (4.4 pounds to 8.8 pounds). In addition, as noted in an earlier review of the literature by Bonow and Eckel,2 the more recent studies also show that losing weight, irrespective of the diet used, has favorable effects on lipid and lipoprotein risk factors.

It is evident from these large studies with different weight-loss diets that it is difficult to achieve and sustain an
appreciable weight loss. Moreover, these studies show for the most part that there is no one “best” macronutrient profile for weight loss. In the POUNDS LOST Study, the message is clear that people need to find a diet they like and can follow.11 Interestingly, Dansinger and colleagues found higher discontinuation rates for the Atkins and Ornish diet groups, suggesting that people found these diets to be too extreme.1 However, Gardner reported a slightly greater weight loss on the Atkins Diet.7 The clinically important “take-home” message is that since diet is for a lifetime, patients must find one that works for them. Unfortunately, the data from these large clinical trials reinforce the challenges associated with significant and sustained weight loss (>10 kg to 20 kg/22 pounds to 44 pounds)).

Now for the daunting question about what weight-loss diet to recommend for your patients. It is a given they need to cut calories. The American Heart Association and the 2010 Dietary Guidelines for Americans are championing a very simple strategy for cutting calories that focuses on decreasing solid fats and added sugars (SoFAS). Americans currently consume 37% of their calories from SoFAS—empty calories that provide energy but few essential nutrients.12 Major sources of added sugars in the diet are soda, energy drinks and sports drinks, grain-based desserts, sugar-sweetened fruit drinks, dairy-based desserts and candy. Major food sources of solid fats in the diet are full-fat dairy products including cheese, pizza, grain-based desserts and fatty meats.13 Focusing on these high-calorie foods as targets to decrease energy intake is a simple strategy that can be communicated to patients succinctly. A positive message to deliver, along with one that recommends eliminating certain foods in the diet (i.e., SoFAS), is to suggest to your patients that they eat more fruits and vegetables. In fact, fruits and vegetables can replace SoFAS-containing foods in the diet and achieve a double benefit—decrease calories and increase the nutrient density of the diet. In addition, increasing fruits and vegetables will decrease the energy density of the diet and cut calories.12 Encourage computer literate patients to visit the MyPyramid.gov website. The new Dietary Guidelines implementation platform will be released soon, so you also can look for this new program for your patients.

In summary, there are many weight-loss diets available. The particulars of the diet composition matter less than does finding one that works for patients and allows them to achieve significant weight loss for a lifetime. A very simple strategy to communicate to patients in practice is to reduce SoFAS. If you can do just this, you have accomplished much in terms of cutting calories in your patients’ diets. As always, including fruits and vegetables will provide life-long health benefits, decrease energy density & calories and improve diet quality. ■

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References listed on page 33.

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In early 2010, 2,492 active National Lipid Association members were sent the Lipid Pulse survey; of those, 657 respondents (26%) completed the survey, which consisted of questions on staffing, lipid practice, testing and general operational questions. This paper is a commentary on the lipid clinic operational component of the survey response, specifically lipid clinic profitability/solvency and lipid clinic vs. lipid specialist function.

Although the NLA’s 2010 Lipid Pulse Membership Survey posited a brief minimal definition of “lipid clinic”—staff and time specifically dedicated to seeing patients for lipid disorders—and “lipid specialist practice”—not a lipid clinic, but an office that receives referrals from other clinicians for patients specifically for lipid management—there is, in reality, what should be a more discriminating characterization of a lipid clinic.

Although there has been no universally accepted definition of a “lipid clinic,” after having visited and consulted with scores of practices aiming to organize something more than just a generalized interest in “cholesterol control” for their patients, I found it necessary in 2003 to qualify what would constitute a reasonable definition of a more focused clinic approach to managing more difficult dyslipidemia/dyslipoproteinemia cases: a coordinated and systematic process whereby patients who have a lipid and/or lipoprotein disorder are identified, risk-triaged and expediently managed to acceptable lipid/lipoprotein and behavioral goals by a qualified and dedicated staff. The assumption with this definition is that dedicated lipid clinics would address more uncommon and complex lipid disorders while providers, in general, would manage polygenic dyslipidemia in a usual care approach.

Moreover, in contrast to usual care, lipid clinic programs possess a number of additional defining characteristics. For example, they employ defined treatment pathways grounded in currently published consensus diagnostic and treatment guidelines for lipid and lipoprotein disorders, e.g., National Cholesterol Education Program—Adult Treatment Panel III (NCEP ATP III), ADA 2011. Furthermore, in contrast to a usual care approach—a lipid clinic service would have dedicated appointment time slots reserved for the expressed purpose of assessing and treating lipid disorders, in contrast to mixing such care with all other medical concerns on a return office visit. This in no way is meant to infer that a lipid specialist/lipidologist who counsels on dyslipidemia outside of a lipid-clinic-only office visit is not managing his or her patients well. Admittedly, there can be a very thin-line distinction—if any at all—between lipid specialist and lipid clinic functions and operation. However, with the aforementioned definition of a lipid clinic in mind, focusing the entire visit on the lipid disorder ensures the dyslipidemia deserves unifocal emphasis. This exclusive lipid focus underscores the central utility of a lipid clinic, and that is specialization of more complex lipid disorders that deserve more concentrated face-to-face provider time. Lipid clinic staff members should also have particular expertise in lifestyle counseling—perhaps not always to the skill level of a dietitian or a clinical...
exercise specialist, but they should be knowledgeable of the central tenets and recommendations for dietary and physical activity approaches that help manage dyslipidemia.

Regarding lipid clinic profitability and solvency of lipid programs, approximately two-thirds of the Lipid Pulse Survey respondents indicated they operate at break-even or better. This, in actuality, may or may not be true depending on whether this response was based on results of a valid cost/benefit analysis. The current fiscal climate for potential large Medicare physician fee cuts and increasing staff costs mean lipid specialists would benefit from performing a thorough analysis of lipid clinic costs and projected revenue.

One of the issues inherent in performing healthcare-related cost-benefit analysis is that the computation of many components of benefits and costs is intuitively obvious, but there are others for which intuition fails to suggest methods of measurement and sources of benefit such as your impact on system revenue.

Direct costs include staff, materials and, in some cases, laboratory costs. Indirect costs, which should be included in your analysis—and performance—include lipid clinic assigned space costs, facility fees and administrative and medical supervision costs. Revenue benefit includes your collectibles—not billables—but should also include what revenue you generate for your institution or healthcare system in terms of what laboratory services you order (e.g., blood assays) and special diagnostic procedures (e.g., treadmill tests, imaging). In my experience, when these considerations are included in the cost-benefit evaluation, most lipid clinics operate at close to break-even.

The following are several suggestions for improving the fiscal health of your program.*

1. Be judicious with new patient and return visit time. New patient visits should not last longer than 25 minutes and return visits no more than 15 minutes; 20 minutes would be exceptional. This would allow at least two new patient visits an hour or from three to five return visits an hour.

2. One way to improve on patient throughput, or increasing the number of return patients seen in an hour, is to have a standing monthly—or more frequent—75-minute patient group education meeting facilitated by a lipid-specialist staff person. This would allow patients to get practical therapeutic lifestyle instruction as well as problem solving. This process can defer many of the lesser issues and questions patients have from the exam room to the classroom and decrease return visit time. Relatively small “co-payments” of around $10 a patient can be generated from these meetings.

3. Be knowledgeable of the current Medicare allowable payments specific to your geographic area for each of the CPT codes you use in billing for new and return patient visits.

4. Consider a concierge delivery approach—i.e., an annual cash fee for services—to lipid and cardiometabolic risk management programming. This approach is growing in popularity but requires judicious pricing and service packaging.

5. Consider re-engineering your lipid clinic staff to provide alternate-day cardiometabolic risk (CMR) reduction services—focused on high-risk primary prevention metabolic syndrome patients, especially your own system’s employees—with lipid clinic visit days. There are growing financial incentives for CMR programming, particularly when the focus is on deferring diabetes risk.

Although there are going to be financial challenges ahead—there are already—the more your lipid clinic prepares for very real opportunities to improve care and improve solvency, the more it will clearly help contribute to your clinic’s improved solvency and success. You can prepare by considering programs such as pay-for-performance adherence to quality measures initiatives1 and improved skill and proficiency at discounted fee-for-service contracting with at-risk employee groups, particularly those at high risk for cardiometabolic disease.

Disclosure Statement: Mr. La Forge has received honoraria related to speaking from AstraZeneca and Abbott Laboratories. Mr. La Forge has received honoraria related to consulting from Genzyme.

References listed on page 34.

*More definitive written information on each of these recommendations, including treatment pathways, can be provided by emailing the author at rlaforge@nc.rr.com.

To read more about the survey, please see “In Search of Self-Awareness: Results of the National Lipid Association 2010 Lipid Pulse Membership Survey” in the February 2011 issue of the Journal of Clinical Lipidology.
Joyce Ross, NP, CRNP, has long been interested in finding ways to prevent heart disease among the hundreds of patients she has encountered throughout her career.

While studying for the first of her two master’s degrees, she became interested in cardiac care. “I was wondering why we wouldn’t do something about heart disease when we were able to do things like send people to the moon,” Ross said. “When I went back to school for my master’s as a nurse practitioner, the question still plagued me about why prevention was not paramount in the fight against the number one killer of the American population.”

Answering a job ad for a preventive cardiology position at the University of Pennsylvania led her to what turned out to be a perfect match. She worked at the university for 14 years, side-by-side with pioneering physician Dan Rader, MD, before leaving the clinical portion of the practice in June 2010.

Among Ross’s many accomplishments at the University of Pennsylvania was the opportunity in 1996 to be part of a team to start a patient on low-density lipoprotein (LDL) apheresis for the first time in clinical practice in the United States. This patient carries the diagnosis of familial hypercholesterolemia (FH) and is still alive today and happily retired.

When working with FH patients, one of the most important considerations is how to help the overall family, Ross said. Parents should be counseled that their child’s medical problem is genetic in etiology and generally results in poor receptor activity and the liver failing to clear cholesterol from the bloodstream, she said, emphasizing that some families initially feel tremendous guilt in thinking that FH stems from poor diet and exercise patterns at home.

After pediatric patients with FH are diagnosed and begin treatment, Ross refers them to a dietitian to talk about patterns of healthy eating and exercise, which can lead to a drop of 18% to 20% in cholesterol levels and the risk of cardiovascular disease, though she cautions that risk can never be managed fully through lifestyle changes alone.

Based on guidelines from the American Association of Pediatricians (AAP), Ross recommends cholesterol testing in children ages 2 and older if at least one of their parents has a history of hypercholesterolemia and premature cardiovascular disease.

With teenage patients who have FH, the year before college creates an opportunity for Ross to have a “straight talk” visit with them. She asks parents to leave the room so she and her patient can have a frank conversation about lifestyle, including sexual activity, what to eat, exercise, and the potential for starting smoking in...
college. For most, this will be the first time such decisions are up to them.

“Those kids need to talk about birth control if they become sexually active,” she said. “Many of them go off to college on statin therapy and we do not want that stopped, nor do we want a pregnancy to occur in the young female while on statin therapy.”

In addition to her professional interest in preventive cardiovascular medicine, Ross’s concern has personal ties: Her husband’s parents both died at age 43 of coronary events related to severe hypercholesterolemia, and her husband developed heart disease in his early forties. As the mother of five children, including two who have FH, she took great interest in learning about the genetic basis for the disease.

“Healthy eating and exercise can lead to a drop of 18% to 20% in cholesterol levels.”

“I didn’t want to see my children walk down the same path that their father and grandparents had traveled,” Ross said. Since leaving the clinical practice at the University of Pennsylvania, Ross spends most of her time raising awareness about FH and cardiac health, in general, and also works on research protocols. In addition, she tries to spread the word about apheresis clinics to people with severe FH and other patients who may have problems with their statin regimen.

“My major goal is to see medicine grow and develop newer technologies so that we may not even need apheresis in the future, but until then, we have found a way to keep people alive,” Ross said. “Some of my patients may never have lived to be teenagers, but now they are adults with children of their own. This success certainly represents one of the major highlights of my career.”

Member Update

Mary McGowan, MD, has accepted the position of Executive Director for Phase 1-4 Clinics at Medpace in Cincinnati, Ohio.

Provident Clinical Research & Consulting, Inc., founded in 2004 by Kevin Maki, PhD, recently was acquired by Mérieux NutriSciences Corporation. Based in Chicago, Provident provides clinical research and consulting services to the food and biopharmaceutical industries and specializes in designing and conducting clinical nutrition trials aimed at managing risk factors for metabolic and cardiovascular diseases. Provident employs more than 40 people. Dr. Maki and his management team will continue in their current roles within Biofortis-Provident USA.

Dean Karalis, MD, was featured in the American Council on Science and Health newsletter for his role as a lead investigator in a study published in the American Journal of Cardiology. The paper, “Achieving Optimal Lipid Goals in Patients with Coronary Artery Disease,” was published in January 2011 and discusses the difficulties physicians experience when trying to control lipid levels in patients with coronary artery disease.

Beth Malasky, MD, recently relocated from Tucson, Arizona, to Boise, Idaho, where she opened a women’s heart clinic. As part of the move, she switched from the SWLA board and recently began serving on the PLA board.

Judy Collins, MSN, started the Rocky Mountain Chapter of the Preventive Cardiovascular Nurses Association (PCNA) with a regional lecture series in Denver, Colorado.

Healthy eating and exercise can lead to a drop of 18% to 20% in cholesterol levels.
Registration Open for Summer CLU

Join your colleagues in Florida for a two-day intensive learning experience. The Summer Clinical Lipid Update features the theme, “The Lipid Consultant: Consultative Challenges and Practical Answers—A Case Approach” and will be held August 26-28 at the Hilton Bonnet Creek in Orlando. In these cutting-edge sessions, thought leaders will present cases and discuss the latest research, guidelines, controversies and clinical strategies. In addition to the sessions, you can take part in special courses that offer comprehensive training and professional development in Clinical Lipidology.

Register at www.lipid.org/summerCLU and book your hotel room early for the NLA discounted rate.

New Online Education Opportunities

The NLA website features an entire library of online education programs available at www.lipid.org/education, including the following recent additions:

- **NLA vClinic**—The newest case activity for the vClinic, “Patient-centric Approaches to Dyslipidemia: Risk Recognition and Management of Low HDL-C” was developed by James Underberg, MD, Jan McAlister, MSN, NP, and Danielle Duffy, MD.

Work up a patient case in this CME/CE activity, earn CME/CE credit, and see how you perform compared to your peers.

- **Lipid Insights Virtual Journal Club**—To view 2010/2011 Lipid Insights webinar programs, please visit www.lipid.org/education/lipidinsights. All programs have been archived for you to view. Topics include our most recent webinar on recent CIMT guidelines, chaired by Ed Gill, MD, as well as the JUPITER Trial, the ACCORD Trial, the Look Ahead Trial, and The Metabolically Endangered Patient on Antipsychotics.

- The next Lipid Insights program will be held June 1st at 7 p.m. EST. Join Harold Bays, MD, and Ralph La Forge, MSc, as they discuss “Physical Exercise and Lipids: Misperceptions, Practicality, and Things Your Patients (and Perhaps You) Don’t Know.” You can register now at www.lipid.org.

- **Personalizing Lipid Management Webinar**—This CME/CE online program is presented in a case-based interactive format and designed to address gaps in knowledge and skills when treating patients with mixed dyslipidemia and associated multiple comorbidities in clinical practice. Chaired by Peter Toth, MD, PhD.

Opportunities for Trainees

To encourage professional development and specialization in Clinical Lipidology, the NLA invites Fellows and Allied Health Trainees to participate in our conferences at a significantly reduced rate, including our Clinical Lipid Updates, held annually in the spring and summer. In addition, the NLA will offer $500 travel scholarship grants (maximum of 15) to help cover the cost of travel and accommodations. Also, Fellows and Trainees are invited to participate in the Lipid Management Training Course at no charge and may enjoy a complimentary one-year membership to the NLA.

Program Directors, Fellows and Trainees may submit their registration and travel scholarship requests to Sandra Goode at sgoode@lipid.org or call the NLA Office at (904) 998-0854.

Graduate Medical Education

NLA members may enroll their Fellows in a special SAP program that allows the trainees to develop their knowledge base, earn CME/CE credits, and benchmark their performance against peers at other institutions. In addition, Fellows are eligible to receive a free hard copy of NLA-SAP Volume I. If you are a Program Director or involved in trainee lipid education, many training materials are available for your use. For more information, please contact Sandra Goode at sgoode@lipid.org.
News and Notes

FH Campaign Launch

The NLA is excited to unveil its new campaign, “FH: It’s Relative—Know Your Family Cholesterol History” during Annual Scientific Sessions in May. The campaign is focused on spreading awareness of Familial Hypercholesterolemia (FH), a treatable but often undiagnosed cholesterol disorder, to the community at-large including patients, practitioners and the media.

Within the pages of this Lipid Spin issue, you will find several FH-themed pieces to complement the campaign. These useful materials also are available on www.learnyourlipids.com, a patient-friendly website maintained by the NLA that recently underwent a major redesign. Please make it a point to visit the website and share it with your patients as a source for accessible information, including material specific to FH.

Earlier this year, the NLA mailed members a letter announcing the FH Campaign, which includes media tours, ads throughout the Yahoo! Network, a television public service announcement, and national radio programs. In addition, members were asked to complete a brief survey and update their office addresses for use as a referral source on the Learn Your Lipids website. To take the survey and update your office address online, please visit www.lipid.org/FHsurvey.

To prepare for the FH Campaign, an NLA panel of FH experts convened in Miami Beach, Florida, in January to craft an executive summary of FH recommendations and five supporting articles. The executive summary is published in the May/June 2011 issue of the Journal of Clinical Lipidology, and the FH supporting articles and a corresponding self-assessment program (SAP) are included as two supplements with the issue. NLA members will receive these materials with their regular mail subscription to the journal. To order additional supplement materials, please call (904) 683-8843.

FH Patient Conference

In March, about 20 patients with FH and their families met with members from the NELA Chapter, the Pediatric Lipid Group, and the Foundation of the National Lipid Association at a special patient conference in Boston. The patients provided feedback about the messaging and tools for the FH Campaign. Alyssa Boucher, the pre-teen sister of a young FH patient, was so moved by the meeting that she drew an interpretation of what an FH family tree looks like:

Please visit www.learnyourlipids.com to read more about the Boucher Family’s patient experience.

Foundation of the NLA Partners with ASH and ABC in Outreach Initiative

The American Society of Hypertension (ASH), Association of Black Cardiologists (ABC), and Foundation of the National Lipid Association partnered to offer free blood pressure, glucose and cholesterol screenings from May 12-14 at three sites in New York City, Long Island, and Paterson, New Jersey. The outreach initiative was part of an annual event geared towards reaching residents in low-access communities who may face barriers to receiving health screenings.

Member Update in Lipid Spin

Lipid Spin now features a new “Member Update” section to share member announcements, ranging from the personal to the professional. To submit news of a career change, a retirement party or anything else you want to share, log in to the NLA website and submit your entry at www.lipid.org/publications/submit.

Patient Education Tear Sheet

Special thanks go to Vanessa Milne, NP, a NELA member who contributed copy for the FH tear sheet on page 39 of this issue. Look for new patient education pieces in upcoming issues of Lipid Spin.
Mark Your Calendars for Upcoming Foundation Events

- Yankees vs. Mets Subway Series fundraiser—May 21  SOLD OUT!
- Cirque de Soleil “La Nouba™” fundraiser during the Summer Clinical Lipid Update, which will be held from August 26–28, in Orlando, Florida. The cost is $100 per ticket. Register online at www.lipid.org/summerclu.

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Get Involved

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2011 Meetings
May 21–24, 2011
ASH Annual Scientific Meeting
New York, NY

June 24–28, 2011
ADA Scientific Sessions
San Diego, CA

June 26–29, 2011
79th EAS Congress
Gothenburg, Sweden

July 6, 2011
Heart UK 25th Annual Conference
University of Warwick, Coventry
United Kingdom

July 14–17, 2011
SCCT 2011
Denver, CO

August 27–31, 2011
ESC Congress 2011
Roissy, France

September 30–October 5, 2011
The Obesity Society’s
Annual Scientific Meeting
Orlando, FL

2011 NLA Meetings
August 26–28, 2011
Clinical Lipid Update—Summer
Hosted by MWLA and SELA
Hilton Orlando Bonnet Creek
Orlando, FL

2012 NLA Meetings
March 9-11, 2012
Spring Clinical Lipid Update
Hosted by PLA and MWLA
Hilton San Diego Bayfront Hotel
San Diego, CA

May 31-June 3, 2012
NLA Annual Scientific Sessions
Hosted by SWLA
JW Marriott Hotel
Scottsdale, AZ

NLA Professional Development Courses
August 25–26, 2011
Lipid Management Training Course
Masters in Lipidology™ Course
Orlando, FL
Hilton Orlando Bonnet Creek

It’s your NLA Community...
Participate in the conversation online at www.lipid.org/topics.
Excerpt from the “High Apolipoprotein A-1” thread:

“The patient is a 56-year-old African American female with a history of hypertension and family history of CAD (not premature). She came to see me because of an abnormal calcium score. Her LDL was 70 and HDL was 82 and apolipoprotein A-1 was 216 and apolipoprotein B was 57. My thinking was that she should be well protected by the high HDL and APOA-1 but was surprised to find CAC. Is this something you have encountered and, if so, what would you suggest as the next step?” – Indu Poornima, MD

Online Activities
Available at www.lipid.org/events
Clinical Feature References


Lipid Luminations References


Practical Pearls References


EMB Tools for Practice References


Case Study References


Specialty Corner References

5. Breem BJ, Seeley RJ, Daniels, SR, and D’Alessio DA. (2003) A Randomized Trial Comparing a Very Low Carbohydrate Diet and a
Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women. / Clin Endocrinol Metab 88, 1617-1623


Lipid Pulse Membership Survey References


Guest Editorial References


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Each of us can accomplish as much as we will work for, work toward and persist in with maximum effort despite external events and distractions. Perhaps a personal example may be instructive.

My own story begins at age 5, when my 40-year-old father died in a small hospital in Manhattan’s Lower East Side ghetto area. His death was precipitated by pneumonia contracted in a post-operative state after an appendectomy. It was an era before antibiotics.

My life changed.

My mother was a woman in her 30s who had an elementary school education, was a recent immigrant from Poland, and now had the sole responsibility of raising three small boys, the eldest of which was 12 years old. My father had worked hard as a tailor, saved diligently and placed his money on deposit at a local bank, which failed as a result of the Great Depression and bank official embezzlement.

After the lawyers were through with the bankruptcy, as a new widow my mother received a pitiful amount of money every month; we barely survived in our poverty-era, cold-water flat with its shared toilet in the hallway. Our family did not use toilet paper, as most think of it, until I was a teenager.

I was enrolled in a nearby elementary school. One day the teacher took the entire class to the local library and each of us received a library card. The librarian changed my life. I became an avid, yet untutored reader, with no mentor and no father. I had no ambition, no drive, and no athletic ability. I was last to be chosen for the street-centered ball games, where dodging the moving traffic was an accepted part of the environment.

About five years later I developed pneumonia; even a child knows when he is seriously ill. Despite the absence of antibiotics, I survived.

After a protracted recovery I returned to school, where I was required to write an essay. Recalling my hospital stay, I decided what I would write—and eventually do. I knew I wanted to become a doctor. I understood they would poke you, squeeze you and listen to you. Then they would speak in an unknown language and somehow make you well. I thought it was powerful magic, and I knew it made me better.

When I told my friends and family I wanted to be a doctor, they were either cynical or actively discouraging. Very few poor Jewish kids without pull (i.e., money for a bribe) managed admission to the limited, quota-driven medical schools of the day.

In high school, I worked after school delivering clothes and studied enough that my friends called me “Professor.” It was not a compliment in my neighborhood, where crime and violence were more highly regarded at the time. I could not get a date for the school prom, so I spent the night studying and crying to myself.

About that time, right after World War II, the state of New York decided to offer a competitive 12-hour examination that was administered to high school seniors over a two-day period. It was open to all students, regardless of parental income. I managed...
I had difficulty during my first year. I believed everyone was smarter than me, and I knew they were older and had more money. Still, I blossomed during the clinical years and loved the work.

I knew I would not have money for the rest of medical school. I considered finding a girl to marry if her father would pay for my education. Fortuitously, at the end of my freshman year, I was notified by a postcard from the state of New York that I had won a three-year medical school scholarship that had just been initiated. The $750 a year for three years provided the required financial resource.

I finished my medical school training, completed competitive residences and cardiology training and met my share of petty tyrants and obstacles along the way. I dealt with them as best I could. I still do.

This is what I believe: This country permitted me to obtain an education I could not afford and to become someone who continues to make a contribution to society. I have served for years as an unpaid reviewer for a dozen medical journals and have provided requested editorials and reviews for *Lancet*, *JAMA* and the *Archives of Internal Medicine*. I also lecture in colleges and other venues as a volunteer teacher and adjunct professor.

I have been asked to lecture on every continent except Australia.

I believe in working hard, making decisions and making a contribution. Many adults in today’s society have problems in each of these areas. I have enjoyed good luck, good health and good timing. I believe in the American dream; in fact, I have paid New York state back more than 100-fold for the scholarships I received as a student.

I knew as a child the role of poverty in the education and maturation of an adolescent. I set up and funded an essay contest in my old high school. There was little enthusiasm in the teacher’s lounge for the invasion of their turf.

Despite all the angst in our national spirits, in our medical care industry and in our political leadership, indeed, despite all too many recent detractions, the history of our country and our citizens of every generation will permit others to repeat my experiences.

This I believe.

Disclosure Statement: Dr. Nash has no relevant disclosures.
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<th>Enteric Coated to Avoid Fishy Repeat</th>
<th>No Prescription Required</th>
<th>Meets AHA Recommendation in just One Soft Gel</th>
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What Is Familial Hypercholesterolemia?

- Familial Hypercholesterolemia (FH) is an inherited disease, in which a genetic alteration causing high blood cholesterol is transmitted from generation to generation.
- **Familial** means it runs in families; sometimes it is possible to trace the disease over several generations.
- **Hypercholesterolemia** means high blood cholesterol.
- The type of cholesterol that is specifically increased in Familial Hypercholesterolemia is Low Density Lipoprotein-Cholesterol (LDL-C).
- Individuals with FH may look perfectly healthy and are able to have a normal, active life.

Why Is This Important?

FH is the most common genetic disorder. Approximately 1 in 500 people in the world has a genetic alteration that causes FH. If one parent has FH, there is a 50% chance that their son or daughter will also have it. FH is associated with an increased risk of heart disease.

There is no cure for FH but it can be successfully treated.

What Is Cholesterol?

Cholesterol is a fatty substance needed to build cells, make hormones and bile acids.

What Is LDL-Cholesterol?

- Often referred to as “bad cholesterol”
- LDL-cholesterol floats in the blood stream and transports cholesterol from one cell in your body to another cell.
- Too much LDL-cholesterol in your blood stream is not good for you; excess cholesterol can be deposited in the walls of blood vessels making them narrower and causing the onset of heart disease.

Cholesterol Levels in FH

Blood tests may show:
- High levels of total cholesterol
  - Greater than 250 mg/dL in children
  - Greater than 300 mg/dL in adults
- High LDL levels
  - Greater than 170-200 mg/dL in children
  - Greater than 220 mg/dL in adults

When to Suspect FH

This family tree shows four generations affected by FH.

<table>
<thead>
<tr>
<th>Generation</th>
<th>Sample Generation Example</th>
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<tr>
<td>1</td>
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Diagnosis/Symptoms

- A routine blood test shows high cholesterol
- A heart attack before the age of 50-60
- Family history of cardiovascular disease early in life
- Swollen tendons on the heels and hands
- Yellowish areas (cholesterol deposits) around the eyes

What About My Children?

If you have FH your children should be screened and tested as early as possible. People with FH are born with it. An early diagnosis and early changes in diet and eating habits can help reduce the impact later in life.
The aim of treatment is to reduce your LDL-cholesterol to an acceptable level, thereby preventing or delaying heart disease. A lipidologist, a healthcare provider who specializes in treating diseases like FH, can develop the best treatment plan for you. To locate a lipidologist in your area, visit www.learnyourlipids.com.

**Medication**

The most important cholesterol-reducing drugs used to treat FH are **statins**. These medications work by reducing cholesterol production in cells. Other medications such as ezetimibe, niacin and bile acid sequestrants may also be taken to lower LDL levels.

It is important to continue maintaining a healthy diet and lifestyle even if taking a medication.

**Lifestyle Modification**

You can reduce your cholesterol level and protect your heart health by:

- Stopping smoking
- Eating a healthy diet
- Not drinking excessive amounts of alcohol
- Regular physical activity
- Having healthy body weight and shape
- Controlling blood pressure if high

A change in diet is the first step in reducing cholesterol levels. Studies show that cholesterol levels can be reduced by 5-10% simply by changing what you eat.

Physical activity will help reduce your risk of heart disease. Adults should aim for at least 30 minutes of activity five days a week. If this is too difficult, break it down into three 10-minute periods. Any activity you choose should make you feel warm and slightly out of breath, but you should still be able to carry on a conversation. It is a good idea to vary the activity so you do not get bored.

**Apheresis**

In extreme cases of FH where other treatments have failed it may be necessary to mechanically remove LDL-cholesterol from the blood. Apheresis is a treatment similar to kidney dialysis where the patient is connected to a machine where the blood is “cleaned” and then returned to the patient.

**Why Is Lifelong Treatment Necessary?**

Once LDL-cholesterol has decreased as a result of treatment it is important to prevent it from rising again. Your body makes cholesterol on a continuous basis and is exposed to fat and cholesterol in food every day. People with FH cannot regulate cholesterol properly and will need to maintain a healthy diet and lifestyle and continue to take lipid-lowering medication throughout life to keep levels under control.

### Guidelines for a Heart-Friendly Diet

- Eat less fat, particularly less saturated fat
- Replace saturated fat with unsaturated fat
- Eat more foods containing fiber, vegetables and fruit everyday
- Eat less cholesterol-rich food
- Limit food and drinks high in sugar or alcohol
Do you know your family cholesterol history?

Use this tool to learn more about your ancestor’s cholesterol history. When this tool is complete, share it with your healthcare provider to determine if you or your children might be at risk for familial hypercholesterolemia (FH).

For additional information on heart disease and FH visit www.learnyourlipids.com.
The NLA is excited to unveil its new campaign, “FH: It’s Relative—Know Your Family Cholesterol History” during the 2011 Annual Scientific Sessions. The campaign is focused on spreading awareness of Familial Hypercholesterolemia (FH), a treatable but often undiagnosed cholesterol disorder.

Please see the FH tear sheets on pages 39–41 of this issue. These materials and more are available online at www.learnyourlipids.com. To donate please visit www.lipidfoundation.org.