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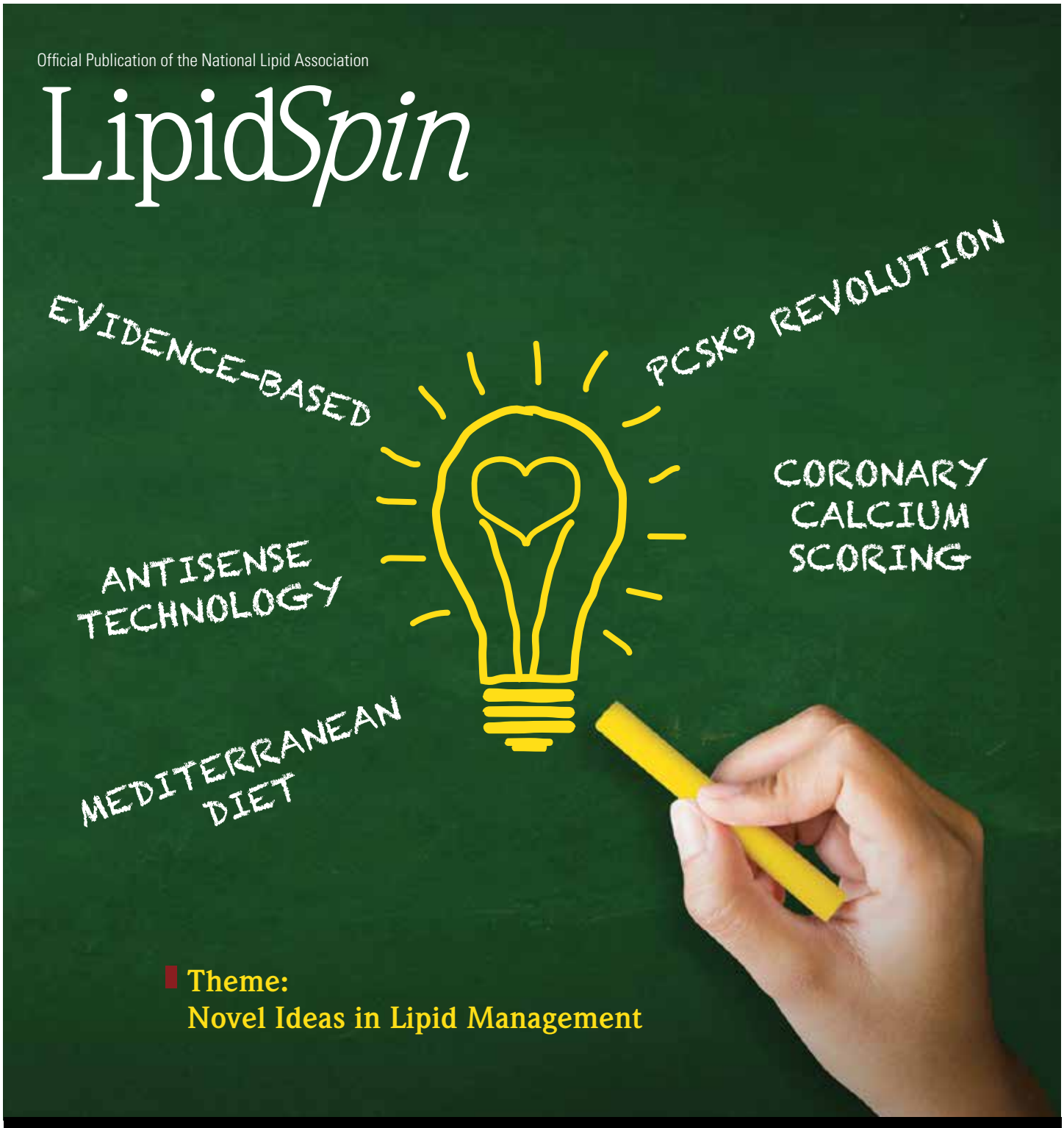
LipidSpin



Theme:
Novel Ideas in Lipid Management

Also in this issue:

The PCSK9 Revolution: Hope or Hype? Latest Clinical Trial Results and Implications

Identifying Risk from Coronary Calcium Scoring

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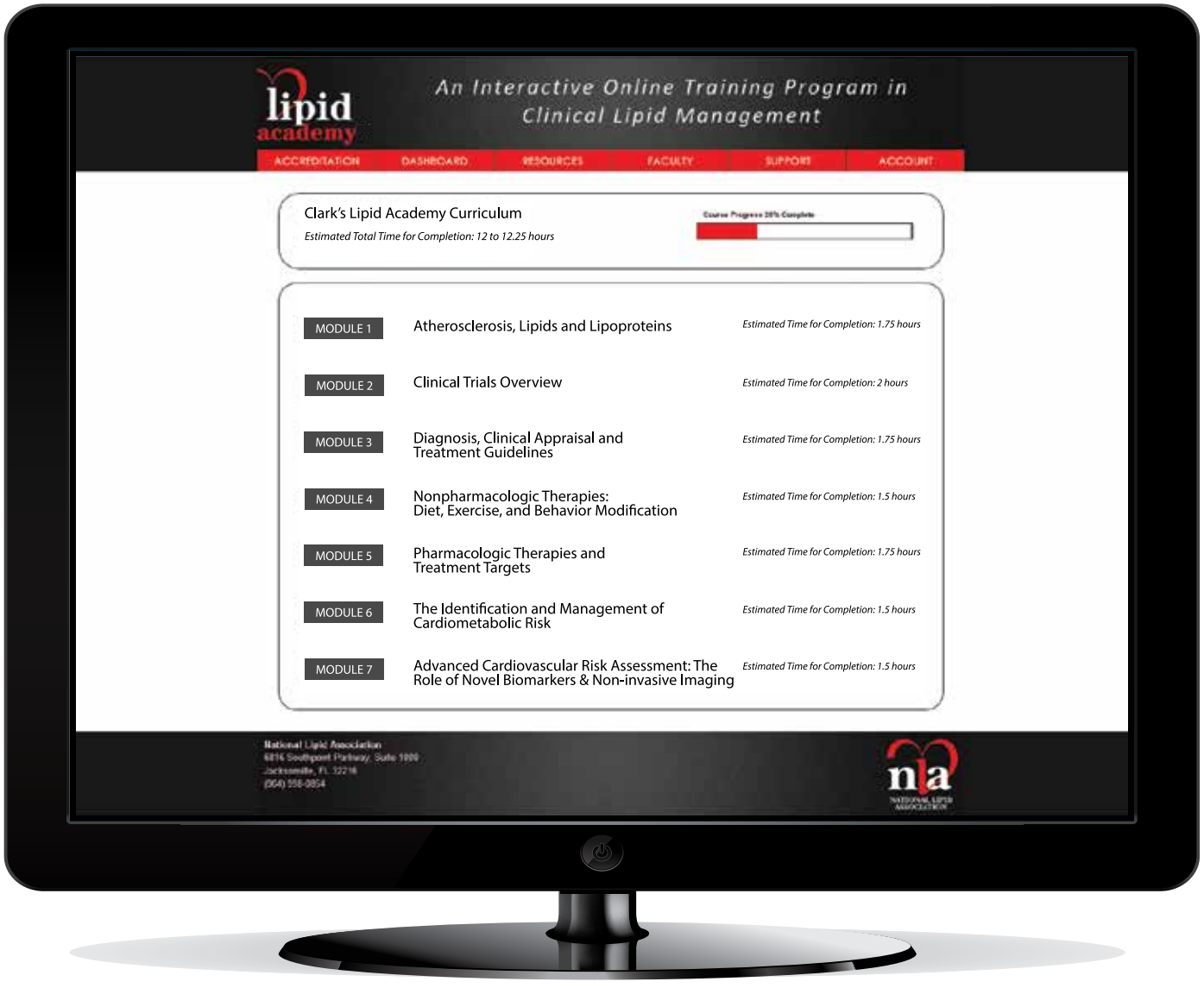

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The National Lipid Association makes every effort to provide accurate information in the *Lipid Spin* at the time of publication; however, circumstances may alter certain details, such as dates or locations of events. Any changes will be denoted as soon as possible. The NLA invites members and guest authors to provide scientific and medical opinion, which do not necessarily reflect the policy of the Association.

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From the NLA President:
A Bright Future

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I am honored and truly humbled to have the opportunity to serve as the President of the National Lipid Association (NLA) during the 2014/2015 term. In just a few months as president, I've seen tremendous strides in the lipid community, which I only hope to continue during the remainder of my term. The initiative taken by members of the NLA and its board during the past year and beyond is not only encouraging — but deeply appreciated. I especially owe a heartfelt "thank you" to the NLA's immediate past-president Matthew K. Ito, PharmD, CLS, FNLA. You've left big shoes to fill.

The 2014 Annual Scientific Sessions in Orlando, Fla., was indeed a successful passing of the torch between Dr. Ito and me. And the sponsoring chapter, the Southeast Lipid Association, should be recognized for all of their hard work.

During this year's Scientific Sessions, the NLA released its draft recommendations for patient-centered management of dyslipidemia. With so many differing guidelines surrounding the management of dyslipidemia — most notably the release of the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines — the NLA worked to convene an expert panel that would provide recommendations to enhance and complement the ACC/AHA guidelines. Following valuable feedback from the lipid community, an executive summary of the NLA's recommendations is scheduled to be published in the September/October issue of the *Journal of Clinical Lipidology*. The feedback that we received from NLA members and other key stakeholder groups was very positive and many suggestions were incorporated in the final document. Phase II of these clinical recommendations is currently in development, and the full paper is scheduled to publish in a later issue of the *Journal.*

Another big initiative from the NLA leadership in the past couple months has been the publication of the NLA Update on Statin Safety 2014 in the *Journal of Clinical Lipidology.* This update included important new information on statin-related muscle side effects along with issues related to statins and diabetes, liver function, cognitive changes, and drug interactions. Another initiative that you may have already participated in was our recent member survey centered on triglyceride education and awareness. The NLA wishes to raise awareness about the significant role triglycerides play in patients' lives. If you participated in the survey — thank you! Your feedback will be a valuable tool in helping us deliver improved educational messages to our members and the public.

As we look ahead, the NLA has many exciting events scheduled. The 2015 Spring Clinical Lipid Update — sponsored by the Pacific Lipid Association and Southwest Lipid Association — will take place Feb. 27– March 1, 2015, in Denver. In addition, the 2015 Annual Scientific Sessions will be hosted by the Midwest Lipid Association June 11–14, 2015, in Chicago. Please check lipid.org/conferences frequently for ongoing updates on all upcoming meetings. Your involvement is important to the future success of our organization. So we hope to see you there!

Again, thank you for this opportunity and privilege to serve as your president. And thank you for your continued support of the National Lipid Association. It does not go unnoticed. Keep the lines of communication open and I am looking forward to your feedback and suggestions. ■

From the PLA President:
We Live in Fantastic Times

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Dr. Rosenblit: I am honored to serve as President of the NLA's Pacific Lipid Association (PLA) Chapter. The PLA membership and its board represent diversity of thought and expertise, but our unity lies in an enthusiasm for atherosclerosis prevention through lipid management. We have a responsibility, based on the best available recommendations, to the provision of best possible care to our individual patients, and, guidance to member and non-member health care professionals, either one-on-one, with inquisitive colleagues, or through other larger educational activities. While attempting these achievements, we often face barriers or resistance, such as insurance coverage restrictions in obtaining a desired biomarker test or an imaging study, or using a desired pharmacologic approach, due to formulary limitations or proprietary drug indications, limiting use to the dictated prescribing information. Furthermore, when so many clinical trials have yet to be designed, we lack level-1 evidence answers to many of our burning atherosclerosis prevention questions.

Additional dilemmas faced are the many surprising negative randomized controlled trials (RCTs) and resultant controversies that challenge us to clarify. Plagued with such trials, we explain the result, not necessarily by a drug that does not work, but by a design flaw, or an in-trial mishap. We heavily rely on positive trials for guidelines. CARDS was a "patients with diabetes-dedicated" RCT that demonstrated significant statin therapy benefits. But another similar diabetes-dedicated cohort, ASPEN, and populations of patients with diabetes, in other large RTCs, i.e. ALLHAT and ASCOT-LLA, received no statistical benefit from statins. The latter negative results were explained, at least in-part, by in-trial mishaps of placebo statin drop-in; so we tend to forget these "negative" trials. The results of meta-analyses, which include both positive and statistically insignificant trials, help us with the conglomerate of trials. Adding to the ever-present negative skepticism are media-driven opinions on the risk of diabetes with statin use. Presumably well-meaning pundits still quote ENHANCE and ARBITER-6 (HALTS), as demonstrations of ezetimibe's failure to benefit, even though the wrong population was studied in the former trial, and CIMT progression was slowed or halted by the drug in the latter placebo-less trial. We still hear about the

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failure of fibrates as add-on therapy to statins, based on ACCORD-Lipid, but those quoting the negative trial, fail to qualify the statement, by not describing the prior four major monotherapy fibrate trials that, albeit, post-hoc and hypothesis-generating, demonstrated consistently (emphasis added) that fibrates provide benefit to those with moderate hypertriglyceridemia (>200 mg/dL) and/or low HDL-C, compatible with fibrate mechanisms of actions. We still continue to hear about the failure of niacin in AIM-HIGH and HPS2-THRIVE, among populations of participant CAD patients, already LDL-C, Non-HDL-C and Apo B optimized, prior to randomization, and not likely to benefit, at least, in the usual trial duration. We hear about the failure of low dose omega-3 fatty acid trials, when perhaps high doses may be required. These "negative" study results, understandably, had an impact on the unique 2013 level-1-evidence-based-only ACC/AHA guidelines. Unqualified media-driven conclusions, clearly, have had an impact on colleague physicians and patients, who often discontinue these medications; the only available adjuncts to statin therapy in the "residual risk" setting. Fortunately, NLA experts, even in the face of a negative RCT, often glean important information, addressing and qualifying the setting, with a conversion to useful and ethical information and provide their membership with website position, opinion or action statements.

While we await the potential for expanded use of newly marketed, and also new more potent investigational products, there is much anticipation with the "NLA Recommendations for Patient-Centered Management of Dyslipidemia," as an adjunct to, or harmonization with, the 2013 ACC/AHA guidelines as well as the many other technical and scientific, national and international guidelines of the past few years. The NLA membership has had the opportunity to add critiques and commentaries to the initial draft submitted by its expert panel members and the Executive Summary is due this Fall. Certainly, implementing these evidence-based recommendations will occupy our agendas, at least, over the next few years, to permit the delivery of the best possible care to our individual patients and guidance to those who deliver that care; these are the best of times for prevention of atherosclerosis.

Dr. Bottenberg: Welcome to this edition of the *Lipid Spin*. The Board of Directors of the Pacific Lipid Association (PLA) have decided to focus our issue on the concept of "novel." Merriam-Webster defines novel as "new and not resembling something formerly known or used." We are privileged to be witnessing dramatic changes in the diagnosis and treatment of lipid disorders, as well as the way we view science. The National Lipid Association (NLA) and its chapters are playing a large role as these novel changes arise.

We are seeing the development of new classes of lipid medications including antisense oligonucleotides, microsomal transfer protein inhibitors (MTP), novel peroxosimal proliferator activating receptors agonists, and diacylglycerol acyl transferase-1 inhibitors (DGAT-1), among others. We are focusing on outcomes.

The NLA has been very busy with publications during the past year. The Statin Safety Task Force has published an excellent paper that answers many patient questions. This is a "must read" for us all. Also, the NLA's Recommendations for Patient-Centered Management of Dyslipidemia is quite valuable to those of us treating patients with lipid disorders. I am impressed that we have a document that recognizes that we treat individual patients and not cohorts of patients.

The Spring Clinical Lipid Update in Maui, Hawaii, was devoted to recognizing the differences in various cultures around the world. We recognized that risk is calculated differently in various populations and that it may need to be treated differently as well. We asked our speakers to keep the content directed toward clinicians who treat patients within these different populations. This meeting was one of my favorites.

The NLA Annual Meeting in Orlando, Fla., focused heavily on raising awareness of familial hyperlipidemia (FH). The challenges of making an appropriate diagnosis were discussed in detail, the need for cascade screening was emphasized, and decisions on when to begin lipid therapy was debated. The meeting was quite a success.

My tenure as president of the PLA has been one of the highlights of my career as a physician. I have enjoyed every minute of it. I encourage all who read this to volunteer for the various NLA committees and board positions as they become available. For those without the time, I encourage you to volunteer to speak at your local hospitals and local community groups. Members of the NLA are in a great position to usher in these changes let's continue to lead with novel ideas and strategies. ■

Letter From the *Lipid Spin* Editors: Tele-Lipidology?

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"I sometimes joke that if you come to our hospital missing a finger, no one will believe you until we get a CAT scan, an MRI and an orthopedic consult. We just don't trust our senses."
~ Dr. Abraham Verghese

Recently, I had the opportunity to re-read an old article on the importance of recognizing that achilles tendinitis in a child might be an early physical finding in familial hypercholesterolemia (FH).[1] Just after this, I happened to read an article in *The New York Times* by a colleague of mine, Dr. Danielle Ofri,[2] which discusses the concerns, issues, and perhaps diminishing role of the physical exam in the provider/patient relationship. The article, which is thoughtful and reasonable in it's assessment and conclusions, got me thinking about how this impacts the specialty of clinical lipidology.

No one practicing clinical lipidology would underestimate the importance of the physical exam. I have written about this before; we have dedicated and entire issue of the Lipid*Spin* to this topic.[3] In the diagnosis of inherited lipid disorders, physical diagnosis skills are crucial. The presence of peripheral stigmata of cholesterol deposition such as: xanthoma, xanthelasma, corneal arcus, palmar xanthoma, planar xanthoma, lipemia retinalis, and eruptive xanthoma are all well recognized as part of the physical diagnosis leading to detecting and treating lipid disorders. Diagnostic criteria for many lipid disorders such as familial hypercholesterolemia include the physical exam findings.

In her article, Dr. Ofri points out that the insertion of electronic medical records into the office visit creates a barrier between the patient and the practitioner — often removed when both enter the exam room. While the discovery of physical findings can take place here, often this is when the best "eye-to-eye" contact takes place. Personally, I find this is the time that subtle and seemingly less important aspects of the patients' medical history come to light. This may also be the time that an accompanying partner, spouse or parent is absent, perhaps an opportunity for patients to answer questions more honestly.

Although the EMR is one barrier to this process, it can also be of help. A well-designed EMR will ask for presence or absence of physical findings to assist in the diagnosis. It may also act as a prompt for additional studies or lab testing. On the other hand, this proliferation of additional available testing might also serve to disconnect the clinical lipidologist from the physical exam. While imaging studies, biomarkers, sterol absorption markers, genetic testing, and lipoprotein analysis can be useful in the diagnosis and treatment of patients with lipid disorders, their proliferation can sometimes cloud issues in diagnosis and management. Recent data published in Europe and from clinical trials here in the U.S. has changed the way we think of patients with FH. Overlap between phenotype and genotype is not uncommon, and variations in clinical presentation seem to be the norm rather than the exception.[4]

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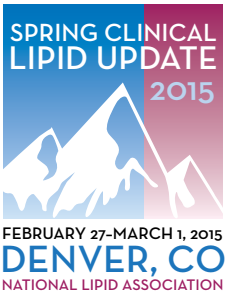
NLA Events Calendar



2015 National Lipid Association Clinical Lipid Update—Spring
Hosted by the Pacific and Southwest Chapters
February 27–March 1, 2015
Grand Hyatt Denver
Denver, Colorado

2015 National Lipid Association Scientific Sessions
Hosted by the Midwest Lipid Association
June 11–14, 2015
Palmer House Hotel
Chicago, IL

2015 National Lipid Association Clinical Lipid Update—Fall
Hosted by the Northeast and Southeast Chapters
September 18–20, 2015
Omni William Penn Hotel
Pittsburgh, PA

Lipid Academy
February 26–27, 2015
Denver, CO

June 10–11, 2015
Chicago, IL

September 17–18, 2015
Pittsburgh, PA

Masters in Lipidology
February 26–27, 2015
Denver, CO

June 10–11, 2015
Chicago, IL

September 17–18, 2015
Pittsburgh, PA

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This leads me to a final proliferative development that I find both exciting and potentially concerning — the slow but steady development of telemedicine and its role in our field of clinical lipidology.[5,6] One might think that the online intake of a history and lab data, along with a phone interview or video-chat might be sufficient for evaluation of a patient with a lipid disorder. For many without access to a specialist this might be true.[7] I do not, however, believe that this process is better than or should replace face-to-face interaction. If these live visits continue to diminish and marginalize the physical exam, we might as well all put on our bedroom slippers, pull up a monitor, and go to work!

"Declare the past, diagnose the present, fore-tell the future."
~ Hippocrates ■

References are listed on page 35.

Clinical Feature:
The PCSK9 Revolution: Hope or Hype? Latest Clinical Trial Results and Implications

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In the late 1980s and in the 1990s, the emergence of the powerful statin drugs transformed treatment of dyslipidemia. Since then they have become the standard of care for managing this condition. Not since that era has there been as much energy, excitement, and promise to further advance our efforts to treat dyslipidemia as that afforded by the development of pro-protein convertase subtilisin-like kexin type 9 (PCSK9) monoclonal antibody therapy. The most recent Phase III trial results are promising as significant advancement.

PCSK9 is a 692 amino acid mature protein, which consists of three domains: prodomain, catalytic, and its C-terminal end. It is primarily expressed as a secreted protease in the liver, intestines, and kidneys. It exhibits rapid turnover in plasma (<10 minutes), and its removal is facilitated primarily by the low-density lipoprotein (LDL) receptor. PCSK9 is a key regulator of LDL receptor expression and degradation.

LDL receptors usually recycle back to the cell surface after they deliver their load of cholesterol intracellularly. However, when secreted, PCSK9 forms a complex with the epidermal growth factor-like domain A (EGF-A) of the LDL receptor extracellular domain; and thus the PCSK9/LDL receptor complex undergoes endocytosis and subsequent degradation.[1] The resulting presence of fewer LDL receptors to process LDL results in a buildup of plasma LDL. Generally, since increased PSCK9 leads to increased degradation of LDL receptors, inhibition of PCSK9 should lead to a significant decrease in low-density lipoprotein cholesterol (LDL-C). Importantly, use of statins and other drugs that lower LDL-C lead to an increase in PSCK9 secretion, an effect that likely decreases the ability of statins to lower LDL-C.

Interestingly, a number of genetic abnormalities have been noted to affect PCSK9 activity. Consistent with this

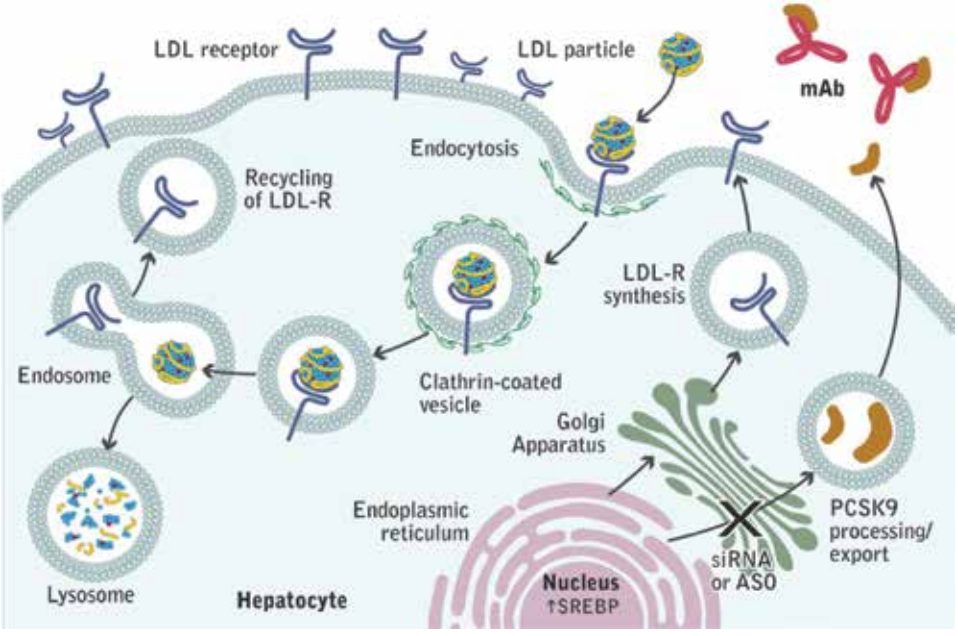

Figure 1. Mechanism of PCSK9 Inhibition. Monoclonal antibodies bind to PCSK9 to prevent the association between PCSK9 and the LDL receptor. The LDL receptor (LDLR) binds the LDL particle and is internalized, and then the LDL particle is degraded in the lysosome, with the LDLR being recycled back to the plasma membrane. Reprinted with permission from Lambert G, Sjouke B, Choque B, et al. The PCSK9 decade: Thematic Review Series: new Lipid and Lipoprpotein Targets for the Treatment of Cardiometabolic Diseases. *J Lipid Res* 2012; 53: 2515-2524.

hypothesis that PCSK9 is a key regulator of the LDL receptor, gain-of-function missense mutations in the PCSK9 gene have been noted to be associated with genetic hypercholesterolemia consistent with the familial hypercholesterolemia (FH) phenotype. In contrast, loss-of-function nonsense mutations have been associated with very low LDL levels and a major reduction in coronary heart disease (CHD) incidence.[2,3]

Potential therapeutic targets for inhibiting the PCSK9 pathway include 1) reducing PCSK9 protein production, 2) reducing PCSK9 mRNA expression, 3) inhibiting PCSK9 binding to the LDL receptor, and 4) inhibiting PCSK9 mediated degradation of the LDL receptor.[4] Many of these strategies are currently being explored with investigational therapies. (Table 1) Of these, using monoclonal antibodies to bind PCSK9 is the strategy that has been most rigorously evaluated to date. When monoclonal antibodies bind to PCSK9, they prevent formation of the PCSK9/LDL receptor complex, leading to a reduction in the degradation of the LDL receptor, thus retaining the ability of LDL receptors to continue to internalize and degrade LDL. (Figure 1)

Lessons Learned from Phase I and II Trials of PCSK9 Monoclonal Antibody Therapy

Early human trials of PCSK9 inhibition with specifically designed monoclonal antibodies provided information regarding efficacy, safety, and tolerability of this strategy. The concepts that were tested included the duration of treatment effect, information on dosing, and intensity of LDL-C reduction with and without the co-administration of statin. For example, a series of randomized, placebo-controlled multiple-dose trials of alirocumab (REGN727) were performed in adults with heterozygous familial hypercholesterolemia (FH) who were receiving atorvastatin (n=21) and those with nonfamilial hypercholesterolemia who were receiving treatment with atorvastatin (n=30) or a modified diet alone (n=10).[5] Among subjects receiving the PCSK9 inhibitor alirocumab, there were no discontinuations because of adverse events. Doses of 50 mg, 100 mg, and 150 mg reduced LDL-C from baseline by 39.2, 53.7, and 61.0 percent, respectively, as compared with placebo ($P<0.001$ for all comparisons). Recently, data were presented on a long-term (up to 64 weeks) extension study of alirocumab in patients with heterozygous FH; in this study LDL-C was reduced by 57 to 66 percent on top of a background of statin and other therapy.[6] These and other studies with alirocumab have demonstrated consistent efficacy, safety, and tolerability.[7,8]

Results have been similar with other PCSK9 inhibitors in development. In Phase II trials, evolocumab (AMG 145) demonstrated up to approximately 60-percent reduction of LDL-C on top of stable statin therapy in persons with heterozygous FH,[9] 20 to 25 percent LDL-C reduction in those with homozygous FH,[10] and 50 percent or greater LDL-C reductions in statin-intolerant patients with or without ezetimibe therapy.[11] In addition, the Open Label Study of Long-Term Evaluation Against LDL-C (OSLER) extension trial of 1,104 patients demonstrated overall 52 percent reductions in LDL-C from baseline over and above any background therapy, as well as sustained improvements in lipoprotein(a) and apolipoprotein B with a similar rate of adverse events to placebo.[12]

There also have been important reports from Phase II studies involving bococizumab (RN316) in statin-treated patients. Here there was demonstrated similar efficacy (reductions in LDL-C of at least 50 percent), safety and tolerability.[13,14] Other PCSK9 monoclonal antibody therapies, including RG7652 and LY3015014, are currently in Phase II studies.

Investigational Agent	Company	Stage of Clinical Development
Monoclonal Antibodies		
Alirocumab (REGN727)	Sanofi (Regeneron)	Phase III
Evolocumab (AMG 145)	Amgen	Phase III
Bococizumab (RN316)	Pfizer (Rinat)	Phase III
MPSK3169A (RG7652)	Genentech (Roche)	Phase II
LY3015014	Lilly	Phase II
PCSK9 Protein-Binding Fragment		
BMS-962476	Bristo-Myers Squibb	Phase I
PCSK9 Synthesis Inhibitors/sRNA		
ALN-PCS02	Alnylam	Phase I
Small Molecule		
SX-PCK9	Serometrix	preclinical

Table 1. Investigational Strategies Affecting PCSK9

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Finally, in addition to monoclonal antibodies, there are a number of other potential strategies to inhibit PCSK9 through other modalities that are in early phase clinical trials. For example, ALN-PCS02 in an investigational anti-sense RNA interference therapeutic that is being studied in Phase 1 studies. Other investigational products under development are listed in Table 1.

Results from Phase III Clinical Trials

Results of Phase III studies with PSCK9 inhibitors have been highly anticipated. Luckily, in the past year we have seen a number of important Phase III trial results either presented or published. The details of the Phase III results available to date with monoclonal antibodies to PCSK9 are outlined in detail below and summarized in. (Table 2)

Phase III clinical trials are those in which the investigational treatment is given to large groups of people to collect information that will allow the drug or treatment to be used safely and confirm efficacy, safety, and tolerability as compared to commonly used treatments. Phase III studies usually are designed in collaboration with the U.S. Food and Drug Administration (FDA) and usually represent the last hurdle to be overcome prior to approval for use in specific clinical indications by the FDA. As of this writing, evolucimab, alirocumab, and bococizumab are all being studied in Phase III clinical trials, and a number of Phase III trials with evolucimab and alirocumab have been completed, and reported and/or published.

The global Phase III program for investigation of alirocumab is known as the ODYSSEY program. Overall, the ODYSSEY program is expected to enroll more than 23,000 subjects in at least 12 planned clinical trials. Of these trials, the first to report was the ODYSSEY-MONO study, in which 103 subjects with LDL-C 100-190 mg/dl and 10-year fatal CVD risk of <5% were randomized to either alirocumab 75-150 mg dosed every two weeks or to ezetimibe 10 mg daily. Use of alirocumab led to LDL-C reductions at 24 weeks of 47.2 percent vs. 15.6 percent in those on ezetimibe.[15] Importantly, many patients were able to achieve a reduction in LDL-C to below 70 mg/dl on the lower dose of 75 mg and did not require uptitration to the 150 mg dose. In general, safety and tolerability of alirocumab was comparable to, or better than, ezetimibe. Another recent one-year open-label study showed further reductions in LDL-C of 57 to 66 percent with alirocumab 150 mg Q2w beyond a statin and ezetimibe in patients with heterozygous FH.[16] Finally, in a placebo-controlled trial on top of atorvastatin therapy, alirocumab 150 mg Q2w was shown to significantly reduce mean LDL particle number (LDL-P) by 63 percent as well as increase HDL particle number (HDL-P) by 11 percent.[17]

The Phase III clinical trial program with evolocumab is known as the Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 in Different Populations (PROFICIO). Recently, a number of Phase III clinical trials with evolocumab have been reported in a wide variety of patient populations. In the LAPLACE-2, study, 1,896 patients with primary hypercholesterolemia were initially randomized to one of five background statin treatments and then further randomized to receive different doses of evolocumab, ezetimibe, or placebo in addition to statin therapy.[18] Overall, use of evolocumab demonstrated reductions

Reference	Population Studied	Drug / Dosage	LDL-C Reduction
LAPLACE-2 (18)	Statin-treated subjects	Evolocumab vs. Ezetimibe or Placebo	55%-76% vs placebo 38%-47% vs ezetimibe
GAUSS-2 (19)	Statin-intolerant subjects	Evolocumab vs. Ezetimibe or placebo	53%-56% vs placebo 37%-39% vs ezetimibe
DESCARTES (20)	Hypercholesterolemia on diet or statin +/- ezetimibe	Evolocumab vs. Placebo	49%-62% vs placebo
ODYSSEY MONO (15)	LDL-C 100-190 mg/dl with 10-year fatal CVD risk 1-<5%	Alirocumab 75-150 mg Q2W vs. Ezetimibe 10 mg	Alirocumab 47.2% compared to base-line Ezetimibe 15.6% compared to baseline
MENDEL-2 (21)	LDL-C 100-190 mg/dl with 10 year CVD risk <10%	Evolocumab vs placebo or ezetimibe	55%-70% vs placebo 38%-40% vs ezetimibe
RUTHERFORD-2 (22)	Heterozygous familial hypercholesterolemia on statin therapy and other indicated lipid-lowering medications	Evolocumab vs placebo	59%-66% vs placebo

Table 2. Summary of Efficacy of PCSK9 Monoclonal Antibody Therapy from Recent Phase III Clinical Trial Data on PCSK9 Inhibitors

in LDL-C of 55 to 76 percent compared to placebo and 38 to 47 percent compared with ezetimibe.

The GAUSS-2 trial randomized 307 subjects with hypercholesterolemia who were unable to tolerate effective doses of statins on at least two occasions in the past to varying doses of evolocumab, ezetime, or placebo.[19] In this study, the mean baseline LDL-C of 193 mg/dl was decreased by 53 to 56 percent from baseline with evolocumab dosed once or twice a month, which was a 37 to 39 percent greater reduction than seen in those treated with ezetimibe. Of the evolucumab-treated patients, 80 to 90 percent of moderate-risk patients and 75 percent of high-risk patients achieved an LDL target of <100 mg/dl compared to only 10 percent of ezetimibe patients.

The Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES)[20] reported on 901 patients given evolocumab 420 mg or placebo every four weeks on top of dietary therapy, atorvastatin 10 mg plus dietary changes, atorvastatin 80 mg or atorvastatin 80 mg plus ezetimibe. Overall, use of evolocumab resulted in LDL-C reductions of 49 to 62 percent reduction across the four groups. In the Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 (MENDEL-2) trial,[21] 614 subjects with LDL-C 100-190 but relatively low cardiovascular risk not on statin therapy were randomized to one of six treatment groups to compare two dosing regimens (140 mg subcutaneously every two weeks or 420 mg subcutaneously every four weeks) with placebo or ezetimibe. In this study, use of evolocumab reduced LDL-C by 55 to 70 percent versus placebo and 38 to 40 percent more than with ezetimibe.

Finally, the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2 (RUTHERFORD-2)[22] randomized 329 patients with heterozygous FH who were on background therapy that usually included statins to evolocumab or placebo, and demonstrated a 59 to 66 percent reduction in LDL-C over and above statin and/or other lipid-lowering therapy. In all five reported evolocumab Phase III studies that have reported to date, safety and tolerability were generally comparable to placebo or ezetimibe comparators.

Outcomes Studies

Important for determining the future role of these agents are clinical outcomes studies designed to examine whether LDL-C reduction from PCSK9 inhibitor therapy, alone or in addition to background statin use, results in further reduction of clinical cardiovascular events. A number of clinical outcome studies with PCSK9 inhibitors are planned and, in many cases, are already enrolling patients. For instance, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study is a secondary-outcomes study planning to enroll 22,500 subjects that will test the hypothesis of whether evolocumab, when used in addition to other dyslipidemia treatments — including statins — will reduce the risk of cardiovascular death, myocardial infarction,

hospitalization for unstable angina or coronary revascularization in subjects who are known to have clinically evident cardiovascular disease.

The ODYSSEY OUTCOMES study also is a secondary-prevention trial that is planning to enroll 18,000 patients and will compare the effect of alirocumab and placebo on the occurrence of cardiovascular events in patients who have had acute coronary syndrome from four to 52 weeks prior to enrollment and are already on other appropriate lipid-lowering medications, including statins. Lastly, the SPIRE 1 and SPIRE 2 trials will examine the effect of bococizumab as compared to placebo in more than 22,000 patients at high risk for cardiovascular events who are already on appropriate lipid-lowering agents, including statins.

Clinical Perspective

In keeping with other contemporary guidelines, the recently released 2013 American College of Cardiology/ American Heart Association Guideline on Cholesterol Management confirms that statins will remain first-line therapy for the treatment of dyslipidemia in patients at elevated cardiovascular risk.[23] Extrapolations from these guidelines suggest that up to 56 million U.S. adults may be eligible for statin therapy.[24] What is clear, however, is that up to 20% of such statin-eligible individuals may either be intolerant to the agents and doses of statin therapy needed to achieve the desired therapeutic response in LDL-C reduction recommended by the new guideline (30–50% on a moderate-intensity statin or at least 50% from a high-intensity statin). Moreover, persons with homozygous or heterozygous FH are well-known to have a reduced response to statin therapy because of their lack of functional LDL receptors and often are far from optimal LDL-C (or non-HDL-C) despite the use of high-intensity statin therapy.

The evidence from the latest clinical trials suggests these groups — those who are statin intolerant and those with familial hypercholesterolemia — as ideal initial candidates for consideration of PCSK9 inhibitor therapy, either alone or in addition to the maximally tolerated dose of statin therapy. The excellent safety and tolerability profile thus far demonstrated has further suggested the promise of these therapies for these groups of patients and, in particular, for the statin-intolerant individual for whom no suitable therapeutic option exists at present. However, even with a patient labeled as "statin intolerant," multiple attempts should be made to get that patient on statin therapy, even a low dose, before consideration of other therapies, including PCSK9 inhibitors when and if they become available.

No other attractive options exist, so we suspect and encourage that PCSK9 inhibitors, when and if approved, will quickly be used in statin-intolerant or FH patients, or for those who do not reach recommended levels of therapeutic response on the basis of statins alone. Whether these agents have a role in secondary prevention for patients at high cardiovascular risk already on high-potency statins remains unclear until we have the results of cardiovascular outcomes studies currently under way. Unfortunately, these critical studies are unlikely to report results prior to 2017.

One intriguing finding of our clinical trials to date with PCSK9 inhibitors has been the effects on lipoprotein(a). Based on our current understanding of lipoprotein(a) physiology and PCSK9 functionality, use of PCSK9 inhibitors would not be expected to have a considerable effect on lipoprotein(a). However, in pooled analysis of Phase II studies with evolocumab, lipoprotein(a) levels have been reduced 25 to 30 percent as compared to placebo.[25]

Similar findings have been demonstrated in Phase III studies with evolucumab and with the other PCSK9 inhibitors in development. Whether these agents will have a role in treatment of patients with high lipoprotein(a) is an important clinical question to be answered in future clinical trials.

Summary

In summary, investigational PCSK9 inhibitors have thus far demonstrated tremendous efficacy in lowering LDL-C with an excellent safety and tolerability profile, either as monotherapy or in addition to statin therapy. Based on these results and the proof of concept supplied by naturally occurring genetic mutations, these products appear to be uniquely positioned to become an important part of our armamentarium in the treatment of dyslipidemia. Importantly, in just a few years, the results of clinical outcomes studies should be available to help us answer the important question of whether there is further incremental clinical event reduction from achieved LDL-C levels beyond that obtained from high-intensity statin use. Making further headway into addressing residual risk that has, thus far, not been achievable from other add-on lipid modifying agents would be truly revolutionary. ■

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References are listed on page 35.

Guest Editorial:
Evidence-Based Medicine Primer

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John is a 55-year-old man who heard on the news that all patients over 50 years old should be taking a statin. He is generally healthy, without high cholesterol, but with a C-reactive protein (CRP) >2. His primary care physician told him that he should watch his diet and exercise more. He would like a second opinion regarding the potential benefits of statins on his risk of having a heart attack or dying prematurely. Would John reduce his risk of major cardiovascular events and death by taking a statin rather than solely relying on diet and exercise?

After conducting a literature search, you determine that the study most applicable to answering your patient's therapy question is the Justification for the Use of Statins in Primary Prevention (JUPITER) trial,[1] which compares rosuvastatin to placebo, in addition to diet/exercise. You recall that randomized controlled trials (RCTs) or systematic reviews are best for answering therapy questions. You recall that JUPITER is a double-blind, randomized trial with blinded outcomes assessors and <1 percent of patients lost to follow-up, but it ended early with only 1.8 years follow-up. Overall, its study design contains most elements that reduce the risk of serious bias. (Table 1) You decide to look at the results. JUPITER shows a 44 percent statistically significant relative reduction in risk of cardiac events with rosuvastatin and a 20-percent reduction in death, which seems pretty good. But you know this is a low-risk group given no history of heart disease and without elevated cholesterol, and you wonder how much absolute benefit John would actually have. You call on a friend, who directs you to the website ktclearinghouse.ca/cebm/toolbox/statscalc, which will easily calculate absolute and relative differences for you. Then you realize it is quite easy to calculate absolute differences yourself, since it is just the difference between the risk of events between the two groups. You find that the absolute reduction in cardiac events with rosuvastatin is 1.2 percent (2.8 to 1.6 percent) and the absolute reduction in death is only 0.6 percent (2.8 to 2.2 percent). Even though the relative reduction in risk is a good magnitude, you are less impressed by the absolute reductions, which seem pretty

small. Plus, there are the potential harms to consider, particularly the development of new-onset diabetes, which has resulted in FDA-mandated monograph changes for statins. You see that the risk of new-onset diabetes in all patients is 0.6 percent higher with rosuvastatin.

You start thinking about another patient of yours, Max, who is higher risk because he already had a myocardial infarction. You definitely treat higher-risk patients like Max with statins, so you decide to review the supportive evidence you use in that treatment decision. You select the Scandinavian Simvastatin Survival Study (4S) trial, the classic landmark study of simvastatin in patients with existing heart disease. Having read the trial before, you recall that it is a double-blind, randomized trial with blinded outcomes assessors, no patients lost to follow-up, and five years of follow-up, a well-executed trial with low risk of bias. 4S shows a 30 percent statistically significant relative reduction in risk of cardiac events with simvastatin (lower than JUPITER), and a 29 percent reduction in risk of death (better than JUPITER). You calculate the absolute reduction in cardiac events in 4S of 6.7 percent and in death of 3.3 percent. These absolute numbers seem more impressive than those seen in a JUPITER population-type patient. You note that few adverse effects were reported in 4S but that creatine kinase (CK) elevation >10x upper limit of normal occurred 0.23 percent more with simvastatin.

You notice that the evidence-based medicine (EBM) website includes the calculation of number needed to treat (NNT) and number needed to harm (NNH), terms you have heard of but have not calculated yourself. You understand that number needed to treat is the number of patients needed to be treated under similar conditions as in the respective clinical trial to avoid one negative event. It seems relatively easy to calculate, simply taking the inverse of the absolute reduction in risk. So, for the 4S trial results, you find that for every 15 patients treated with simvastatin instead of placebo, one cardiac event will be prevented (1/0.067), and for every 30 patients treated with simvastatin instead of placebo, one death will be prevented (1/0.033). The number needed to harm for myopathy from the 4S study is 444 patients (Table 2). So it appears that only a small number of high-risk patients need to be treated before one benefits, while many are exposed before serious myopathy effects may occur. Numerically, the balance clearly favors the potential benefits over the risks in the 4S trial. Although, of course, you need to discuss with your patient and get his or her commitment to the therapy or run the risk of medication non-adherence, which we know is high with statins.

Evaluating Therapy Studies for Bias

Is the study unbiased? (Can I trust that the study results are valid?)

Did the study groups start with the same prognosis?
- Were patients randomized?
- Was randomization concealed?
- Were patients in the treatment groups similar with respect to known prognostic factors?

Was prognostic balance maintained as the trial progressed?
- To what extent was the study blinded?
- Were groups treated equally aside from the study intervention?

Were the groups prognostically balanced at the completion of the trial?
- Was follow-up complete?
- Did the study analysis include all patients who were enrolled in the trial (intention to treat)?
- Was the trial stopped too prematurely?

Table 1: Evaluating Therapy Studies for Bias

> "You realize that the relative reductions in risk that looked so favorable for both studies were misleading when considered in isolation."

Now, turning back to JUPITER and your patient, John, who asked you whether a statin would decrease his risk of having a heart attack or dying prematurely more than diet and exercise would. You calculate an NNT of 84 for cardiac events and 167 for death, and an NNH of 167 for risk of new-onset diabetes. As you closely examine the numbers you calculated in Table 2, you notice that you would need to

	Cardiac events			Death			Side effect	
	Relative risk reduction	Absolute risk reduction	Number needed to treat	Relative risk reduction	Absolute risk reduction	Number needed to treat	Absolute risk increase	Number needed to harm
JUPITER (John)	44%	1.2%	84	20%	0.6%	167	0.6%	Diabetes: 167
4S (Max)	29%	6.7%	15	30%	3.3%	30	0.23%	CK>10x ULN 444

Table 2: Relative and Absolute Risk Reductions

treat many more low-risk patients like John with a statin to prevent a cardiac event or death than high-risk patients like Max. While you intuitively knew this already, putting explicit numbers to the patient cases makes the difference in absolute size of effect more obvious to you. You realize that the relative reductions in risk that looked so favorable for both studies were misleading when considered in isolation. Since the benefit-risk balance is not as obvious as in a high-risk patient, you want to engage in a higher level of shared decision-making with John incorporating his values and preferences.

Overall, the numbers still seem to favor offering treatment to a low-risk patient like John, however, you decide that you will need to let him know the balance between the benefits and the harms of statin therapy. You let John know that, based on well-designed clinical trials, if someone already had heart disease, then only 15 patients would need to be treated before a serious cardiac event was prevented. However, in his case, since he is at low risk for heart disease, 84 patients like him would need to be treated with a statin before one patient would avoid having a serious cardiac event such as myocardial infarction, and the chance of having this benefit is twice as high as having a harm, such as developing diabetes. John says he would really prefer to try more intensive diet and exercise first because of the potential risk of developing new-onset diabetes, and he thanks you for discussing the details with him.

You reflect back on your work and realize that you have learned a lot about how to express the magnitude of the study findings, and have found that calculating both absolute and relative reductions in risk presents a more complete picture that has been helpful in considering the treatment decision questions for your patient. On reflection, you decide that you know some information about what biases clinical trials but realize you need a refresher on study design. You decide to do some further reading online at the JAMA website of the EBM Users' Guide at **jamaevidence.com**.

These examples illustrate the practice of EBM, which includes the following steps:

- create an answerable clinical question
- search for the best evidence
- critically appraise the evidence
  - study design (assessing bias in the methods)
  - results (size of results and precision of results)
- apply the evidence to your patient
- self-assess your skills and abilities

In essence, the goal of EBM is to translate the best evidence into practice. In considering the treatment decisions for these patients, you have incorporated the three key aspects of EBM: the best evidence, your patient's values and preferences, and your clinical expertise. While you have been somewhat reluctant to use the term "evidence-based medicine," since it has been used and misused to the degree that almost everything is called evidence-based medicine or EBM these days, you like the idea of having this explicit framework to help you with your clinical decision-making. You found that there are many tools available for each of the steps of EBM and that you have just scratched the surface on how to express study results in a more meaningful way. Once you get the hang of these simple calculations, you are excited to move on to further EBM tools to help facilitate your patient care. ■

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References are listed on page 35.

EBM Tools for Practice:
Identifying Risk from Coronary Calcium Scoring

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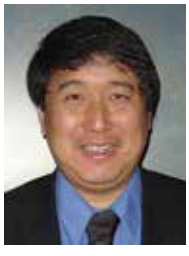

Atherosclerotic cardiovascular disease (ASCVD) is the major cause of morbidity, mortality, and medical costs in the U.S. While ASCVD is largely preventable with a healthy lifestyle and effective medical therapy, identification of individuals at risk for ASCVD events continues to be a challenge. Historically, the Framingham Risk Score (FRS)[1] and now, the Pooled Cohort Risk Equation,[2] are used to estimate 10-year risk of coronary heart disease (CHD) and ASCVD, respectively, and are incorporated into cholesterol treatment guidelines.[3,4] Unfortunately, many patients experiencing ASCVD are not classified as high risk by such approaches.[5] The role of biomarkers and imaging tools has been of interest to those trying to improve risk stratification of asymptomatic individuals. One of the most promising such modalities is coronary calcium scanning by computed tomography (CT); the coronary artery calcium score (CACS) (Figure1) estimates subclinical atherosclerotic burden. The theoretical framework for CACS is based on autopsy studies that consistently demonstrate a unique association between calcification of the coronary arteries and atherosclerosis.[6]

CACS and Prognosis

The prognostic value of CACS is clearly established from a wealth of prospective studies performed in tens of thousands of patients, with strong associations found with ASCVD events and mortality.[7-10] Among the largest, the Multi-Ethnic Study of Atherosclerosis (MESA) study[7] enrolled 6,722 black, Hispanic, Chinese, and white participants. The four-year follow-up of this cohort demonstrated that, compared to individuals with a CACS of 0, those with CACS 1-100 had a 3.9-fold and those with a CACS >100 a 7.1-fold greater risk of CHD events. Also, a normal scan (score of 0) is considered to indicate a "warranty period" of up to five years free from developing future CHD events.[11]

CACS Provides Added Clinical Utility over Global Risk Assessment

Improved discrimination from adding information from CACS can be shown from measures such as the C-statistic, based on the area under the receiver operating characteristic (ROC) curve, which evaluates the overall performance of the risk model. MESA and other

prospective studies have demonstrated improvements in the C-statistic over standard risk factors and/or FRS. Notably, MESA confirmed the incremental value of CACS for predicting CHD events to be consistent across all ethnic groups[7]. However, many advocate the use of the net reclassification index (NRI), which quantifies the clinical utility of a diagnostic test, although —importantly — the NRI depends on the cut points chosen (e.g., for classification of risk category based on 10-year risk of CHD). The NRI is a measure of the appropriate upgrading or downgrading of risk based on the new information provided by a diagnostic test, in this case CACS. Three large trials of distinct populations have shown a significant improvement in the NRI when using CACS to refine risk estimates. In the MESA study, the NRI for the entire population was 25 percent. However, when focusing on the intermediate risk population (the population in which CACS testing is proposed) the NRI increased to 55 percent.[12] The Heinz Nixdorf Recall study found that use of CACS in subjects classified as low-intermediate risk (6 to 20 percent) based on FRS led to reclassification of 31 percent of subjects.[13] Additionally, the Rotterdam study demonstrated an NRI of 52 percent in subjects in the intermediate risk group (in this case 10 to 20 percent by FRS).[14] Overall, the NRI based on CACS in risk-stratification is substantial, particularly in those at intermediate risk, and help define which patients need more aggressive medical management.

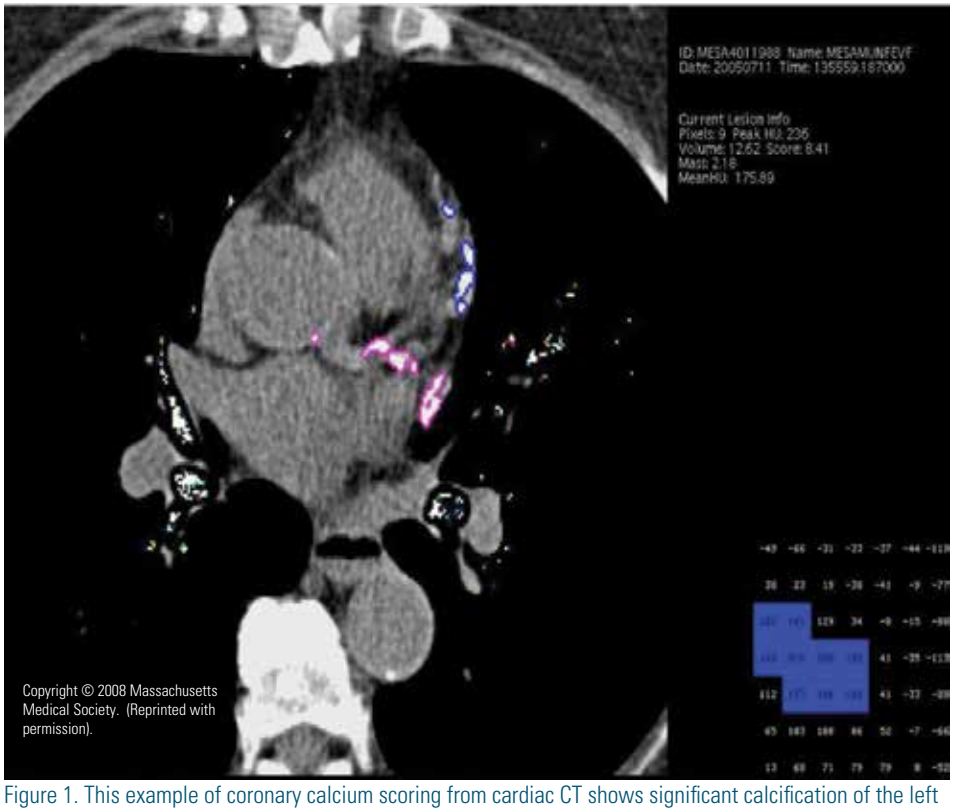

Figure 1. This example of coronary calcium scoring from cardiac CT shows significant calcification of the left main, left circumflex, and left anterior descending arteries.

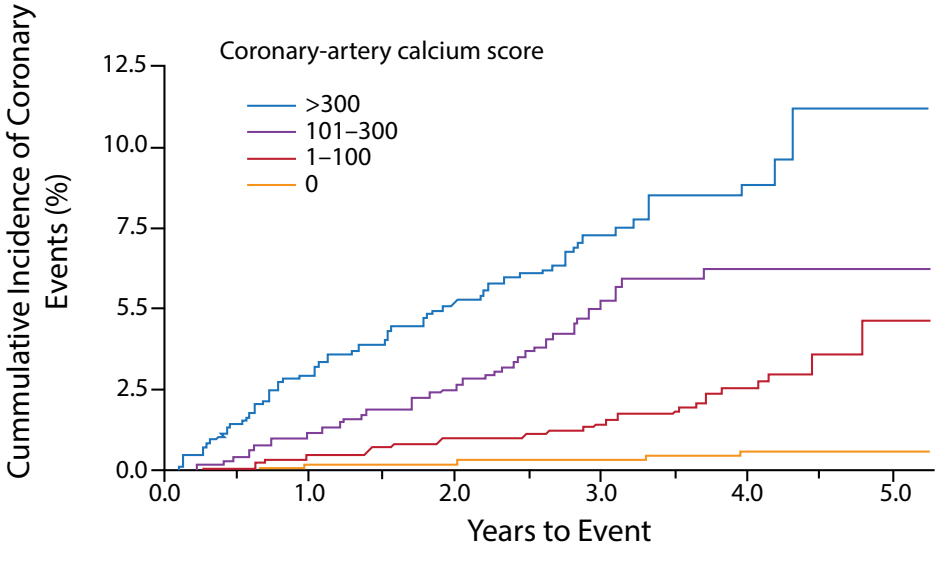

Figure 2. Cumulative incidence of coronary heart disease events by CACS category: Multiethnic Study of Atherosclerosis (from the New England Journal of Medicine, Detrano RC et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups, Volume 358, pages 1336-45, Figure 1 Copyright © 2008 Massachusetts Medical Society. Reprinted with permission).

The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER trial) demonstrated that those with a low-density lipoprotein cholesterol (LDL-C) <130 mg/dL but high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L may benefit from treatment with rosuvastatin.[15] In an analysis from MESA,[16] 950 subjects were found to meet the JUPITER criteria. Interestingly, almost half of those identified had a CACS of 0. Applying JUPITER event-reduction estimates, statin treatment would likely be neither clinically effective nor cost effective (number needed to treat [NNT] = 549). In contrast, most events (74 percent) occurred in individuals with CACS > 100 and, in this group, statin treatment was estimated to be highly effective (NNT = 24). More recently, even greater "efficacy" for prevention of CHD events was shown when applying results of recent polypill trials to MESA, with

NNTs of 18-20 for those with CACS ≥100 and 38-54 for those with CACS of 1-99, but not in those with CACS = 0 (NNTs 81-130).[17] Thus, CACS appears to have significant utility in identifying those most likely to benefit from preventive therapies.

> "CACS is likely to be the most useful screening test to improve risk assessment in those at intermediate risk."

CACS Compared to other Screening Tests

The most robust evidence comparing the utility of CACS to other screening tests derives from Yeboah, et al.,[18] where a direct comparison of the improvement in risk prediction was made using several different biomarkers and screening tests among intermediate risk subjects in MESA. Ankle-brachial index, hsCRP, family history and CACS were all independent risk predictors for incident CHD and ASCVD (brachial flow-mediated dilation and carotid intima-media thickness were not) over FRS and provided significant improvements in C-statistic over FRS alone. However, CACS provided superior risk reclassification compared with the other risk markers. (For incident CHD, the NRI with CACS was 0.659, brachial flow-mediated dilation was 0.024, ankle-brachial index was 0.036, carotid intima-media thickness was 0.102, family history was 0.160 and high-sensitivity CRP was 0.079).

Clinical Recommendations for Use of Coronary Calcium Scanning

On the basis of these consistent observations, the 2010 ACC/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults provided a class IIa recommendation for performance of CACS in intermediate-risk patients and in those aged 40 years and above with diabetes.[19] Recent ACC/AHA Guidelines on the Assessment of Cardiovascular Risk also noted that CACS is likely to be the most useful screening test to improve risk assessment in those at intermediate risk[2] and suggested consideration of CACS evaluation when a treatment decision based on global risk assessment is uncertain. The recent ACC/AHA blood cholesterol management guideline specifically notes that a CACS of >300 or ≥75th percentile for age, gender and ethnicity provides support to revise risk assessment upward and, hence, potentially inform treatment (initiation or intensification) decisions.[4] ■

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References are listed on page 35.

Lipid Luminations:
Antisense Technology: A Novel Strategy for Targeted Drug Development

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The origins of the field of antisense technology date back to 1978, when Zamecnik — who 22 years earlier made the landmark discovery of transfer ribonucleic acid (tRNA) — and Stephenson first reported the ability to inhibit transcription, translation, and replication of Rous sarcoma virus in chicken fibroblasts with the use of small complimentary oligonucleotides.[1] Zamecnik subsequently used antisense oligonucleotides to block replication of influenza, human immunodeficiency virus (HIV), Mycobacterium tuberculosis, plasmodium species, and others.[2] In 1987 he was the first to describe the existence of microRNAs (miRNA), which are endogenous regulators of gene transcription and translation.[2]

In 1992, only 14 years after the initial report of gene silencing by Zamecnik and Stephenson, the journal *Science* designated the burgeoning field of antisense technology and the first experimental use of antisense compounds in humans as one of the top 10 most promising advances in scientific research that year.[3,4] As an additional sign of the importance of this field, the 2006 Nobel Prize in Medicine was awarded to Andrew Fire and Craig Mello for the discovery of RNA interference, the process of gene silencing by double-stranded RNA.[5,6]

In principle, the messenger RNA (mRNA) of any gene can be blocked with antisense technology, but there are numerous technical hurdles that must be surmounted to produce an efficacious and well-tolerated pharmaceutical agent that can reach the target organ and successfully bind and block the target mRNA. Although the realm of antisense development dates back several decades, the first antisense drug in clinical use, fomivirsen (Vitravene), was not FDA-approved for treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients until 1998. The second antisense drug in clinical use, mipomersen (Kynamro), was approved only last year — in January 2013

Examples of areas of application of antisense therapy in clinical trials registered at clinicaltrials.gov. Numbers in parentheses indicate the number of trials.

Atrial fibrillation (1)	Leukemia (17)
AIDS (3)	Lymphoma (12)
Asthma (5)	Melanoma (5)
Carcinoma (26)	Mipomersen (16)
Coronary artery disease (4)	Muscular dystrophy (2)
Crohn's disease (2)	Rheumatoid arthritis (1)
Diabetes (4)	Ulcerative colitis (3)
Ebola virus (1)	Viral hepatitis (6)

Table 1.

— for treatment of homozygous familial hypercholesterolemia (FH). The use of fomivirsen subsequently declined after the advent of highly active antiretroviral therapy (HAART) for treatment of (HIV) infection, which virtually eliminated the occurrence of CMV retinitis. The use of mipomersen continues.

Many new antisense drugs are in various stages of clinical development and are anticipated to greatly expand the breadth of therapeutic interventions that are available for prevention and treatment of disease. ISIS Pharmaceuticals, founded in 1989 by Stanley Crooke, has been a leader in the field, but many other companies have been active in antisense drug development (e.g. Sarepta Therapeutics, Antisense Pharma, Antisense Therapeutics, Gene Signal, Prosensa, Hybridon, Alnylam, and others). There are currently 124 clinical trials related to antisense therapy that are registered at **clinicaltrials.gov** and are either active, completed, or terminated.[7] Examples of areas of investigation are shown in Table 1. Studies also are in progress testing the efficacy and safety of antisense oligonucleotides targeting apolipoprotein CIII (apo CIII) for treatment of hypertriglyceridemia, apolipoprotein(a) [apo(a)] for treatment of elevated lipoprotein(a), C-reactive protein (CRP) for modulation of inflammation and development of atherosclerosis, and other targets related to atherosclerosis and diabetes. This field represents an exciting and promising new era of targeted drug development and disease management.

Terminology Related to Antisense Technology

Antisense Oligonucleotide (ASO): A short sequence of single-stranded bases (often about 20 bases) that is complimentary to a mRNA sequence of interest and can block translation

DNA: Deoxyribonucleic acid, the backbone of genes and chromosomes

Messenger RNA (mRNA): mRNA is produced from genes by transcription and is read to produce proteins through the process of translation. mRNA consists of a sequence of nucleotides that are arranged in so-called codons, each of which contains three nucleotides that encode a single amino acid or a stop codon (terminates protein synthesis)

microRNA (miRNA): Small endogenous non-coding fragments of RNA that are involved in modulation of transcription and translation through binding to complimentary sequences of mRNA

RNA: Ribonucleic acid, the message produced from genes by transcription. RNA can be messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA) or micro RNA (miRNA)

Ribosomal RNA (rRNA): rRNA is a sequence of nucleotides that combine with proteins to form ribosomes that catalyze the covalent bonding of amino acids to the end of the growing peptide chain during translation of mRNA

Ribosome: A particle comprised of mostly ribosomal RNA in combination with protein that moves along a strand of messenger RNA during translation and facilitates covalent binding of amino acids at the growing end of the translated protein

RISC: RNA-induced silencing complex (RISC) is a nuclear complex that targets RNA for degradation by helicase and other RNAses

RNAse: One of many enzymes that degrade RNA

Small interfering RNA (siRNA): siRNA is double-stranded RNA that is complimentary to an mRNA sequence of interest and can block translation

Small nuclear RNA (snRNA): snRNA is a sequence of nucleotides that is involved in splicing pre-mRNA in the nucleus

Small nucleolar RNA (snoRNA): snoRNA is a sequence of nucleotides that is involved in methylation of bases or isomerization of uridine in pre-rRNA

Transfer RNA (tRNA): tRNA is a sequence of nucleotides that facilitates the transfer of amino acids to nascent proteins during translation of mRNA. Each tRNA binds a specific amino acid and recognizes the corresponding codon in mRNA

Transcription: The process of reading genes to produce ribonucleic acid (RNA) in the first step of gene expression

Translation: The process of reading messenger RNA (mRNA) to produce proteins in the second step of gene expression

Table 2.

The basic principle of antisense technology is the suppression of gene transcription or mRNA translation with an interfering short sequence of bases that is complementary to the gene of interest. For readers who are unfamiliar with the terminology in this field, some of the terms are defined in Table 2. In most cases, the mRNA is targeted with an oligonucleotide that blocks translation and typically targets the mRNA for degradation. Antisense oligonucleotides (ASOs), such as mipomersen and other ASOs in development, are designed to bind a complimentary sequence of mRNA and block translation, but also target the mRNA for degradation typically by RNAse H, which frees the ASO molecule to repeatedly bind and degrade multiple mRNA molecules. Double-stranded small interfering RNA (siRNA) sequences block translation by binding of a single antisense strand of the siRNA to the complimentary strand of mRNA of interest, but also target the mRNA for degradation through the RNA-induced silencing-complex (RISC) pathway.

> "There are currently 124 clinical trials related to antisense therapy that are registered at clinicaltrials.gov and are either active, completed, or terminated."

Mipomersen is a 20-base pair second-generation ASO that is complementary to mRNA for apoprotein B-100, the primary structural protein in very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and lipoprotein(a) particles.[8] Binding of mipomersen to the complimentary strand of mRNA targets the mRNA for degradation by RNAse H, which depresses production of apoprotein B-100 and decreases the plasma concentration of LDL cholesterol by 25 to 37 percent, with similar decreases in VLDL cholesterol, apoprotein B-100, and lipoprotein(a). Although mipomersen is FDA-approved at a dose of 200 mg subcutaneously weekly only for treatment of homozygous FH, the results of several six-month blinded placebo-controlled clinical trials have demonstrated efficacy in heterozygous familial hypercholesterolemia and other subjects with refractory hypercholesterolemia. The results of long-term open-label studies have demonstrated sustained efficacy and stability of side-effects over two to four years.[9,10]

The future of antisense technology remains bright and has the potential to produce major breakthroughs in our ability to manage many human diseases, some of which are currently untreatable or difficult to manage with existing interventions. Expectations are high for the completion of clinical trials that will lead to clinical availability of important new antisense medications in coming years. ■

Disclosure statement: Dr. Duell has received honorarium from Merck, Aegerion, Genzyme, and Novartis, and has received research grants from Bristol-Meyrs Squibb and Genzyme.

References are listed on page 36.

Practical Pearls:
Effects of the Mediterranean-Style Diet on CVD Risk Factor

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Introduction

In the late 1980s, the Mediterranean-style eating pattern received attention after the results of the Lyon Diet Heart Study were published. More recently, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on Lifestyle Management to Reduce Cardiovascular Risk Work Group examined studies involving the Mediterranean-style dietary pattern when developing its diet recommendations, which include: "consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red meats."[1] The traditional Mediterranean-style eating pattern includes a high consumption of fruits and vegetables; unrefined bread and cereals; potatoes, beans, nuts, and seeds; olive oil or canola oil as the primary fat source; lower-fat dairy products; fatty fish and poultry consumed in low to moderate amounts; eggs consumed less than four times weekly; little red meat consumption; and wine consumed in low to moderate amounts.[1-3] Therefore, according to ACC/AHA Guidelines on Lifestyle Management, the Mediterranean-style diet is one of several dietary patterns that may be followed by patients to reduce cardiovascular disease (CVD) risk. The challenge has been determining which components of the Mediterranean eating pattern provide its beneficial effects. Research that has examined single components or nutrients of the Mediterranean-style food pattern has failed to support evidence of CVD prevention. More recent research has focused on a Mediterranean Diet (MedDiet) score to determine the association of adherence to the Mediterranean dietary pattern and a decreased risk of CVD risk factors, CVD, and mortality, in general.

Butter/Margarine	Olive Oil
1 tsp	3/4 tsp
1 tbsp	2 1/4 tsp
1/4 cup	3 Tbs
1/3 cup	1/4 cup
1/2 cup	1/4 cup + 2 tbsp
2/3 cup	1/2 cup
3/4 cup	1/2 cup + 1 tbsp
1 cup	3/4 cup

Source: thepassionateolive.com/wp/baking-with-olive-oil-instead-of-butter/

Table 1. Substitution of olive oil for butter in baking[12]

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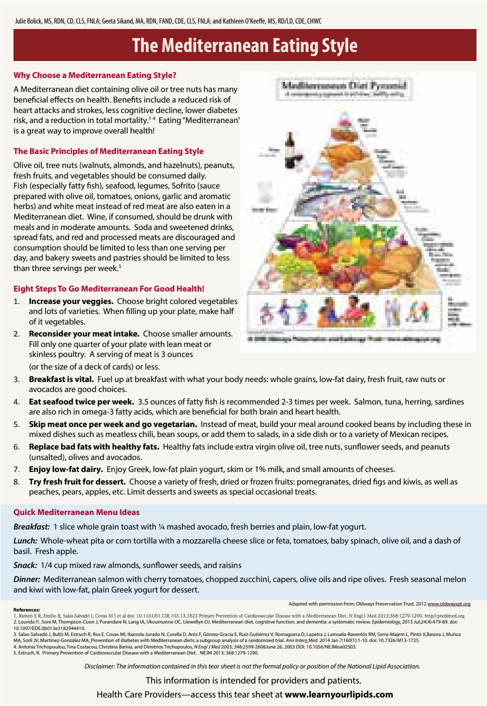
Julie Bolick, MS, RDN, CD, CLS, FNLA; Geeta Sikand, MA, RDN, FAND, CDE, CLS, FNLA; and Kathleen O'Keeffe, MS, RD/LD, CDE, CHWC

The Mediterranean Eating Style

Why Choose a Mediterranean Eating Style?

A Mediterranean diet containing olive oil or tree nuts has many beneficial effects on health. Benefits include a reduced risk of heart attacks and strokes, less cognitive decline, lower diabetes risk, and a reduction in total mortality.[1-4] Eating "Mediterranean" is a great way to improve overall health!

The Basic Principles of Mediterranean Eating Style

Olive oil, tree nuts (walnuts, almonds, and hazelnuts), peanuts, fresh fruits, and vegetables should be consumed daily.
Fish (especially fatty fish), seafood, legumes, Sofrito (sauce prepared with olive oil, tomatoes, onions, garlic and aromatic herbs) and white meat instead of red meat are also eaten in a Mediterranean diet. Wine, if consumed, should be drunk with meals and in moderate amounts. Soda and sweetened drinks, spread fats, and red and processed meats are discouraged and consumption should be limited to less than one serving per day, and bakery sweets and pastries should be limited to less than three servings per week.[5]

Eight Steps To Go Mediterranean For Good Health!

1. **Increase your veggies.** Choose bright colored vegetables and lots of varieties. When filling up your plate, make half of it vegetables.
2. **Reconsider your meat intake.** Choose smaller amounts. Fill only one quarter of your plate with lean meat or skinless poultry. A serving of meat is 3 ounces (or the size of a deck of cards) or less.
3. **Breakfast is vital.** Fuel up at breakfast with what your body needs: whole grains, low-fat dairy, fresh fruit, raw nuts or avocados are good choices.
4. **Eat seafood twice per week.** 3.5 ounces of fatty fish is recommended 2-3 times per week. Salmon, tuna, herring, sardines are also rich in omega-3 fatty acids, which are beneficial for both brain and heart health.
5. **Skip meat once per week and go vegetarian.** Instead of meat, build your meal around cooked beans by including these in mixed dishes such as meatless chili, bean soups, or add them to salads, in a side dish or to a variety of Mexican recipes.
6. **Replace bad fats with healthy fats.** Healthy fats include extra virgin olive oil, tree nuts, sunflower seeds, and peanuts (unsalted), olives and avocados.
7. **Enjoy low-fat dairy.** Enjoy Greek, low-fat plain yogurt, skim or 1% milk, and small amounts of cheeses.
8. **Try fresh fruit for dessert.** Choose a variety of fresh, dried or frozen fruits: pomegranates, dried figs and kiwis, as well as peaches, pears, apples, etc. Limit desserts and sweets as special occasional treats.

Quick Mediterranean Menu Ideas

Breakfast: 1 slice whole grain toast with ¼ mashed avocado, fresh berries and plain, low-fat yogurt.

Lunch: Whole-wheat pita or corn tortilla with a mozzarella cheese slice or feta, tomatoes, baby spinach, olive oil, and a dash of basil. Fresh apple.

Snack: 1/4 cup mixed raw almonds, sunflower seeds, and raisins

Dinner: Mediterranean salmon with cherry tomatoes, chopped zucchini, capers, olive oils and ripe olives. Fresh seasonal melon and kiwi with low-fat, plain Greek yogurt for dessert.

Adapted with permission from: Oldways Preservation Trust, 2012 www.oldwayspt.org

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Disclaimer: The information contained in this tear sheet is not the formal policy or position of the National Lipid Association.

This information is intended for providers and patients.
Health Care Providers—access this tear sheet at **www.learnyourlipids.com**

See the Mediterranean Diet Tear Sheet on page 37.

Evidence

Researchers involved in the European Prospective Study into Cancer and Nutrition (EPIC) evaluated the effect of individual components of the Mediterranean-style eating pattern on all-cause mortality among the Greek cohort (n = 23,349 men and women, not previously diagnosed with cancer, coronary heart disease, or diabetes).[4] Adherence to the characteristics of the traditional Mediterranean-style eating pattern was assessed using a 10-point MedDiet scale (range of scores zero to nine, with higher scores indicating greater adherence). A higher MedDiet score (i.e., higher adherence to the eating pattern) was associated with a statistically significant reduction in total mortality. The contribution of the components of the Mediterranean dietary pattern to a lower risk of all-cause mortality in the EPIC study were: higher consumption of alcohol (within the moderate range, 23.5%); lower intake of meat and meat products (16.6%); higher intake of vegetables (16.2%); higher intake of fruits and nuts (11.2%); higher intake of monounsaturated to saturated fat ratio (10.6%); and a higher intake of legumes (9.7%).[4]

The PREDIMED Study[5] — otherwise known as the "Effects of Mediterranean diet on the primary prevention of cardiovascular disease" intervention study — examined whether a Mediterranean diet supplemented with either extra-virgin olive oil (15 liters provided every three months[6]) or mixed nuts (1,350 g walnuts, 675 g almonds, and 675 g hazelnuts provided every three months[6]) prevented CVD in 7,447 subjects at high CVD risk. The primary endpoint was the rate of major cardiovascular (CV) events (i.e., cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Compared to the control group, the multivariable-adjusted hazard ratio for a CV event was 0.70 (95% confidence interval [CI]: 0.54 to 0.92) for the Mediterranean-style diet supplemented with extra-virgin olive oil, and 0.72 (95% CI: 0.54 to 0.96) for the Mediterranean-style diet supplemented with mixed nuts. A point to consider regarding the PREDIMED study is that both Mediterranean-style diet intervention groups received more intense dietitian counseling than the control group, which may have biased the results.[7]

Overall, a higher adherence to the Mediterranean-style eating pattern has been associated with a decreased risk of multiple CVD risk factors, the metabolic syndrome, and CVD mortality.[8,9] The beneficial effects identified in studies are most likely the result of an interaction between the Mediterranean-style eating pattern components versus a single food group.[8] The specific CVD risk factors that have been associated with the Mediterranean-style eating pattern include improvements in blood lipid levels and particle size, reductions in blood pressure, decreased insulin resistance, improved glucose control, improved anti-inflammatory markers, and a decreased risk of stroke.[8,9] The substantially reduced risk of CVD associated with Mediterranean-style dietary patterns has been found in the absence of weight gain.[2,10]

Practical Applications

An important point to emphasize to patients is that the Mediterranean-style eating pattern is not simply a matter of using extra-virgin olive oil instead of butter — it is a *lifestyle*. Practitioners should advise and encourage patients to embrace the traditional Mediterranean style of *living*. Lifestyle habits that typically accompany and may contribute to the beneficial effects of the traditional Mediterranean-style eating pattern are daily physical activity; awareness of portion sizes and eating mindfully (i.e. awareness of physical cues of hunger and satiety, and using all of the senses in choosing to eat food that is both satisfying and nourishing[11]); meals in the company of others; maintaining or achieving a healthy body weight; and moderation as an overall lifestyle approach. Switching to the Mediterranean-style eating pattern may seem overwhelming to some patients. Patients should be encouraged to choose one or two of the Mediterranean-style eating pattern components to add to their current eating habits. Simple suggestions to offer to patients are included in the tear sheet of this Lipid*Spin* and may include using extra-virgin olive oil in food preparation (see Table 1 for substitution of olive oil for butter in baking); using avocado instead of butter, cream cheese, and mayonnaise; eating 1 ounce of nuts and/or nut butter each day; and focusing on mindful eating and flavorful cooking (go to **oldwayspt.org/recipes** for ideas). For personalizing patients' cardio-protective dietary patterns, consider referral to a registered dietitian nutritionist (RDN).[1] ■

Disclosure statement: There are no disclosures to report.

References are listed on page 36.

Case Study:
A Case of 'Non-Critical' Stenosis

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S.W. is a 46-year-old male who presented to my office to establish a patient-physician relationship. He had moved to my area six months ago and was running low on his prescription medication. Approximately one year ago, he had developed chest pain consistent with angina and underwent a treadmill stress test was both subjectively and objectively positive, with 2mm ST depression in his anterior precordial leads. He underwent coronary angiography that demonstrated a 90 percent mid-left anterior descending (LAD) stenosis, which was successfully stented with a drug-eluting stent, according to his records. In addition, the angiogram demonstrated 30 percent stenoses of his right coronary artery and his mid-circumflex obtuse marginal branch. His medications included atorvastatin 40 mg, ASA 81 mg, Clopidogrel 75 mg, and metoprolol succinate 25mg daily. He became completely asymptomatic and, on his own, he reduced his atorvastatin dose to one-half tablet daily, because he was under the impression that his remaining disease was "mild." Laboratory studies at the time of his angiogram revealed the following:

Total cholesterol: 299 mg/dL
Triglycerides: 200 mg/dL
High-density lipoprotein (HDL) cholesterol: 39 mg/dL
Low-density lipoprotein (LDL) cholesterol: 220 mg/dL
Fasting glucose: 93 mg/dL

He has never smoked cigarettes. He denies a history of autoimmune disease or kidney disease. His father died suddenly at age 46, but no other information was available. His mother is 75 years old and healthy. He has two daughters, who have not had their cholesterol tested. He has one healthy younger brother who has two children.

His physical examination reveals a blood pressure of 130/86. Waist circumference is 41 inches. The remainder of his physical examination is otherwise unremarkable. Laboratory studies on his current medications reveal:

Total cholesterol: 220 mg/dL
Triglycerides: 160 mg/dL
HDL cholesterol: 38 mg/dL
LDL cholesterol: 150 mg/dL

Shortly after returning to my office to

discuss his lab work, S.W. developed atypical chest pain not necessarily related to exertion. Based on his history, a cardiology consultation was requested.

Dr. Rob Greenfield:
When I interviewed and examined this patient, he claimed to be asymptomatic, having had no chest discomfort during the past week. Clearly he needed a "functional study" to exclude coronary ischemia, because he was a patient with prior revascularization (coronary bypass or coronary angioplasty). In this case, I felt that an imaging component should be included in the stress test evaluation to help localize ischemia, if present. In general, a nuclear stress test is more sensitive and more specific than stress echocardiography.* We did not want to miss a "culprit" lesion, so we chose a nuclear stress test. To "rule out" disease in low-risk patients with a low index of suspicion and to avoid unnecessary radiation exposure I would have chosen a stress echo.

His maximal stress cardiolite was negative for ischemia or prior infarct and normal perfusion was displayed. This suggested that his stent had remained patent and that his so-called "non-flow-limiting" disease in his right coronary and circumflex vessels had remained "non-critical."

Despite the negative stress test, I explained to the patient that there is no coronary lesion that should be considered "mild." The literature well documents that most myocardial infarctions are caused by plaques that are less than 50 percent in their luminal stenosis. (Figure 1) Many of these plaques are underestimated by angiography. This has been well demonstrated by intravascular ultrasound (IVUS) in which large intramural plaques that do not compromise luminal diameter can be detected by IVUS but not by angiography. (Figure 2) These plaques usually have large lipid cores in the walls of the coronaries; they are more subject to plaque rupture and subsequent thrombotic occlusion. (Figure 3)

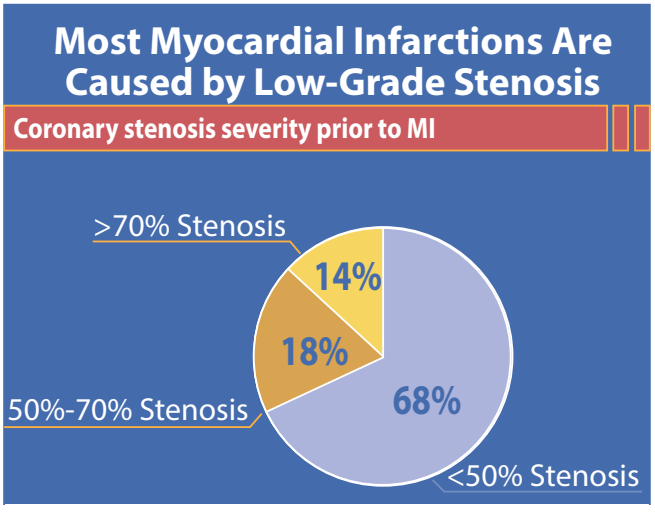


Figure 1. Pooled data from four studies: Ambrose et al, 1988; Little et al, 1988; Nobuyoshi et al, 1991; and Giroud et al, 1992

It is important to remember that atherosclerosis is an inflammatory disease fueled by atherogenic lipoproteins. Assessing coronary disease merely by a two-dimension coronary angiogram may underestimate the extent of disease. Most of a patient's plaque burden lies within the wall of the artery. What we actually appreciate by angiograph is merely the tip of the iceberg and we obtain merely a "lumen-o-gram."

Glagov showed many years ago that as coronary arteries develop increasing plaque burden, they expand and become larger. This is a process known as "positive remodeling."[1] Angiography to assess this can be quite misleading, because the lumen remains well preserved until the disease is far advanced. Our patient's 30 percent luminal stenoses may actually misrepresent unstable plaques. Large lipid cores in the walls of the coronary artery are not detected by cardiac catheterization and may require stabilization by aggressive lipid-lowering therapy.

For all of the above reasons, I concurred with Dr. Bottenberg that aggressive lipid therapy was necessary to "delipidate" the patient's plaques in order to slow progression of his disease and possibly to effect plaque regression.

Total cholesterol (LDL) mg/dL cutpoints (80 percent probability)

	First-degree relative with FH†	Second-degree relative with FH	Third-degree relative with FH
Age (years)			
<20	220 (155)	230 (165)	240 (170)
20-29	240 (170)	250 (180)	260 (185)
30-39	270 (190)	280 (200)	290 (210)
≥40	290 (205)	300 (215)	310 (225)
Diagnosis (FH is diagnosed if total cholesterol levels exceed the cutpoint)			

Table 1. U.S. MedPed Program diagnostic criteria for heterozygous familial hypercholesterolemia.

†familial hypercholesterolemia.

Dr. Bottenberg:
S.W.'s case represents a fairly typical of patients I see in my office. It is not unusual for a patient to develop a false sense of security when he hears another physician say the words "mild disease" or "noncritical stenosis." To support the information he received from Dr. Greenfield, I spend a great deal of time explaining atherosclerosis, its progression, and how plaque rupture can leads to events. It is vital that the patient understands his disease process to fully participate in treatment.

He received a 32-percent reduction in his LDL cholesterol on atorvastatin 20 mg daily. I increased his atorvastatin to 40 mg daily. I used the "Rule of Six" (doubling the dose of a statin usually only produces approximately an additional 6 percent LDL-C reduction).[2] I suspected that this alone would not allow him to achieve either a target LDL of less than 100 mg/dL (non-HDL < 130) or a total LDL reduction of 50 percent. Therefore, I asked him to add ezetimibe 10 mg daily. Alternatively, I may ask him to try to increase his atorvastatin to 80 mg daily, pending his tolerance of the 40 mg dose. Achieving an optional target of less than 70 mg/dL and non-HDL cholesterol < 100mg/dL may require adding a third agent. In this regard, I may consider a bile acid resin or niacin.

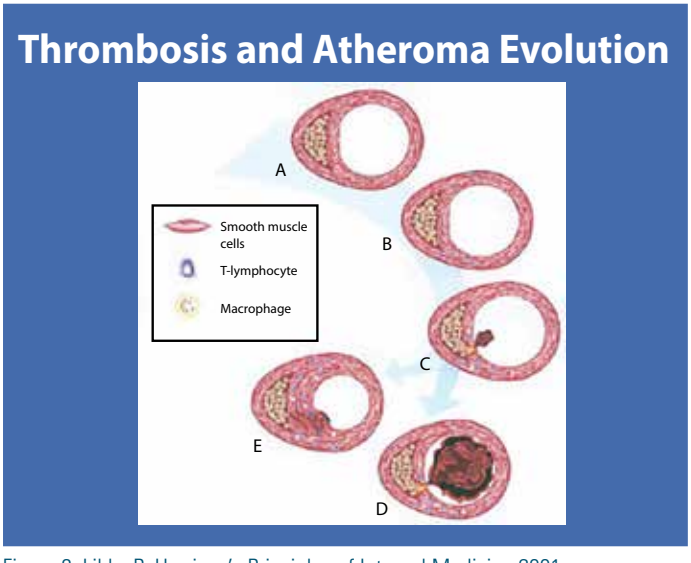
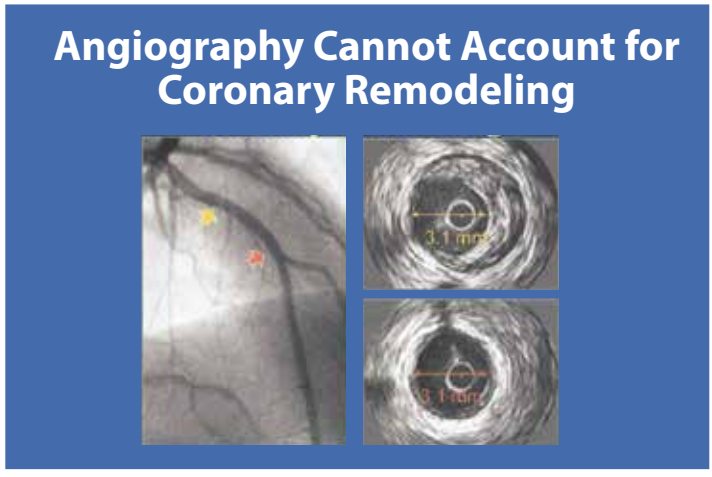


Figure 3. Libby P. Harrison's Principles of Internal Medicine 2001

He meets criteria for having the metabolic syndrome: large waist circumference, pre-hypertension, elevated triglycerides, and low HDL. With established disease, this may place him in a "very high-risk category," underscoring the need for very aggressive lipid-lowering therapy. In addition, he is scheduled to see our staff dietitian. We typically calculate a patient's protein and calorie requirements and ask the patient to divide them evenly throughout the day. We recommend modest exercise. I anticipate repeating his lab work in six to eight weeks.

His very high LDL cholesterol and the sudden death of his father at age 46 raises the possibility that he may have heterozygous familial hyperlipidemia.[3] Cascade screening is appropriate. We discussed this with the patient and had him ask his daughters to obtain cholesterol screenings. We have asked him to have his brother's cholesterol tested, as well as his brother's two children. We typically use the MedPed criteria for the diagnosis of familial hyperlipidemia (FH). (Table 1)



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Drs. Greenfield and Bottenberg:
In high risk patients with coronary disease and dyslipidemia, we believe that an aggressive approach is warranted. A close working relationship among the patient, and his physicians can decrease his lifetime risk of future cardiovascular events including stroke, peripheral arterial disease, and acute coronary syndrome. Because of specialized training, National Lipid Association (NLA) members can offer unique skills and perspectives that are likely to improve outcomes. ■

**There is wide variation amongst published studies for sensitivity and specificity and varies depending on whether there is one, two, or three vessel disease. In general, stress echo may be 70 to 90 percent sensitive and 70 to 80 percent specific and nuclear stress ranges between 85 and 90 percent sensitive and 80 and 90 percent specific. The specificity of stress echo may be somewhat less due to the presence of other forms of structural heart disease such as left ventricular hypertrophy, etc.*

Disclosure statement: Dr. Bottenberg has no disclosures to report. Dr. Greenfield has received speaker honorarium from Aegerion and was a principle investigator with Sanofi.

References are listed on page 36.

Chapter Update:
Progress in the Pacific

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Seven years ago, the Pacific Lipid Association's (PLA's) inaugural meeting took place on Jan. 18, 2007, at the Sheraton Hotel and Marina in San Diego. Recently, March 13–16, 2014, we jointly hosted the 2014 Spring Clinical Update (CLU): Atheroprevention: Global Perspectives and Evolving Concepts. We partnered with the Southwest Lipid Association to hold the educational meeting at the Waldorf Astoria Grand Wailea Hotel on the island of Maui, Hawaii. In 2007, our first president was Thomas P. Bersot, MD, who subsequently became president of the National Lipid Association (NLA) from 2008 to 2009. The NLA's Immediate Past President, Matthew K. Ito, PharmD, was PLA president from 2009 to 2010.

The PLA president's torch was recently passed on from B Alan Bottenberg, DO, to current PLA President Paul D. Rosenblit, MD, PhD, for the year 2014-2015. Congratulations to all of our past and present leaders for guiding the PLA to where we are today.

The following highlights significant activities of the PLA and its membership during the past year (2013-2014). The 5th Annual Orange County Symposium, "A Brave New World: Navigating Through Problems in Contemporary Cardiovascular Disease Prevention and Management," under the direction of Brian M. Chesnie, MD; Robert S. Greenfield, MD; Paul D. Rosenblit, MD, PhD; and Nathan D. Wong, PhD; was held Nov. 2, 2013, in Anaheim, Calif., at the Hilton Anaheim. This comprehensive one-day symposium addressed lifestyle management, obesity, clinical lipidology, cardiometabolic risk, diabetes, and hypertension. The conference was jointly sponsored by the American Society for Preventive Cardiology and endorsed by the PLA, the California chapter of the American Association of Clinical Endocrinologists (AACE) and the California chapter of the American College of Cardiology (ACC). Faculty for the conference included Yehuda Handelsman,

MD; J. Antonio G. López, MD; and Geeta Sikand, MA, RD.

Dr. Handelsman is chair and program director of the annual World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease. The 11th annual congress took place Nov. 7–9, 2013, at the Hilton Universal City in Los Angeles.

In October 2013, California passed Senate Bill 493 Pharmacy Practice, which establishes pharmacists as health care providers in California. This bill allows pharmacists to be granted an advanced practice license that allows them to perform patient assessments; order and interpret drug therapy-related tests; make referrals; and initiate, adjust, or discontinue drug therapy in collaboration with other health care providers. For pharmacists to practice under the advanced scope, they need to apply for and be granted an advanced practice pharmacist license from the California Board of Pharmacy. Pharmacists who qualify to apply for the license need to meet two of the following three criteria: 1) completion of a one-year residency in which >50 percent of time was involved with direct patient care, 2) actively manage patients for at least one year through a collaborative practice agreement, and 3) certification in a relevant area of practice. Eric K. Gupta, PharmD, has engaged the credentialing committee of the California Board of Pharmacy and asked them to consider the Accreditation Council for Clinical Lipidology's Clinical Lipid Specialist examination as relevant certification.

With the work of John R. Nelson, MD, and the NLA on behalf of the California members of the NLA, the passage of SB 1215 by Sen. Ed Hernandez was defeated. This bill would have eliminated the in-office exception to the self-referral prohibition for advanced imaging that is performed within a physician's office and that is compensated on a fee-for-service basis. This would have set a dangerous precedent by prohibiting a physician who participates in a fee-for-service system from providing care directly to his or her patient in the most effective means possible. Eliminating in-office exception separates the patient from the physician who can best understand the patient's individual needs.

Other PLA members who have played active leadership roles include:
* Wayne S. True, MD, who recently served as chair of the NLA Membership Committee.

* J. Antonio G. López, MD, who serves as chair of the Honors and Awards Committee, chair of the NLA Underrepresented Minorities Membership Task Force, and chair of the PLA Cholesterol/Lipid Screening Committee.

* Thomas P. Bersot, MD, PhD, who serves on the board of directors of the Foundation of the NLA.

* Eliot A. Brinton, MD, who serves as president of the American Board of Clinical Lipidology.

* Geeta Sikand, MA, RD, who serves as secretary for the Accreditation Council for Clinical Lipidology.

* Joshua W. Knowles, MD, PhD, who serves on the board of directors of the Familial Hypercholesterolemia Foundation.

PLA members who have served on the board of the NLA this year include: Edward A. Gill, MD; Eliot A. Brinton, MD; Matthew K. Ito, PharmD; Wayne S. True, MD; and Benjamin J. Ansell, MD.

On June 1, 2013, Daniel Steinberg, MD, PhD, emeritus professor of medicine, Division of Endocrinology and Metabolism, Department of Medicine at the University of California San Diego School of Medicine, received the Distinguished Achievement Award, the highest honor conferred by the NLA, during the Annual Scientific Sessions in Las Vegas. This award is presented to an individual widely known for a major contribution to clinical lipidology — research, teaching, publishing or service — whether as a single accomplishment or through the work of a lengthy career.

As evidenced in the past year, the PLA continues to be an active and dynamic organization. We look forward to the important issues and exciting events of the upcoming year. ■

Disclosure statement: Dr. Fujii has no disclosures to report. Dr. López has received honoraria from Abor Pharmaceuticals LLC, Amarin, AstraZeneca, Bristol-Meyers Squibb Co., Diadexus, Forest Pharmaceuticals, and Pfizer. Dr. Lopez has received research grants from Amgen, Iverson Genetics Diagnostics, National Heart Lung and Blood Institute, National Institutes of Health, and United Biosource LLC.

Member Spotlight:
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Caring for people is of the utmost importance to Dr. Wayne True, which is evident from his hectic daily schedule, volunteer mission work, and recent foray into the world of politics.

As a board certified family medicine physician and lipidologist, Dr. True saw firsthand the need to serve his country and represent his patients in a more direct way. As a result, he sought election to the U.S. House as a representative to the 53rd Congressional District of California.

Working with more evidence-based outcomes has become the main focus of Dr. True's goals in the advancement of the field of lipidology. His medical group insists on having an evidence-based outcome before using new treatments, tests, or remedies with patients. He wants to always ensure that the tests he uses will improve patient outcomes. This belief in the importance of evidence-based outcomes is what pushed him to pursue this recent passion for politics. Dr. True's frustration and skepticism of certain guidelines for treatments with no evidence to support them influenced him to run for Congress.

Though he did not win the primary in June, he admits that he will not stop doing what he is passionate about — providing good, honest medical care. You can read more about Dr. True's run for Congress at **waynetrueforcongress.com**.

Currently, Dr. True works for Sharp Rees-Stealy Medical Centers in San Diego. Having previously worked in private practice, he has found that since affiliating with Sharp, he can run a more efficient office and dedicate more time to patient care, rather than spending time searching through files and managing an office. Dr. True says the best part of his job is being able to give consultations about diet, lifestyle, and exercise to his patients. He spends a lot of time with patients discussing effective diets and ultimately tries to steer them toward an overall healthier lifestyle. Some patients have even taken to Dr. True's daily routine and will join him at the gym at 4:00 a.m.

Dr. True is dedicated to his regimented schedule, allowing himself two hours at the office every morning before the doors open for patients at 8:00 a.m. During this time, Dr. True reviews files for the day so he can spend every available minute meeting with patients to help them reach their goal.

Dr. True first became interested in the field of lipidology when he began ordering advanced lipid tests — such as the VAP and NMR LipoProfile — and realized he did not fully understand the results. He attended a few International Atherosclerosis Society meetings, where he had the opportunity to meet several lipid researchers from Milan, Italy, who developed ApoA-1 Milano, and see their data up close. He was excited to learn he

could become more closely involved with the National Lipid Association (NLA) and quickly became active with the Pacific Lipid Association as a member of the board.

When he is not working more than 12-hour days and focusing on his campaign, Dr. True enjoys photography and hiking the trails in San Diego, which are very enticing due to the city's seemingly perfect weather. He also has quite a green thumb and manages to keep a few orchid plants in constant bloom. Some of his most treasured time has been spent on his mission trips to Peru. Since 1997, Dr. True — with the help of Christian Emergency Relief Teams International — has made an annual trip to provide medical care to those in need. These trips typically turn into family summer vacations while he leads teams of 20 to 35 people into the jungles and mountains of Peru.

Dr. True has enjoyed studying in the field of lipidology and is grateful for the resources that the NLA has provided him. He feels fortunate to have served on the PLA board, as well as multiple committees including chair of the Membership Committee. His passion and commitment to lipidology, the NLA, and to his patients make him an inspiration to others in the NLA community. ■

Education and Meeting News and Notes

NLA Renews Agreement with ReachMD

The National Lipid Association (NLA) is pleased to announce the renewal of its contract with ReachMD, a healthcare production company that produces and broadcasts the NLA-sponsored Lipid Luminations series on the iHeartRadio and TuneIn Radio platforms. This program, which airs 12 times a year, focuses on the field of lipidology and aims to highlight recent advances in lipid management and heart disease. Some of the main topics discussed in this series include scientific and clinical research updates, new treatment options, and best practices in patient care.

ReachMD

ReachMD.com/LipidLuminations

An archive of past recordings on a vast array of topics is available at **lipid.org/communications/reachmd** or at the ReachMD website. The iHeartRadio channel for ReachMD can be found at **iheart.com/talk/show/202-ReachMD-Series-Lipid-Lumin/**.

Journal of Clinical Lipidology Now Available on your iPad

The *Journal of Clinical Lipidology* Newsstand iPad app is now available at no cost to National Lipid Association members and Journal subscribers. To access the Journal for free on your iPad, download The JCL app and log in with your JCL username and password. The app allows you to download each issue onto your iPad and gives you immediate access to full-text content. In addition, check out the smartphone app HealthAdvance, which gives you access to all full-text articles on your phone. For more information, visit **lipid.org/jclapp**.

Get Involved in the NLA's Trainee Scholarship Program

lipid academy

Do you manage fellows, residents, or non-physician trainees who have a focus in lipid management? Tell them about the NLA's Trainee Scholarship Program! Fifteen scholarships are available for each NLA Lipid Academy Course, each including a $500 travel grant and courtesy conference attendance — plus NLA membership for fellows and trainees is always complimentary. Due to the popularity of this program for the Annual Scientific Sessions Lipid Academy, scholarships went quickly to trainees from University of Colorado, NYU, Boston Medical Center, University of Pennsylvania, and several others. Contact **sgoode@lipid.org** for more information on future scholarship opportunities.

Southwest Chapter of the NLA Hosts Lipid Clinic Through Project ECHO

Project ECHO

The Southwest Chapter of the NLA hosted a special, one-time lipid clinic through the University of New Mexico's Project ECHO. The Lipid teleECHO Clinic took place July 30 and featured a didactic presentation from speaker Randy W. Burden, PharmD, MDiv, FNLA, CLS, titled "Taking a Statin Can Really be a Pain." The presentation, which was free to all members, was followed by 30 minutes of case presentations from the audience. For more information on Project ECHO, visit **echo.unm.edu**.

NLA Partners with RealCME

The National Lipid Association (NLA) has partnered with RealCME to host a virtual case activity on hypertriglyceridemia in children. Drs. Don Wilson, Catherine McNeal, and Piers Blackett have created a scenario of a 6-month-old female patient in a virtual office setting for health care professionals with an interest in pediatric cases. The activity consists of testing your existing knowledge and gauging your growth after your participation, diagnosis and treatment discussions from the authors, and stimulating questions on the information presented. Visit **lipid.org** to participate!

Join the NLA's Newest Workgroup on Women's Health

A new workgroup is forming for those who have a common interest specific to Women's Health. Dr. Robert Wild is leading the formation of the group and a general information page has been set

up at **lipid.org/about/committees/WH**. Other member-based workgroups within the practice management council include: the Pediatric Workgroup and the Nutrition Workgroup.

These groups are meant to be driven by the interests of members, and are not necessarily task or agenda driven. Although there is informality, the workgroup serves to fulfill specific professional needs within the organization. Beyond just being a section on the NLA website to network and exchange ideas, these groups also can meet informally at annual and regional meeting sites to discuss common issues. Requests to join a workgroup can be made by contacting the staff person indicated on the group Web page. The group leader will be contacted about your participation.

Suggestions for other workgroups are welcome but are dependent on identifying a specific leader willing to facilitate the discussion. If you have an idea for a workgroup, please send your suggestion to Louisa Paran, assistant director of practice management **(lparan@lipid.org**). If no workgroup exists, please remember you are always encouraged to post in the member topic discussion areas of the website.

NLA Joins CMHA in Cardiometabolic Think Tank

The CardioMetabolic Health Alliance (CMHA) invited the National Lipid Association (NLA) as a participant in an invitation-only Cardiometabolic Think Tank: Focusing on Care Models and Approaches. The event held on Friday, June 20, 2014, was attended by the NLA President, Dr. Terry Jacobson, at the American College of Cardiology's (ACC) Heart House in Washington, D.C.

A group of expert stakeholders discuss how to create an interdisciplinary approach to care that optimizes cardiometabolic management in the U.S. at the American College of Cardiology's Heart House in Washington, D.C., on June 20, 2014.

NLA President Terry Jacobson, MD, (Center) and fellow medical experts, attend the invitation-only Cardiometabolic Think Tank June 20, 2014, at the American College of Cardiology's Heart House in Washington, D.C.

The CMHA is an interdisciplinary collaboration between the American College of Cardiology (ACC), the National Minority Quality Forum (the Forum), the American Association of Clinical Endocrinologists (AACE) and the Association of Black Cardiologists (ABC).

The purpose of this program is to engage expert stakeholders in a facilitated, action-driven, discussion around the question of how to create an interdisciplinary approach to care that optimizes cardiometabolic management in the United States.

Connect with the NLA on Social Media

Social media is not only a great way to stay connected to all the latest news and information surrounding the National Lipid Association, but it's a useful tool for meeting and interacting with friends and colleagues across the lipid community. To join in on the fun, make sure you find us on Facebook (facebook.com/nationallipid) and Twitter (@nationallipid). Search for the hashtag #NLAIndy to see the latest updates or join the discussion on the 2014 Fall Clinical Lipid Update in Indianapolis, and visit Facebook regularly for updates on all the latest happenings in Indianapolis.

NLA Mourns Loss of SWLA Member

The National Lipid Association is sad to report that Gumaro Garza, MD, an active member of the Southwest Lipid Association, passed away July 29, 2014, after suffering a myocardial infarction and subsequent cardiogenic shock. Garza resided in Edinberg, Texas, and was very active in the treatment of dyslipidemia in the Mexican-American population. He is survived by his ex-wife, Christine Garza, PhD, who is also a member of the SWLA chapter, and his daughter.

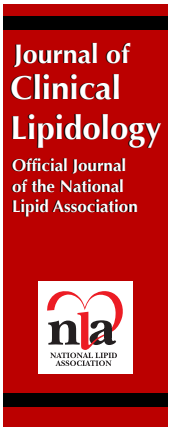
Access Past Patient Tear Sheets on Learn Your Lipids Website

You can access past patient tear sheets from past issues of the LipidSpin by going to **learnyourlipids.com** and clicking on "Patient Handouts" under the "Education Resources" tab on the website's toolbar. Choose from a variety of patient tear sheets including:

- Physical Finding Tear Sheet
- Lower Your Triglycerides with Lifestyle Tear Sheet
- Lifestyle Management Tear Sheet
- "What is Familial Hypercholesterolemia?" Tear Sheet
- FH Patient Tear Sheet
- Advanced Lipid Testing Tear Sheet
- Lower Your ApoB or LDL Particle Number Tear Sheet
- HDL-C Tear Sheet
- The Facts About Fats Tear Sheet

Check the Learn Your Lipids website regularly to find newly added patient handouts and educational information.

Journal of Clinical Lipidology Sees Significant Increase in Impact Factor



The 2013 Impact Factors were recently released and the *Journal of Clinical Lipidology* (JCL) saw a significant increase — from 2.741 (2012) to 3.587. The Journal is now ranked 53rd out of 254 journals in its category (pharmacology and pharmacy). The Thomson-Reuters Impact Factor represents the ratio of articles quoted in other scientific publications compared to the total qualifying articles during the years 2012 and 2013. "This a very large change in one year and we should all be pleased," says W. Virgil Brown, MD, FNLA, Editor-in-Chief of the JCL. "It has been a team effort. The NLA has been a tremendous help with the review articles and position statements. These, plus Elsevier's strong support, have made my job easy. Thanks to all who have worked on publications and enriched our Journal."

2014 Young Investigator Competition

Congratulations to Karl Richardson, MD, fellow at Vanderbilt University Medical Center, and Marisa Schoen, BA, of the Thomas Jefferson University, who co-authored the abstract "Statins and Cognitive Function: A Systematic Review" and placed first at the 2014 Annual Scientific Sessions in Orlando, Fla. You can view this abstract on Page 33 of this issue of the Lipid*Spin*. In addition, you can view a downloadable version of this abstract online at **lipid.org/util/eposters/PDF/153.pdf**. The Young Investigator Competition was sponsored by an educational grant from LipoScience Inc.

Statins and Cognitive Function

Karl Richardson* MD, Marisa Schoen* BA, Benjamin French PhD, Craig A Umscheid MD MSCE, Matthew D Mitchell PhD, Steven E Arnold MD, Paul A Heidenreich MD MS, Daniel J Rader MD, Emil M deGoma MD (*Co-first authors, equal contribution)
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; Stanford University Medical Center, Stanford, CA

Objective

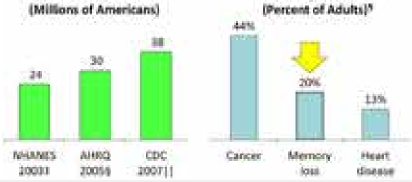
- To examine the effect of statins on cognitive function.

Background

- February 28, 2012 – The U.S. Food and Drug Administration (FDA) announced important changes to the safety label of cholesterol-lowering statin drugs, including a new warning regarding the potential for cognitive impairment with statin use:

  "Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once the drug was no longer being taken."

- This labeling decision was based on an FDA review of clinical trial data, published literature, and the FDA adverse event reporting database (AERS):
  - 3 clinical trials (n=30,615); 6 cohort studies, 4 case-control studies (n=15,744)
    - No evidence that statin use is associated with cognitive decline or incident dementia
  - Case series of cognitive impairment with statin use
  - 1,698 reports (crude counts) of cases of memory impairment in AERS through January 1, 2011*
- To date, the detailed methods of the FDA's analysis have not been made available; 1 report indicates that substantial weight was placed on case reports†.
- Large randomized control trials (RCTs) have demonstrated relative risk reductions of 20-30% for myocardial infarction, 20% for ischemic stroke, 10-15% for all-cause mortality with statin use.
- 1 in 5 adults age 45-64 years take a statin drug.||
- According to a recent poll, cognitive decline ranks second only to cancer among leading health concerns of adults age 45-65 years.¶



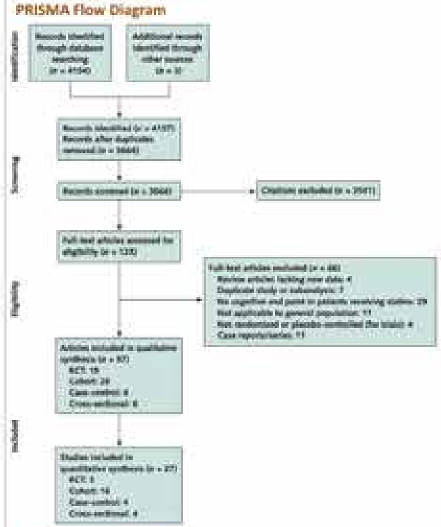
Methods

Literature search

- Data Sources:
  - PubMed, Embase, and Cochrane Library databases from inception through October 2012
- Inclusion criteria:
  - Publications reporting cognitive endpoints in adult patients receiving statin therapy
  - Placebo-controlled, randomized trials; cohort, case-control, cross-sectional studies
  - English language

Methods (Cont.)

PRISMA Flow Diagram


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 4154)
Additional records identified through other sources (n = 3)
Records identified (n = 4157)
Records after duplicates removed (n = 3664)
Records screened (n = 3664)
Citations excluded (n = 3541)
Full-text articles assessed for eligibility (n = 123)
Full-text articles excluded (n = 66)
Articles included in qualitative synthesis (n = 57)
RCT: 19
Cohort: 28
Case-control: 4
Cross-sectional: 6
Studies included in quantitative synthesis (n = 27)
RCT: 3
Cohort: 16
Case-control: 4
Cross-sectional: 4

Risk of Bias Assessment

- Cochrane Risk of Bias Assessment Tool
- Newcastle-Ottawa Scales

Assessment of Quality of Evidence

- Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Outcomes

Cognitive Diagnoses	Cognitive Performance Scores
• Dementia (all-cause) • Alzheimer disease • Mild cognitive impairment/ cognitive impairment without dementia	• Global cognitive performance • Cognitive domains (5) - Frontal-executive function and working memory - Declarative memory - Procedural memory - Attention - Processing speed • Elementary processes (2) - Visuoperception - Motor speed

FDA Adverse Event Reporting Databases

Cognitive-associated adverse event (AE) reporting rate:
- # Cases with cognitive-related AE reports / # U.S. prescriptions
- # Cases with cognitive-related AE reports / Total # Cases with AE reports

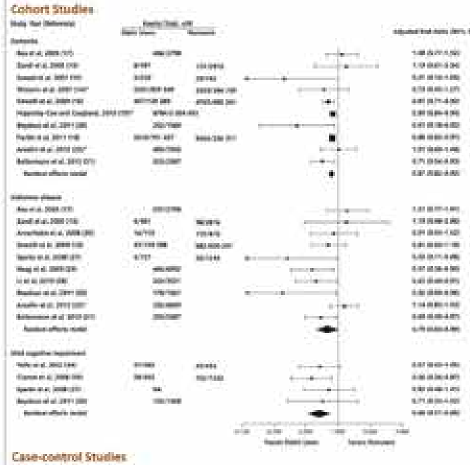
"Negative Controls":
- Losartan (1995)
- Clopidogrel (1997)

Results

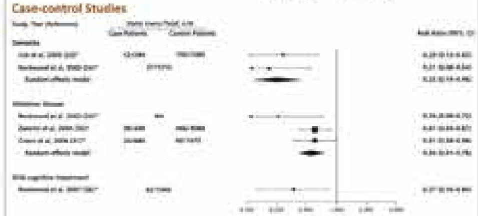
Table 1. Summary of Relative Risk Meta-analyses

	Dementia	Alzheimer	MCI
RCT	RR 1.00 [0.61-1.64] 1 · 20,536	–	RR 0.98 [0.93-1.03] 1 · 20,536
Cohort	RR 0.87 [0.82-0.92] 10 · 4,340,137	RR 0.79 [0.63-0.99] 10 · 759,553	RR 0.66 [0.51-0.85] 4 · =4,019
Case-control	OR 0.25 [0.14-0.46] 2 · 2679	OR 0.56 [0.41-0.78] 3 · =5758	OR 0.37 [0.16-0.86] 1 · 1,040
Cross-sectional	OR 0.54 [0.22-1.33] 1 · 845	OR 0.45 [0.35-0.58] 1 · 57,104	OR 0.97 [0.87-1.09] 3 · =24,595

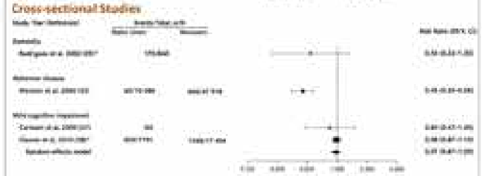
Cohort Studies



Case-control Studies



Cross-sectional Studies



Results (Cont.)

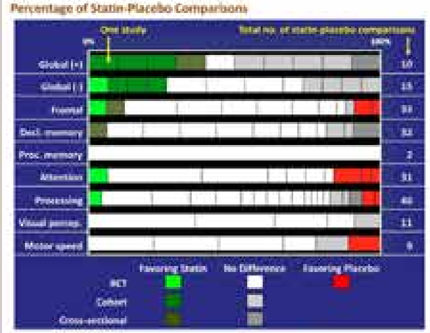
Table 2. Summary of Cognitive Performance Tests in RCTs

Cognitive Domain or Elementary Process	Total	No Difference*	Favoring Statin	Favoring Placebo
Global (among cognitively intact)	1	1 (100)	0	0
Global (among cognitively impaired)	8	7 (88)	1 (12)	0
Frontal-executive function and working memory	30	25 (83)	2 (7)	3 (10)
Declarative memory	24	24 (100)	0	0
Procedural memory	2	2 (100)	0	0
Attention	31	24 (77)	2 (6)	5 (16)
Processing speed	41	36 (88)	2 (5)	3 (7)
Visuoperception	10	10 (100)	0	0
Motor speed	8	7 (88)	0	1 (13)

Cognitive Tests, n (%)

*No statistically significant difference (P ≥ 0.05) in end-of-treatment or change from baseline scores between statin and placebo groups.

Percentage of Statin-Placebo Comparisons


One study
Total no. of statin-placebo comparisons
0%
100%
Global (+)
Global (-)
Frontal
Decl. memory
Proc. memory
Attention
Processing
Visual percep.
Motor speed
10
15
33
32
2
31
40
11
9
Favoring Statin
No Difference
Favoring Placebo
RCT
Cohort
Cross-sectional

FDA Adverse Event Reports of Cognitive Impairment

Losartan:	1.6 per million prescriptions
Clopidogrel:	1.9 per million prescriptions
Statins:	1.9 per million prescriptions

Clinical Implications

- No evidence of an increased risk of dementia, Alzheimer disease, or mild cognitive impairment/cognitive impairment without dementia.
- No evidence of worsened cognitive performance scores in any of the domains examined.
- No evidence of an increased rate of cognitive-associated adverse event reports in the FDA postmarketing surveillance databases.
- Large, well-designed RCTs are still needed, particularly those evaluating high-dose statin therapy.

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Foundation Update

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St. Louis, MO
Diplomate, American Board of Clinical Lipidology

FOUNDATION of the National Lipid Association

nla community
connect • collaborate • contribute

Discuss this article at
www.lipid.org/lipidspin

The Foundation of the National Lipid Association (NLA) is constantly searching for new ways to reach members and educate the public about cholesterol disorders. And we're always encouraged by the support we receive.

This year we are excited to welcome a new member to the Foundation Board of Directors. Wenter Blair, an FH patient and a wonderful patient advocate, has agreed to serve on our board. Wenter recently shared with us her own personal FH story. As a healthy and active 40-year-old, Wenter had a heart attack. After being treated, she was diagnosed with familial hypercholesterolemia (FH). And when genetic tests were done, they discovered her son also had the condition.

Wenter is very active in the patient community and has made tremendous strides all on her own in raising awareness about FH. We are pleased to have her unique perspective and creative energy on our Board.

In addition to relevant health campaigns, the Foundation hosts events at every meeting to raise money and awareness for its cause.

The Foundation's most recent fundraising event at the 2014 Annual Scientific Sessions was hugely successful — and tons of fun. More than 70 people gathered on Saturday, May 3, to enjoy an evening of dinner, dancing, and games with friends and colleagues. The evening featured a delicious buffet, giant Jenga and Connect Four, trivia, a photo booth, and dancing to music of the 70s, 80s, and 90s. It was truly an evening to remember, and we thank all of you who were able to attend.

Our next fundraising event is taking place at the Fall Clinical Lipid Update (CLU) in Indianapolis on Saturday, Aug. 23 from 7 p .m. to 9 p.m. This event will feature a one-of-a-kind wine tasting experience at Tastings, located just a short walk from the hotel. Tastings has more than 100 wines, and has been voted Indianapolis's Best Wine Bar four consecutive years.

These fundraising events are not just a great way to network and get to know fellow NLA members, but they go a long way towards helping to build educational awareness and public backing for lipidology.

We are also looking forward to launching a new campaign for Cholesterol Education Awareness Month this September. Our campaign will focus on education about triglycerides, what they are and the impact they can have on health.

We thank you for your continued support and look forward to seeing you at future Foundation events. ■

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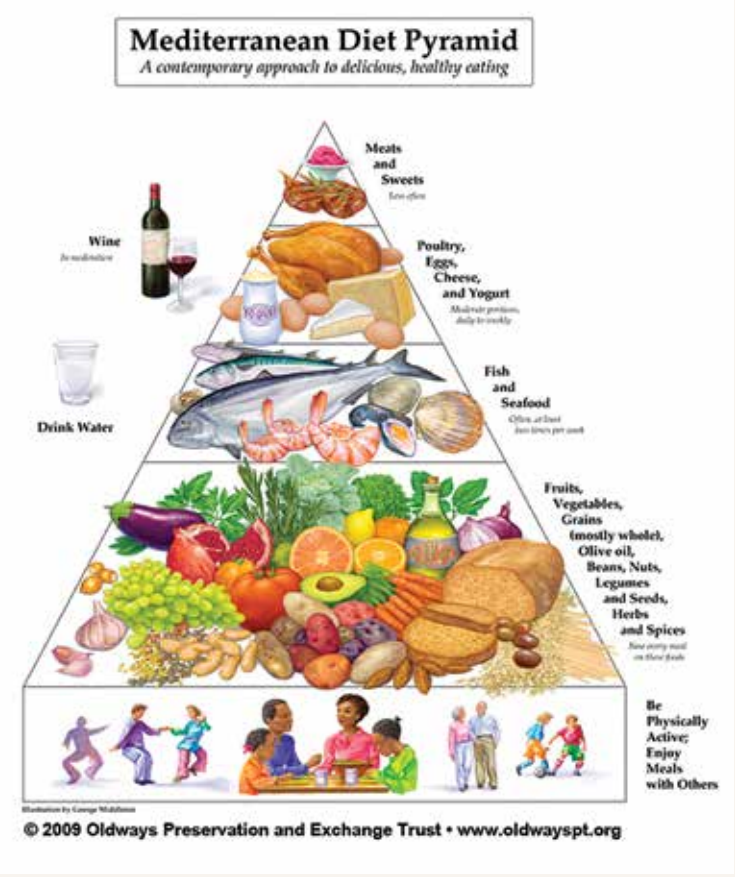
The Mediterranean Eating Style

Why Choose a Mediterranean Eating Style?

A Mediterranean diet containing olive oil or tree nuts has many beneficial effects on health. Benefits include a reduced risk of heart attacks and strokes, less cognitive decline, lower diabetes risk, and a reduction in total mortality.[1-4] Eating "Mediterranean" is a great way to improve overall health!



The Basic Principles of Mediterranean Eating Style

Olive oil, tree nuts (walnuts, almonds, and hazelnuts), peanuts, fresh fruits, and vegetables should be consumed daily. Fish (especially fatty fish), seafood, legumes, Sofrito (sauce prepared with olive oil, tomatoes, onions, garlic and aromatic herbs) and white meat instead of red meat are also eaten in a Mediterranean diet. Wine, if consumed, should be drunk with meals and in moderate amounts. Soda and sweetened drinks, spread fats, and red and processed meats are discouraged and consumption should be limited to less than one serving per day, and bakery sweets and pastries should be limited to less than three servings per week.[5]

Eight Steps To Go Mediterranean For Good Health!

1. **Increase your veggies.** Choose bright colored vegetables and lots of varieties. When filling up your plate, make half of it vegetables.
2. **Reconsider your meat intake.** Choose smaller amounts. Fill only one quarter of your plate with lean meat or skinless poultry. A serving of meat is 3 ounces (or the size of a deck of cards) or less.
3. **Breakfast is vital.** Fuel up at breakfast with what your body needs: whole grains, low-fat dairy, fresh fruit, raw nuts or avocados are good choices.
4. **Eat seafood twice per week.** 3.5 ounces of fatty fish is recommended 2-3 times per week. Salmon, tuna, herring, sardines are also rich in omega-3 fatty acids, which are beneficial for both brain and heart health.
5. **Skip meat once per week and go vegetarian.** Instead of meat, build your meal around cooked beans by including these in mixed dishes such as meatless chili, bean soups, or add them to salads, in a side dish or to a variety of Mexican recipes.
6. **Replace bad fats with healthy fats.** Healthy fats include extra virgin olive oil, tree nuts, sunflower seeds, and peanuts (unsalted), olives and avocados.
7. **Enjoy low-fat dairy.** Enjoy Greek, low-fat plain yogurt, skim or 1% milk, and small amounts of cheeses.
8. **Try fresh fruit for dessert.** Choose a variety of fresh, dried or frozen fruits: pomegranates, dried figs and kiwis, as well as peaches, pears, apples, etc. Limit desserts and sweets as special occasional treats.

Quick Mediterranean Menu Ideas

Breakfast: 1 slice whole grain toast with ¼ mashed avocado, fresh berries and plain, low-fat yogurt.

Lunch: Whole-wheat pita or corn tortilla with a mozzarella cheese slice or feta, tomatoes, baby spinach, olive oil, and a dash of basil. Fresh apple.

Snack: 1/4 cup mixed raw almonds, sunflower seeds, and raisins

Dinner: Mediterranean salmon with cherry tomatoes, chopped zucchini, capers, olive oils and ripe olives. Fresh seasonal melon and kiwi with low-fat, plain Greek yogurt for dessert.

Adapted with permission from: Oldways Preservation Trust, 2012 www.oldwayspt.org

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