pot·pour·ri
noun /ˌpouˈpuːri:/

1. a mixture of dried flower petals, leaves, and spices that is used to make a room smell pleasant

2. a collection of different things

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49 Patient Tear Sheet
In April 2016, an expert consensus decision pathway on the role of non-statin therapies for lowering LDL-C in the management of atherosclerotic cardiovascular disease (ASCVD) risk was published in the *Journal of the American College of Cardiology*. This document, which was endorsed by the National Lipid Association (NLA), and with the diligent and consistent work of our Immediate Past President Carl Orringer, MD, as one of its authors, provides practical guidance for clinicians and patients in situations that were not covered by the joint 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. The need for such a document was emphasized by recent additions to the body of knowledge for risk factor reduction in cardiovascular disease. Since the publication of the last guidelines, the Food and Drug Administration has approved a new class of medications termed proprotein convertase subtilisin/kexin 9 or, most often referred to as, PCSK9 inhibitors for high-risk patients who may require additional therapies to bring the LDL-C to a more acceptable threshold. The recent results of the HPS2-THRIVE and IMPROVE-IT trials have also provided new data that provided new evidence with regard to the addition of second non-statin agents when additional lowering is warranted.

The publication of these new guidelines are in concert with the standards and recommendations made by the NLA, and we are excited to endorse the work of the initial “think tank,” which resulted in this publication. We are further pleased to report that Dr. Orringer has accepted the invitation of the ACC committee when it convenes this Fall in Washington, DC, as it moves its work forward assessing and making recommendations for barriers around implementation of evidence-based LDL-C lowering therapies for ASCVD reduction. We are grateful for the ongoing energy that he brings to this work and look forward to outcomes from this meeting.

Algorithms found within the current document provide a suggested clinical workflow for consideration of additional non-statin therapies. Ten points were specifically highlighted to assist the provider to fully understand and implement its recommendations.

1. The decision pathway was created to address GAPS in recommendations for LDL-C lowering to reduce ASCVD in high-risk subsets based on recent clinical trial evidence and the introduction of a new class of lipid-lowering medication

2. The 2013 ACC/AHA cholesterol guidelines identified four major statin benefit groups, which remain intact and include:
   a. Patients ≥ 21 with clinical ASCVD
   b. Adults ≥ 21 years of age with LDL-C ≥ 190 mg/dL (after ruling out secondary causes)
   c. Adults 40–75 years old without known ASCVD but with diabetes, with LDL-C 70-189 mg/dL
d. Adults 40–75 years without ASCVD or diabetes, with an LDL-C 70–189 mg/dL, and an estimated 10-year risk for ASCVD of > 7.5 percent, as determined by the pooled cohort equations.

3. The 2013 guidelines recommended using either high- or moderate-intensity statin therapy for primary and secondary prevention, with dose adjustments as identified for adverse effects, elderly population, comorbidities, or drug-drug interaction.

4. The evidence-based recommendations from the 2013 guidelines provided the framework for the newest guideline and incorporated the most recent clinical trial data and the newly approved PCSK9 inhibitors.

5. Three questions were utilized to provide more detailed recommendations for specific patient scenarios.
   a. In what patient populations should non-statin therapies be considered?
   b. In what situations should non-statin therapies be considered?
   c. If non-statin therapies are to be added, which agents or therapies should be considered and in what order?

6. All pathway recommendations include assurance that the patient is consistent with ongoing healthy lifestyle recommendations.

7. Fasting LDL-C levels should be assessed regularly after the initiation of lipid-lowering medications, and every three to 12 months thereafter as appropriate.

8. In cases of suspected statin intolerance, the provider should include temporary discontinuation of statin therapy, lower dosing, re-challenge preferably with 2–3 different statins that utilize different metabolic pathways, and intermittent (1–3 Xs weekly) dosing of long half-life statins.

9. In selected high-risk patients (those with existing ASCVD or those with an LDL-C ≥ 190 mg/dL), use of non-statin therapies may be considered if maximally tolerated statin therapy has not achieved ≥ 50 percent reduction in LDL-C from baseline.

10. Guidance on other factors are also provided including the absolute LDL-C level achieved, the extent of available scientific evidence for safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering in ASCVD event reduction, cost, convenience and medication storage, pill burden, route of administration, potential to jeopardize adherence to evidence based therapies, and, importantly, patient preferences.

The panel emphasized that LDL-C levels are not firm triggers for adding medication, however, there are factors that may be considered within the broader context of an individual’s clinical situation. Specific recommendations for add-on medications include:

1. A referral to a lipid specialist or registered dietitian may be considered for higher-risk patients with statin intolerance, and is strongly encouraged for patients with familial hypercholesterolemia (FH).

2. Ezetimibe (Zetia) is the first non-statin medication that should be considered for most patients.

3. Bile acid sequestrants (BAS) may be considered as second-line therapy who are not able to tolerate ezetimibe, but they should be avoided in patients with triglycerides > 300 mg/dL.

4. PCSK9 inhibitors may be considered if LDL goals are not achieved on maximally tolerated statin and ezetimibe therapy in higher-risk patients with ASCVD or FH. These agents are not recommended in primary prevention patients who do not have FH.

5. In patients with homozygous hypercholesterolemia (HoFH), referral to a lipid specialist is strongly recommended, for potential considerations for use of lomitapide, mipomerson, and LDL apheresis as necessary.
The annual Potpourri edition of the Lipid Spin is one of my favorites. What is published typically reflects what is in the forefront of the minds of several clinical lipidologists and clinical lipid specialists. I have spent the past several months debating how the 2016 American College of Cardiology Expert Consensus Decision Pathway, endorsed by the National Lipid Association (NLA), will change my practice.1 I have also anticipated (fretted might be a better word) how approval of generic rosuvastatin will or will not be embraced by most insurers. I’m puzzled about the Food and Drug Administration’s decision to allow omega-3 fatty acid products to be promoted off-label. Skeptics also cite that women and diverse patients (i.e., not white patients) have not been adequately represented in primary prevention outcome trials evaluating statin therapy. The JUPITER trial in 2008 had a reasonable number of women and non-white patients and demonstrated a significant reduction in CV events with rosuvastatin 20 mg daily versus placebo.4 However, JUPITER included only patients with elevated hs-CRP, which is a risk marker for CV events. The HOPE-3 included 28 percent Hispanic patients and 45 percent Asian patients. Patients were enrolled based on the “uncertainty principle,” meaning patients who were excluded had clear indications or contraindications for statin therapy. This means there was reasonable doubt of the benefits of statin therapy in the study population because they were intermediate-risk primary prevention without elevated hs-CRP or diabetes. Considering the results and the diversity of the population, the HOPE-3 expands the patient population with proven evidence that statin therapy reduces CV events.

The safety results of HOPE-3 were also important. Rosuvastatin was associated...
with small, but significant increase in muscle symptoms and need for cataract surgery compared to placebo. However, there was no increased risk of new onset diabetes with rosuvastatin, which is in contrast to other clinical trials. This should garner further interest. The HOPE-3 is not without limitations. There was only a 26.5 percent difference in LDL-C between rosuvastatin 10 mg daily and placebo. The study dose of rosuvastatin is moderate-intensity so this difference should have been much greater, even with some nonadherence. Nonetheless, CV events were reduced and the reduction is similar to what has been demonstrated in other clinical trials with a comparable amount of LDL-C lowering. This supports the LDL hypothesis.

The HOPE-3 trial adds to the already rich evidence base supporting statin therapy in primary prevention patients. Considering that the rate of ASCVD events seen in the placebo rate is similar to a 10-year ASCVD event rate of approximately 10 percent, these primary patients are candidates for moderate-to-high intensity statin therapy according to the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. Most importantly, it provides additional data in diverse patients who are intermediate-risk. Expect to hear more about HOPE-3 in the near future.

It is a privilege to be the co-editor of LipidSpin. I hope you enjoy this Potpourri edition as much as I have!

References are listed on page 45.
It is a great time to be a clinical lipidologist and I want to thank all of the readers for a wonderful year as co-editor of LipidSpin! It has been the year of the PCSK9 inhibitor introduction and that has captured everyone’s attention. But that is not all that is going on in clinical lipidology; our field is rolling and we have tried to cover as much of it as possible in the LipidSpin this past year.

Since our last Potpourri issue, we have covered primary prevention, lipid specialty care, guidelines, unusual dyslipidemias, and lipid myths.

Our LipidSpin predecessors, Robert Wild, MD, and Jamie Underberg, MD, congratulated the NLA last year for devoting their efforts to special populations, and then called for authors to address this further. Right on cue, our next edition on primary prevention was devoted to gender specific management, metabolic syndrome in youth, and elderly care.

We reminded our colleagues that clinical lipidologists offer an important expertise, and thus, we were updated on PCSK9 inhibitors, CETP inhibitors, myopathy, and the unusual presentation of tuberous xanthomae.

We devoted an entire issue to the importance of guidelines and learned how to meld public health standards with a personalized medicine approach to care.

More focused attention to very special circumstances followed in the unusual dyslipidemia issue. We saw articles on an unusual response to a very low carbohydrate diet, reviews on sitosterolemia and LAL-deficiency, and then a case of red yeast rice associated myopathy.

Our last completed issue on lipid myths was particularly well received. We got the big picture on HDL and insulin, reviews of chelation therapy, coconut oil, butter vs. margarine, and summaries on major nutrition topics and dietary supplements. I have never felt as well prepared for the cocktail party conversations as I did after reading that issue.

I hope you enjoy this Potpourri issue of the LipidSpin. This is a great time to recognize what our colleagues are thinking about. We included articles on PCSK9 inhibitors, causes of secondary hyperlipidemia, measuring low LDL-C levels, coronary artery calcium scoring, fish oil, red yeast rice, CETP inhibitors, treating the elderly, pseudohypertriglyceridemia, and the finding of a very specific FH founder effect in Pennsylvania Amish.

In fact, every issue is a bit of a potpourri meant to reflect the thoughts and character of the NLA membership. We have had contributions from seasoned veterans, young trainees, nutritionists, pharmacists, physicians, nurses, young, and old. I feel thankful to have the opportunity to co-edit the issues with Joseph Saseen, PharmD, the Publications Committee members who act as peer reviewers, and of course the chapter presidents who carry the reigns for each issue.

Melissa Heyboer, the NLA Communications Manager, keeps us all in line, on time, and well organized. Her attention and care has made this job truly a joy. I look forward to every submission and every issue; and I look forward to our second year with this LipidSpin team.
Patients of all ages and with all kinds of problems seek help in our busy family medicine clinic (10 providers, 33,000 visits a year), which is part of a four-clinic network of the Oregon Health & Science University (OHSU) Family Medicine Department. I work independently (although we do collaborate) from the OHSU Preventive Cardiology Division as the only lipidologist within our department, taking referrals from my colleagues.

When the U.S. Food and Drug Administration (FDA) approval dates were approaching for PCSK9 inhibitors, I contacted field medical teams of Sanofi/Regeneron (alirocumab) and Amgen (evolocumab). I wanted both scientific information and access to pamphlets, coupons, and other resources. OHSU does not allow the dispensing of samples to patients in office. However, both companies offered assistance programs allowing patients to get started on free samples sent to their homes within one to two weeks from an office visit. They also offered help with reimbursement/insurance specialists, who were crucial to getting the patients approved by insurance.

I was preparing several of my high-risk patients for the advent of new drugs. Many of them were eagerly following the news, while others were hesitant, afraid of the “new statins.” The day after the FDA approved alirocumab, the first patient willing to embrace the new treatment was already in my office. In total, I started 13 patients on PCSK9 inhibitors. Unfortunately, three of them were denied by their insurance and thus discontinued therapy.

I always offered both PCSK9 inhibitors to my patients without recommending one over the other. So far, insurers did not have a preference, but this is likely going to change in the immediate future. My first six patients were started on alirocumab because it was the first drug available in July 2015. All were started on the lowest dose, 75 mg, every two weeks. 1 Because of their excellent response, their dose was not increased. Once evolocumab entered the market, most patients chose it over alirocumab because of the advertised 30-day storage at room temperature without need for refrigeration (vs. 24 hours for alirocumab). Most of my patients have an active lifestyle, and therefore it was a clear advantage. All patients on evolocumab used the biweekly dosing of 140 mg. Not a single patient wanted the monthly administration of three consecutive injections. 2 After initiation of either alirocumab or evolocumab, low-density lipoprotein cholesterol (LDL-C) and low-density lipoprotein particle (LDL-P) decreased 50 to 70 percent. I have observed no major effects on high-density lipoprotein cholesterol (HDL-C) or triglyceride levels, except in one case, when the latter increased.

Dummy autoinjectors were used to demonstrate drug administration during the initial office visit. I worked together with my patients to fill out the paperwork, including the prescription for the specialty pharmacy. Forms were changing initially almost every week. Patients could also fill out requests for free samples and financial assistance provided by the companies.
One patient came for an office visit to perform the first self-administration in my presence. Another patient was initially afraid to inject himself but, after four visits, he was comfortable enough to continue them at home. None of the other patients had any issue initiating injections at home. Patients occasionally reported minor pain/irritation at injection sites. One patient reported cold symptoms with each injection. Even the most skeptical patients did not report any other side effects. One potential candidate for this therapy had refused the use of injectable drugs.

The FDA approval for the PCSK9 inhibitors is to use them as an “adjuent to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol.” In addition, evolocumab is indicated to treat homozygous familial hypercholesterolemia (FH).

My patients started PCSK9 inhibitors for a range of indications. Two of them were prescribed PCSK9 inhibitors for secondary prevention. One patient had heterozygous familial hypercholesterolemia (HeFH) with coronary artery bypass grafting (CABG) at age 36 and subsequent angina while on rosuvastatin 40mg and ezetimibe 10 mg. After starting a PCSK9 inhibitor her LDL-C is now at 84 mg/dL. Another patient had recurrent coronary events after CABG followed by stenting, despite taking atorvastatin 80 mg plus ezetimibe 10 mg. His LDL-C hovered above 70 mg/dL. Now, it has been successfully lowered to 35 mg/dL.

The remaining 11 patients were prescribed PCSK9 inhibitors for primary prevention in the context of HeFH (eight) or mixed dyslipidemia (three), the latter being an off-label indication. All of them have at least some degree of statin intolerance, but only five patients reported statin-associated myalgias. One patient complained of constipation with statins, ezetimibe, and basically any drug that was not injectable. Another patient reported rashes with statins, niacin, and ezetimibe. The rest reported “clouded minds” or some degree of cognitive impairment. All of them have tolerated PCSK9 inhibitors without problems.

Real-life prescribing of PCSK9 inhibitors means a tough fight with insurance companies. Initially, many insurers rejected the drugs because they did not fit algorithms based on the 2013 American Heart Association/American College of Cardiology (AHA/ACC) guidelines. Some insurers even argued that they were “experimental drugs.” With time, insurers created a more uniform application process demanding details of previously attempted therapy with statins and other agents. Application forms often request the prescription to be written by or in consultation with cardiologists, endocrinologists, or “lipid specialists.” Such designation did not appear initially on some forms. Insurance companies were often unaware of our existence. The ability of clinical lipidologists to prescribe PCSK9 inhibitors has been now added to the forms I have seen so far, being a welcomed recognition of our specialty.

For some patients, the path to get insurance approval was easy; for others, it was not. Some became angry and frustrated. They saw excellent lipid profiles after using free samples, which turned again into bad numbers, when insurance refused the approval. Some insurers approved PCSK9 inhibitors only if the patient fulfilled Dutch Lipid Clinic Criteria for definite HeFH with a score greater than eight, refusing to accept the National Lipid Association (NLA) and AHA criteria. One of my patients had a score of eight with an untreated LDL-C of 204 mg/dL. His insurance refused him PCSK9 inhibitors despite him having an Agatson score of 390 demonstrating asymptomatic atherosclerotic cardiovascular disease (ASCVD). Moreover, his genetic testing was negative, which in the insurers view, closed the case. This patient reacted to statins with time- and dose-dependent cognitive impairment; therefore he cannot use them as they impair his work. In contrast, a different insurer provides the same drug to a patient with truly psychogenic statin intolerance with mixed dyslipidemia and a baseline LDL-C of 150 mg/dL. These two examples demonstrate striking differences in access to PCSK9 inhibitors depending on the insurance company. To get PCSK9 inhibitors approved, insurers often request fulfillment of the NLA criteria for statin intolerance. Frequently, insurers also request proof of failing ezetimibe therapy before approving PCSK9 inhibitors.

It is frustrating that insurance clerks without lipid knowledge make decisions jeopardizing patient care. They do not understand arguments about elevated Lp(a) or elevated LDL-P/apoB/non-HDL-C, following pre-set insurance algorithms. Fortunately, recently published guidance from the ACC about non-statin therapy is of help in the discussion. The return of LDL-C goals in the document clarifies what constitutes the need for “additional lowering of LDL-C.” The completion of cardiovascular outcome studies will surely provide even more arguments for a wider use of PCSK9 inhibitors. Hopefully, once bocozucimab (Pfizer) receives FDA approval, increased competition will drive their price further down.

This has been a challenging introduction of this new class of drugs. It has come with a fight. It truly challenges my resolve given the time consuming, faulty, and sometimes random criteria for approval.

References are listed on page 45.

Dr. Wójcik has no disclosures to report.
The approach to understanding hypercholesterolemia, hypertriglyceridemia, or both, starts with consideration of the underlying lipoprotein abnormalities present.1,2 This is followed by asking to what degree genetic or acquired causes explain the observed abnormalities. Since those with lipoprotein abnormalities and increased risk for either atherosclerotic cardiovascular disease (ASCVD) or pancreatitis are candidates for drug therapy, finding acquired causes and instituting lifestyle changes could spare drug treatment or, at a minimum, reduce the intensity of such treatment. We present an informative case to illustrate issues related to secondary hyperlipidemia where a search for the cause and not pharmacotherapy is the primary approach.

**Case 1.** A 43-year-old man with a history of minimal-change kidney disease and type 2 diabetes had been off steroid therapy for almost one year. Because of his diabetes, he was given atorvastatin 10 mg daily. He developed chronic clostridium difficile (CD) infection and required a fecal microbial transplant. This led to acute worsening of his nephrotic syndrome and high-dose prednisone therapy (60 mg/day). Cautioned to avoid weight gain, he presented to a lipid clinic with minimal weight change but elevated cholesterol and triglyceride, raised high-density lipoprotein cholesterol (HDL-C), and elevated low-density lipoprotein cholesterol (LDL-C), and non-HDL-C (Table 1). Concerned, he asked to discuss his treatment options.

Yet the recent onset of his hyperlipidemia and his complicated medical history made consideration of secondary causes crucial. A report from a lipid specialty clinic noted that the most frequently encountered secondary causes of hyperlipidemia included excessive alcohol intake, uncontrolled diabetes, and overt albuminuria.3 Recent guidelines list secondary causes of hyperlipidemia often encountered in clinical practice (Table 2).1 The patient was advised to adhere to a healthy lifestyle by increasing his activity level and decreasing his caloric intake. His statin dosage was not changed. Over the next month, his prednisone was tapered from 60 mg to 14 mg daily. Two months later, his repeat lipid panel had significantly improved. His lipid improvements were attributed to the resolution of his acute episode of nephrotic syndrome, decreased steroids, and improved lifestyle and weight...
control. He did not wish further lipid medications and indicated he wished to work further on lifestyle changes with the hope of improving his lipid measurements.

As part of the clinical discussion before lipid medication is given, it is essential to review secondary causes of hyperlipidemia. Although thyroid may be more common, both renal- and liver-associated lipid abnormalities illustrate the importance of pausing to find a secondary cause. One renal cause is nephrotic syndrome. This often is accompanied by elevated LDL-C, triglycerides, and lipoprotein(a), and normal or decreased HDL-C.4 The mechanism underlying abnormal lipid levels includes increased hepatic synthesis of apoproteins B, C-II and E, but without increased production of apoproteins A-I and A-II.5,6 These metabolic derangements lead to markedly elevated cholesterol levels. In a cohort of 207 nondiabetic patients with nephrotic syndrome, the LDL-C was noted to average 208 mg/dl.7 Such a marked elevation in the LDL-C could prompt an initiation of a high-intensity statin per the current 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.1 But high-intensity statin therapy may not be immediately required if the mechanism of increase in LDL-C is reversible5 and can resolve with specific treatment of the underlying causes of nephrotic syndrome. This is reflected in recommendations by the Kidney Disease International Global Outcomes (KDIGO) guidelines for treatment of nephrotic syndrome. KDIGO supported our management with a weak recommendation for not initiating statin therapy for minimal-change disease when clinical resolution with normalization of the lipid profile is likely.8

Although space limitations preclude another case, clinicians also should be aware of liver-related causes of elevated lipids. For example, non-alcoholic fatty liver disease (NAFLD) may be accompanied by the atherogenic lipid triad of high triglycerides, elevated small dense LDL,9 and a low HDL-C.10 These lipid derangements are associated with increased ASCVD risk.11 This requires an initial focus on lifestyle change with subsequent consideration of statin use. In the setting of stable liver disease, NAFLD itself is not a contraindication to statin therapy.12 Primary biliary cholangitis, on the other hand, alters cholesterol metabolism by causing reflux

<table>
<thead>
<tr>
<th>Patient’s Labs</th>
<th>VISIT 1 3/12/2015</th>
<th>VISIT 2 5/25/2015</th>
<th>VISIT 3 7/24/2015 Prednisone60 mg/day</th>
<th>VISIT 4 9/12/2015 Prednisone 12 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>153</td>
<td>167</td>
<td>336</td>
<td>215</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>180</td>
<td>202</td>
<td>299</td>
<td>268</td>
</tr>
<tr>
<td>HDL-C</td>
<td>33</td>
<td>53</td>
<td>105</td>
<td>59</td>
</tr>
<tr>
<td>LDL-C</td>
<td>84</td>
<td>74</td>
<td>171</td>
<td>102</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>120</td>
<td>114</td>
<td>231</td>
<td>156</td>
</tr>
</tbody>
</table>

Table 1. Clinical Case Data

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL-C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td>Saturated or trans fat, weight gain, anorexia nervosa</td>
<td>Weight gain, very-low-fat diets, high intake of refined carbohydrates, excess alcohol intake</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-alcohol, acne medications, atypical antipsychotics, B-beta-blockers, C-chemotherapy, D-diuretics, diabetes medications, E-epilepsy, F-fibrillation meds, G-glucocorticoids, H-HIV medications (protease inhibitors), I-immunosuppressants</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, relaxfene, tamoxifen, beta blockers (not alpha beta blockers such as carvedilol), thiazide diuretics</td>
</tr>
<tr>
<td><strong>Diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome, biliary obstruction</td>
<td>Hypothyroidism, obesity, pregnancy</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td><strong>Disorders and altered states of metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism, obesity, pregnancy</td>
<td>Diabetes (poorly controlled); hypothyroidism, obesity, pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from Reference 1 with permission.

Table 2. Secondary Causes of Hyperlipidemia Commonly Encountered in Clinical Practice*
of biliary lipids into the circulation and downregulation of lethicin-cholesterol acetyltransferase (LCAT) activity, resulting in an increase in triglycerides, LDL-C, and HDL-C (although HDL-C decreases with disease progression). However, the elevation in LDL-C is driven by the accumulation of lipoprotein-X, a lipoprotein that is resistant to in-vitro oxidation and which some believe may protect against atherogenesis. Thus, lipid derangements secondary to cholestasis may not increase ACSVD risk.

Finally, medications may cause secondary elevations of lipids. We offer the following list of medications that can affect lipids. Most drug effects are mild but the drugs that greatly raise triglycerides can lead to pancreatitis. Often, it may be especially useful to focus on lifestyle interventions to minimize the effects on lipids. We suggest a mnemonic (ABCDEFGHI) for remembering frequently encountered classes of medications that affect lipids (Table 2).

**Conclusion:** The new cholesterol guidelines were notable for providing guidelines that focus on defining at-risk clinical groups, prioritizing interventions supported by strong evidence, and recommending clinician-patient risk discussions in lower-risk primary prevention before statin assignment despite the risk score. They advised the need to consider secondary causes of lipid abnormalities before assuming that lipid changes were primary. Identification of secondary causes whether they be medication, dietary, or related to diseases or disorders of metabolism is crucial before pharmacotherapy for lipids is given. Importantly, patients also may benefit from intensive lifestyle counseling to mitigate many changes in lipid parameters that can accompany secondary causes. Thus, when you see abnormal lipids, remember to search for a secondary cause(s); it’s worth the pause.

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*Written permission was obtained from the patient.

Disclosure statement: Dr. Ducharme-Smith has no disclosures to report. Dr. Laczay has no disclosures to report. Dr. Raygor has no disclosures to report. Dr. Stone was the lead author of the 2013 ACC/AHA Cholesterol Guidelines.

References are listed on page 45.
Recent clinical trial data has strengthened the argument that lowering low-density lipoprotein cholesterol (LDL-C) to levels well below those previously targeted provides incremental benefit in terms of lowering the risk of atherosclerotic cardiovascular disease (ASCVD). The increased use of high-intensity statins, irrespective of baseline LDL-C, has resulted in clinicians more frequently encountering LDL-C levels below 40 mg/dL. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) blood cholesterol guidelines suggest considering a statin dose reduction when LDL-C is persistently <40 mg/dL. This recommendation may be misconstrued as meaning LDL-C levels <40 mg/dL are harmful and may carry the unintended consequence of patients at high risk for ASCVD receiving a statin that is less than the recommended intensity. Furthermore, LDL-C levels below 40 mg/dL, as estimated by the Friedewald equation \[ \text{LDL-C} = \text{[total cholesterol]} - \text{[HDL-C]} - \frac{\text{[TG]}}{5} \], often are inaccurate in the setting of elevated triglyceride (TG) levels. What follows is a discussion focused on how clinicians caring for patients at risk for ASCVD may interpret very low levels of LDL-C, including practical suggestions for how to approach this clinical conundrum.

Historically speaking, there has been limited experience with extremely low levels of LDL-C. Gestational and neonatal LDL-C levels have been reported to be in the range of 30–70 mg/dL and individuals with familial hypobetalipoproteinemia have LDL-C levels in the range of 0–20 mg/dL for homozygotes and 30–50 mg/dL for heterozygotes. In the past decade, contemporary clinical trials have reported increased numbers of patients with LDL-C levels <40 mg/dL (Table 1).

The basis for the ACC/AHA recommendation stems from the treatment approach employed in certain clinical trials in which an LDL-C <40 mg/dL was an arbitrary threshold set for investigators to consider a down titration of statin therapy. In fact, the ACC/AHA detailed supplemental full panel report states that there is no evidence of harm when LDL-C remains <40 mg/dL on statin therapy, a point which is echoed in the 2014 National Lipid Association (NLA) Recommendations for Patient-Centered Management of
Dyslipidemia.\textsuperscript{2,13}

In the Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL) trial, which compared atorvastatin 80 mg a day to simvastatin 20–40 mg a day in patients with a history of myocardial infarction (MI) (baseline LDL-C 121 mg/dL), investigators were given the option to decrease statin doses if LDL-C fell below 39 mg/dL.\textsuperscript{11} Similarly, in the HDL Atherosclerosis Treatment Study (HATS) trial, which compared various doses of simvastatin in combination with niacin in patients with angiographic evidence of coronary artery disease (baseline LDL-C 125 mg/dL), investigators were given the option to reduce the statin dose if LDL-C was <40 mg/dL.\textsuperscript{12} Conversely, in the Collaborative Atorvastatin Diabetes Study (CARDS) trial, which compared atorvastatin 10 mg a day to placebo in patients with diabetes (baseline LDL-C 117 mg/dL) the study drug was continued regardless of LDL-C level and the data and safety monitoring board did not identify any safety concerns in patients with LDL-C <39 mg/dL.\textsuperscript{14}

In patients at very high risk for ASCVD events, the NLA guidance recommends against statin dose reduction when LDL-C measures <40 mg/dL, presuming there are no tolerability- or safety-related concerns.\textsuperscript{13} Support for this recommendation can be found in data from both the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) and the Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) PCSK9 inhibitor trials, wherein safety analyses of patients obtaining LDL-C <40 mg/dL, and even those <25 mg/dL, showed adverse event rates similar to those with LDL-C >40 mg/dL.\textsuperscript{6,7}

“A growing body of evidence suggests that LDL-C levels can be safely driven to very low levels in individuals at high risk for ASCVD.”

Most laboratories report Friedewald estimated LDL-C unless TG are >400 mg/dL, in which case a direct LDL-C is reported. However, research by Martin and colleagues has demonstrated that even at mildly elevated TG levels (i.e. >150 mg/dL), the Friedewald equation becomes increasingly inaccurate at lower levels of LDL-C.\textsuperscript{3,15} The reason for the discrepancy between estimated and directly measured LDL-C stems from the fact that the equation assumes a fixed ratio (5:1) of TG to VLDL-C. Employing a fixed factor of 5 to estimate VLDL-C from TG creates a problem in that TG:VLDL-C ratio is not constant across a range of TG and total cholesterol (TC) values. To get around this problem, one should assess non-high-density lipoprotein cholesterol (non-HDL-C) levels, which is the primary goal of therapy in the NLA Recommendations, or consider using an adjustable factor for the TG:VLDL-C ratio based off TG.\textsuperscript{13,15}

A recent scenario encountered in our practice involved a 68-year-old patient with established ASCVD (MI w/stent in 2014) and diabetes mellitus taking atorvastatin 40 mg once daily. A fasting lipid panel revealed: TC 136, TG 385, HDL-C 42, LDL-C 17, and non-HDL-C 94 mg/dL. Since triglycerides were <400 mg/dL, the reported LDL-C represented a Friedewald estimation. Her primary care physician expressed concern about the patient’s LDL-C being too low and suggested a reduction in atorvastatin dose. In this scenario, one could start by pointing out that non-HDL-C is near 100 mg/dL, which would provide rationale for not decreasing the statin dose to maintain the recommended intensity of statin and ensure optimal ASCVD risk reduction. Next, using a method proposed by Martin,

<table>
<thead>
<tr>
<th>Clinical Trial (publication year)</th>
<th>Number of Patients Achieving Very Low LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td>OSLER\textsuperscript{6} (2015)</td>
<td></td>
</tr>
<tr>
<td>ODYSSEY LONG-TERM\textsuperscript{7} (2015)</td>
<td></td>
</tr>
<tr>
<td>IMPROVE-IT\textsuperscript{1} (2015)</td>
<td>5,926</td>
</tr>
<tr>
<td>JUPITER\textsuperscript{8} (2008)</td>
<td>4,154</td>
</tr>
<tr>
<td>PROVE-IT\textsuperscript{9} (2004)</td>
<td></td>
</tr>
<tr>
<td>TNT\textsuperscript{10} (2005)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Clinical trials reporting the number of subjects achieving very low LDL-C.
et al., 15 the TG:VLDL-C ratio would be 9.5, which would yield an estimated LDL-C of 53 mg/dL. Finally, one could request that the laboratory parse out a direct LDL-C from the blood sample. In fact, this was performed in this case and the directly measured LDL-C was 52 mg/dL. Each of these strategies should lead to the same conclusion for this patient: It is reasonable to continue atorvastatin at the current dose.

A growing body of evidence suggests that LDL-C levels can be safely driven to very low levels in individuals at high risk for ASCVD. Clinical outcomes data from PCSK9 inhibitor trials are anticipated in the near future and may address some of the safety concerns that have been raised with treating to very low LDL-C levels (eg, hemorrhagic stroke and cognitive effects). When an LDL-C <40 mg/dL is encountered, a statin dose reduction may not be necessary, particularly in patients at high risk for ASCVD. Exceptions might include the presence of advanced age, statin drug interactions, or patient-reported side effects. Further complicating matters is the fact that when TG are elevated and LDL-C is driven to very low levels, the accuracy of the Friedewald equation is severely compromised. When concerns arise over a seemingly “too low” LDL-C and direct measurement is impractical, it is important to remember that non-HDL-C serves as an inexpensive means by which to estimate circulating levels of atherogenic particles. Taking these steps may help to minimize inappropriate statin dose reductions in patients with LDL-C below 40 mg/dL.

Disclosure statement: Dr. Lamprecht has no disclosures to report. Dr. Stadler has no disclosures to report.

References are listed on page 45.

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Statins currently stand as the cornerstone of therapeutic strategies for the reduction of atherosclerotic cardiovascular events. However, despite their chronicled successes over the past 30 years since the U.S. Food and Drug Administration (FDA) approved lovastatin, multiple analyses of clinical trial data reveal residual cardiovascular risk in patients treated with statins, even those achieving optimal reduction of low-density lipoprotein cholesterol (LDL-C). Therefore, the pharmaceutical industry has turned to new therapeutic modalities to modulate this residual risk in statin-treated patients.

A major area of focus over the past 10 years has been modulation of cholesteryl ester transfer protein (CETP). Interest in this target was based on several observations, including:

- The physiologic actions of CETP in increasing high-density lipoprotein-cholesterol (HDL-C)²
- The involvement of high-density lipoproteins (HDLs) in the reverse cholesterol transport pathway and the inverse association of high-density lipoprotein cholesterol (HDL-C) concentration with cardiovascular disease incidence⁷
- A link between genetic variants of CETP activity and the risk for coronary artery disease⁸,⁹

Pfizer developed and tested the first CETP inhibitor, torcetrapib. In the Phase 3 Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, patients treated with torcetrapib had significantly higher rates of major cardiovascular and cerebrovascular events, and higher mortality resulting from cancer and infection.¹⁰ The trial, and all further development of torcetrapib, was terminated in December 2006. It is largely accepted that off-target effects on cortisol, endothelin-1, and aldosterone led to the observed adverse outcomes.¹¹ Dalcepray, developed by Hoffman-La Roche, followed torcetrapib. In the Phase 3, Dalcepray in Stable Coronary Heart Disease Patients with Recent Acute Coronary Syndrome (dal-OUTCOMES) trial, treatment with dalcepray did not alter the risk of major cardiovascular events.¹² The study was stopped early based on a futility analysis and Roche discontinued development of dalcepray in May 2012. In other studies, it was shown that dalcepray did not have any off-target adverse effects; however it did not have any appreciable effect on LDL-C, which was the major reason cited for the negative results. Eli Lilly recently halted development of evacetrapib in October 2015, after a planned interim analysis of its Phase 3 Aalskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension (ACCELERATE) trial also demonstrated insufficient efficacy. Results of the study were presented at the 2016 American College of Cardiology Scientific Sessions and publication of the full results are expected this year. Evacetrapib had no off-target effects, decreased LDL-C by 37 percent, and increased HDL-C by 130 percent, yet did not decrease atherosclerotic cardiovascular
Lipid Spin • Volume 14, Issue 4 • August 2016

CETP Inhibitor Pharmaceutical Company Stage of Development Status

Torcetrapib Pfizer Phase 3 ILLUMINATE (NCT00134264) terminated December 2, 2006, for lack of efficacy and adverse effects

Dalcetrapib Roche/DalCor Phase 3 dal-OUTCOMES (NCT00658515) terminated in September 2012 for lack of efficacy. dal-GenE (NCT02525939) ongoing

Evacetrapib Eli Lilly Phase 3 ACCELERATE (NCT01687998) terminated for lack of efficacy

Anacetrapib Merck Phase 3 REVEAL (NCT01252953) ongoing. After futility analysis, trial will continue until January 2017

TA-8995 Amgen/Dezima Phase 2 No Phase 3 trial announced

Table 1. Developmental Stages of CETP Inhibitors

<table>
<thead>
<tr>
<th>CETP Inhibitor</th>
<th>Other Lipid-Lowering Treatment</th>
<th>% Change from baseline to end of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C</td>
</tr>
<tr>
<td>Torcetrapib10</td>
<td>Atorvastatin</td>
<td>-24%</td>
</tr>
<tr>
<td>Dalcetrapib12</td>
<td>Statin</td>
<td>NS</td>
</tr>
<tr>
<td>Evacetrapib13,21</td>
<td>Statin</td>
<td>-37%</td>
</tr>
<tr>
<td>Anacetrapib22</td>
<td>Statin</td>
<td>-36%</td>
</tr>
<tr>
<td>TA-899519</td>
<td>ND</td>
<td>-28-69%</td>
</tr>
</tbody>
</table>

NS = not significant, ND = no data

Table 2. Efficacy of CETP Inhibitor on Various Lipid Parameters

After three straight negative outcomes trials, significant questions exist about the validity of CETP as a therapeutic target for reducing residual risk. However, there are two CETP inhibitors that remain in different phases of development and one that has been resurrected based on pharmacogenomics data.

Following the announcement of the termination of evacetrapib, Merck added a futility analysis to its planned interim review of the Phase 3 Rapid Evaluation of Vessel Healing After Angioplasty (REVEAL) trial of its CETP inhibitor, anacetrapib. On Nov. 13, 2015, Merck announced that, based on this analysis, REVEAL would continue with no changes to its original planned completion date. In the months since this announcement, many have questioned the reasons underlying this decision given three past CETP inhibitor failures and Merck’s huge capital investment in anacetrapib. There are some reasons speculated as to why this decision was made. First, although anacetrapib has similar effects on LDL-C and HDL-C as evacetrapib, the REVEAL trial is more than twice as large as ACCELERATE, which increases the statistical power to detect a difference in associated outcomes. Second, anacetrapib reduces lipoprotein (a) (Lp (a)) by about 32 percent. This effect is thought to be shared by evacetrapib. However, at the time of this writing, no data for evacetrapib was available for comparison. Nevertheless, should REVEAL prove positive and anacetrapib make it to market, one area of concern is its unusually long terminal half-life. In a subset of 30 patients from its Phase 2 Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial, low concentrations of anacetrapib were detectable in plasma as late as four years after the last dose was taken. Using population pharmacokinetic modeling, the estimated half-life was 550 days. Although no accumulation of drug is expected, it remains what impact this would have in patients who suffer adverse drug reactions or who become or expect to become pregnant during treatment.

On Sept. 16, 2015, prior to Eli Lilly’s announcement about evacetrapib, Amgen acquired the oral CETP inhibitor TA-8995 in a deal to purchase Dezima Pharma, which had developed TA-8995 to that point. Data from its Phase 2 Cholesterol ester transfer protein inhibition by TA-8995 in Patients with Mild Dyslipidaemia (TULIP) trial identified several potentially advantageous properties. First, it
decreased LDL-C up to 69 percent, increased HDL-C up to 177 percent, decreased apolipoprotein B (apo B) up to 51 percent, and decreased Lp (a) up to 35 percent, making it the most potent CETP inhibitor. Second, it decreased apolipoprotein A-I (apo AI) up to 63 percent and increased cholesterol efflux up to 37 percent, suggesting functional HDL particles. Third, it has a much shorter half-life — about two weeks compared to anacetrapib.19 There has been no announcement by Amgen as to whether TA-8995 will enter a Phase 3 clinical trial.

Following Roche’s termination of the development of dalcetrapib, investigators at the Montreal Heart Institute conducted a retrospective analysis of a cohort of patients from the dal-OUTCOMES and Safety and Efficacy of Dalcetrapib on Atherosclerotic Disease Using Novel Non-invasive Multimodality Imaging (dal-PLAQUE-2) studies. A single nucleotide polymorphism (SNP) identified at a specific location in the adenylate cyclase type 9 (ADCY9) gene on chromosome 16 was found to be associated with cardiovascular events in dalcetrapib-treated patients. In patients homozygous for the minor allele (AA), there was a 39 percent decrease in the trial’s composite endpoint, which was coronary heart disease death, resuscitated cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, unstable angina, or urgent coronary revascularization. In patients homozygous for the wild-type allele (GG), there was a 27 percent increase in the same endpoint. No such genetic differences were observed in patients receiving placebo.20 This analysis was sponsored by Roche, which subsequently filed for patents covering this genetic marker for use with dalcetrapib and the other CETP inhibitors. A different pharmaceutical company, DalCor, acquired exclusive licensing rights from Roche for the use of dalcetrapib and the genetic marker. DalCor is sponsoring its own Phase 3 trial, the Effect of Dalcetrapib vs. Placebo on CV Risk in a Genetically Defined Population with Recent ACS (dal-GenE). The trial plans to enroll 5,000 patients who recently have been hospitalized with acute coronary syndrome and have a previously identified AA genotype of the ADCY9 gene. It started recruiting patients in March. There have been several criticisms of this trial including a lack of foundational knowledge about the functions of the ADCY9 gene and its link the mechanism of CETP.

“Of the four CETP inhibitors that have been brought to clinical trials, three have been abandoned due to lack of clinical benefit or off-target effects.”

In summary, of the four CETP inhibitors that have been brought to clinical trials, three have been abandoned due to lack of clinical benefit or off-target effects. Anacetrapib and TA-8995 remain in development. The REVEAL trial with anacetrapib is large enough that it may ultimately show cardiovascular benefit, yet it remains to be seen whether the benefit will be appreciable enough for clinical utility. TA-8995 showed some promising results in its phase II study; however, similar results were demonstrated with other CETP inhibitors that ultimately did not translate to improvements in outcomes of their phase III trials. Dalcetrapib has been resurrected based on observed benefit in a genetic subgroup of patients. While this shows promise for dalcetrapib and possibly the other CETP inhibitors as well, there are unknowns about the plausibility of the genetic link. ■

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References are listed on page 45.
Coronary Artery Calcium Scoring in Decision Making: the MESA Score

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Evaluation of a patient’s risk for cardiovascular disease (CVD) is the basis of deciding whether to institute statin therapy. The 2013 ACC/AHA Guidelines on the Assessment of Cardiovascular Risk recommend using the Pooled Cohort Equation to predict the 10-year risk of having an atherosclerotic cardiovascular disease (ASCVD) event in non-Hispanic Whites and African Americans, 40 to 79 years of age. This calculation includes all forms of cardiovascular disease, including stroke and coronary heart disease (CHD). Several other risk calculators have been developed to assess an individual’s CVD risk, however, all have limitations. Risk calculators provide a bio-statistical approach that estimates risk for a specific patient population but not necessarily for an individual. This approach can identify those patients at high risk based on traditional risk factors, but frequently does not address those with low or intermediate risk who contribute most of the population-attributable risk.

Coronary artery calcium (CAC) is a disease score that integrates the effect of genetics, environment, traditional risk factors, biomarkers, and the unknown. It correlates with the degree of atherosclerosis and the risk of developing symptomatic cardiovascular disease. The Multi-Ethnic Study of Atherosclerosis (MESA) score is a new coronary heart disease (CHD) risk calculator that incorporates CAC score in addition to the traditional risk factors of demographics, cholesterol, systolic blood pressure, diabetes, smoking, family history of CHD, and the use of hypertension or cholesterol medications. The following cases will illustrate the added clinical utility of the CAC and MESA scores.

LS is a 57-year-old white female whose father had a myocardial infarction (MI) in his 40s. She stopped smoking in her 30s and has no history of hypertension or diabetes. Her calculated 10-year risk of ASCVD using the ACC/AHA Pooled Cohort Equations is 1.5 percent and her lifetime risk is 27 percent. She had a chest computed tomographic angiography in 2009 because of chest pain, which showed no evidence of “any significant obstruction,” but did demonstrate calcification in the proximal left anterior descending artery. A follow-up CAC score was 247 Agatston units, placing her in the 97th percentile for her age. Her MESA 10-year CHD risk score was 2.5 percent without her CAC score and 6.7 percent with the score. A standard lipid
profile showed cholesterol 158 mg/dL, triglycerides 128 mg/dL, HDL-C 58 mg/dL, and LDL-C 74 mg/dL. She had a normal NMR LipoProfile, lipoprotein-associated phospholipase A2 (Lp-PLA2), lipoprotein[a] (Lp(a)), and flow-mediated dilatation. Because of her absolute CAC score, she was placed on a high-intensity statin and aspirin. Of note, her older sister also had a similar lipid profile and a significantly elevated CAC score.

LE is a 68-year-old white female referred by her primary care physician after the patient developed myalgias on numerous occasions. Her cholesterol was 249 mg/dL, triglycerides 119 mg/dL, HDL-C 57 mg/dL, and LDL-C was 168mg/dL. She had no history of hypertension, smoking, or diabetes mellitus. Her father had a MI in his 50s. Her calculated 10-year ASCVD risk was 8.5 percent using the ACC/AHA calculator. Her MESA risk score was 6.4 percent without her CAC score and 2.6 percent with her CAC score of zero. After reviewing the information with the patient, it was decided not to pursue statin therapy or start aspirin. She was instead referred for weight management.

These cases help to demonstrate that incorporating the CAC score into risk calculations can alter patient management. The ACC/AHA 2013 Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recognize the effectiveness of statins in reducing cardiovascular risk in four clinical scenarios: patients ≤75 years of age with clinical ASCVD, patients ≥21 years of age with LDL-C ≥190mg/dL, patients 40–75 years of age with diabetes mellitus, and patients 40–75 years of age with an estimated 10-year ASCVD risk ≥7.5 percent, based on the ACC/AHA Pooled Cohort Equations. CAC score can be used for cardiovascular risk stratification in patients who do not fall into one of these four categories when there is uncertainty regarding statin therapy. The 2013 guidelines state that CAC score may be considered (Class IIb recommendation) to inform treatment decision-making in patients when such a decision is unclear after conventional risk assessment. The authors of the guidelines should be commended for supporting the use of “non-traditional” risk factors to aid in clinical decision-making.

INTERHEART: A Global Case-Control Study of Risk Factors for Acute Myocardial Infarction evaluated 15,152 cases of acute myocardial infarction in 52 countries. There were nine risk factors that accounted for 93 percent of the population-attributable risk. The individual risk factors that had the largest impact were apolipoprotein B/apolipoprotein A-1 (58.9 percent), psychosocial factors (43.5 percent), and smoking (40.7 percent). Abdominal obesity had a greater impact than hypertension and diabetes. In 6 percent of the study population, no conventional risk factor was identified. It has been reported that only 60 to 70 percent of patients who present with early atherosclerosis will have traditional risk factors. There are 64 genomic loci associated with CAD. Only one-third are related to traditional risk factors, while two-thirds are related to endothelial function, inflammation, and smooth muscle cells. CAC score provides insight into the effect that these pathophysiological processes have on an individual’s risk of CVD.

The CAC score is most likely to affect the management of patients deemed at intermediate or low risk for CVD based on traditional risk factors. A zero CAC score in the MESA trial was the strongest negative predictor with a diagnostic likelihood ratio (DLR) of 0.41 for CHD and 0.54 for CVD. DLR quantifies the change in risk obtained with knowledge of a test result and a value less than one indicates that the test result is less likely to be seen in those with disease and may be used to downgrade risk. However, a zero calcium score does not mean there is no CAD. Gottlieb, et al. reported that a zero CAC score had a negative predictive value of 68 percent in finding a greater than 50 percent stenosis in patients referred to cardiac catheterization for symptoms. Defining the 10-year risk category by using an absolute calcium score — such as <100 being low risk and >400 being high risk — is more predictive than

![Figure 1. CAC score compared to FRS](image-url)
indexing the score for age.\textsuperscript{7} Based on the results of the Heinz Nixdorf Recall, MESA, and Rotterdam studies, the ACC/AHA supported revising an individual’s risk assessment upward if a patient has a CAC score of greater than 300 Agatston units or 75\textsuperscript{th} percentile for their age. Interestingly, statins may actually increase CAC score through “de-lipidation” of soft, cholesterol-laden plaques leading to a rise in calcium density. Therefore, serial CAC scores should not be used to determine the Framingham Risk Score (FRS).\textsuperscript{8} This figure demonstrates the presence of CAC, even in those individuals deemed low risk.

In the MESA study, CAC varied by age (Figure 2). Even at the extremes of age 45–50 versus 75–80, CAC was predictive of risk (Figure 3).\textsuperscript{9}

Area under the curve (AUC)/c-statistic evaluates the ability to discriminate between patients who will and will not develop the defined event. A review of various calculators shows that most generally have an AUC of 0.75\textsuperscript{10} (1 is perfect and 0.5 is random). Inclusion of CAC in the MESA risk score significantly improves the prediction for 10-year CHD risk compared to using traditional risk factors alone. The AUC increased from 0.75 to 0.8. External validation in both the Dallas Heart Study and Heinz Nixdorf Recall studies showed very good discrimination and calibration.\textsuperscript{11}

In assessing a patient’s cardiovascular risk, CAC score provides additional information when added to traditional risk factors. The MESA score is a new clinical tool that incorporates CAC score into CHD risk assessment. Ultimately, there is no perfect risk calculator that can substitute for clinical decision-making. A healthcare provider must integrate all of the available information to arrive at a joint decision with the patient regarding management.

Disclosure statement: Dr. Goldenberg has no disclosures to report. Dr. Meng has no disclosures to report.

References are listed on page 46.
Often there is a dichotomy regarding information published in the lay press versus what is presented in the medical literature. So it’s nice when both agree, except on those rare occasions, when both get it wrong.

Despite numerous epidemiologic and observational studies to the contrary, *Men’s Health* had a recent article titled “Is Fish Oil the New Snake Oil?”1–4 They based that on several recent “high-profile reviews” in “trusted medical journals” that no longer supported the original health claims regarding fish oil. They were referring to two review articles recently published in the medical literature.5,6 The result is an uncertainty for both physicians and the public regarding the use of omega-3 fish oil.

The problem, though, is not a lack of benefit from using omega-3 fatty acids (OM3), specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The problem is that there was a lack of quality fish oil studies included in these two review articles.5,6

When looking at OM3 trials, there are six things to be aware of:

1. Was the study trying to show short-term or long-term benefits? **Short-term benefit:** (One to two years on OM3) a reduction in fatal cardiovascular events, generally because of a reduction in ischemic, induced ventricular tachyarrhythmias.7 Potential anti-arrhythmic actions of OM3:
   - A membrane-stability effect by enrichment of the myocardial membrane with OM3
   - Electrophysiologic effects on various ion channels
   - Autonomic effects, such as reduction in heart-rate variability and increased vagal tone
   - Reduction in perfusion arrhythmias
   - An anti-inflammatory effect

**Long-term benefit:** (>3 years on OM3) a reduction in non-fatal or fatal cardiac events, such as acute coronary syndrome. Potential mechanisms include an anti-inflammatory and/or an antithrombotic effect. Do not look for a reduction in long-term benefits when examining studies with a short time span.

2. Was the patient receiving an appropriate dose? Short-term benefit trials need at
Cardiovascular Benefits of Omega-3 Use

1. Reduction in ischemic induced ventricular arrhythmias.
   - Multiple anti-arrhythmic effects (4, 7, 12, 21, 24, 26)
   - Dose: 0.5–1.0 Gm

2. Reduction in acute coronary syndrome, fatal and nonfatal.
   - Anti-inflammatory effects with possible plaque stabilization (9, 20, 25, 27, 28)
   - Anti-thrombotic effects (29)
   - Dose: ≥1.5 – 2.0 Gm

3. Reduced mortality and improved LV function in heart failure patients.
   - Improvements in endothelial function, hemodynamics, remodeling, and cardiac energetics (15, 22, 23)
   - Dose: ≥1 Gm

(See Reference List for citations)

Table 1.

least 0.5–1.0 gm/day of OM3, while the long-term trials generally require ≥1.5–2.0 gm/day.

3. Were OM3 blood levels obtained to show that the treated group had an adequate OM3 blood level vs. the control group? People have different OM3 absorption abilities, different genetic handling of OM3, and the fish they eat may contain significantly different levels of OM3. OM3 levels cannot be assumed to be adequate.8, 9

4. Was the population large enough for the study? Primary prevention trials need to have a much larger study population than secondary prevention trials.

5. Was there a limitation on fish intake by the control group? Too much intake by the control group could mask any benefit seen in the treated group.

6. What was the concurrent therapy used? Aggressive revascularization and multiple drug therapies may lessen the incidence of fatal cardiac events to such an extent that it is hard to demonstrate benefit in short-term studies. Long-term trials are not as affected by concurrent therapy.

Men’s Health seems to have keyed on the two recent review articles that claimed there was insufficient evidence of secondary prevention with OM3 use. Kwak evaluated 14 studies, while Rizos looked at the same 14 plus six additional studies.5, 6 Both meta-analyses had numerous shortcomings: 11 studies had follow-up ≤2.5 years, 11 had samples sizes of only 50–550, nine had no fish restriction, 14 had no measured omega-3 level, and most were not designed to detect cardiovascular endpoints.10

Of the eight studies in the review articles that had more than 550 patients:

Those showing benefit:
DART randomized 2,033 men with recent myocardial infarction (MI) to OM3 — either oily fish or fish capsules — vs. the control.11 There was a 29 percent reduction in all-cause mortality (primarily cardiac) over two years. The best reduction in events was seen in those taking fish capsules vs. simply increasing fish intake, which may indicate a threshold effect for OM3.

GISSI Prevenzione had 11,323 patients <3 months post-MI randomized to 1 gm of OM3 vs. the control. Sudden cardiac death (SCD) was reduced by 47 percent at four months (p=0.048).12 Note: There was minimal invasive treatment post-MI and only moderate medication use.

JELIS involved 18,645 high-risk or vascular-disease patients put on placebo vs. 1.8 gm of EPA.13 A five-year follow-up showed a 19 percent reduction (p=0.011) in major coronary events, primarily unstable angina and nonfatal MIs. Most risk reduction occurred after 2.5 years. Post-hoc analysis: 53 percent reduction in cardiovascular (CV) events in patients with elevated triglycerides and low HDL-C.14

GISSI-HF involved 6,988 patients with New York Heart Association (NYHA) class II-IV and an average ejection fraction of 33 percent, randomized to placebo vs. 1 gm OM3. Follow-up was 3.9 years.15 There was a significant 9 percent reduction in mortality (p=0.041) and 8 percent reduction in mortality and admissions for chronic heart failure (CHF) (p=0.009). Survival curves started to diverge after two years.

Those showing no benefit:
OMEGA randomized 3,804 immediate post-MI patients to OM3 1 gm vs. olive oil.16 There was no difference in SCD at one year. Problems: The study was underpowered. Aggressive post-MI therapy, including percutaneous coronary intervention in 78 percent, dropped the expected SCD rate of 3.5 percent down to 1.5 percent. Also, 44 percent of placebo patients were ingesting fish several times a week.

Alpha Omega Trial had 4,837 participants with prior MI.17 Participants were randomized to placebo or 400 mg OM3 and followed for 3.5 years. Overall, there was no reduction in CV event rates, but diabetics had a 50 percent reduction in coronary heart disease (CHD) events...
and rate of arrhythmic events similar to GISSI. **Problems:** Participants were given an inadequate dose of OM3 and follow-up was too short. The JELIS curve didn’t start to diverge until 2.5 years.

**ORIGIN** randomized 12,536 high-risk patients with impaired fasting glucose to placebo vs. 900 mg of OM3 with a 6.2-year follow up.\(^\text{18}\) There was no difference in event rates. **Problems:** Patients received an inadequate dose for long-term benefits. The placebo group was ingesting 40–568 mg of OM3 a day. There was no measured OM3 level.

**SU.FOL.OM3** had 2,501 patients with a history of cardiovascular disease randomized to OM3 600 mg vs. placebo.\(^\text{19}\) They were followed for 4.7 years. There was no difference in cardiovascular events. **Problems:** Patients received an inadequate dose. There was no fish restriction in the placebo group. It was underpowered.

So despite the inclusion of these suboptimal “no benefit” studies, omega-3 use in the larger of the two meta-analyses still favored a reduction in all-cause mortality, sudden death, and MI, although these reductions were not statistically significant. What was significant was the **reduction in cardiac death (p=0.01)** seen in the meta-analysis. The usual p-value for significance is ≤0.05 so this result was impressive. Rizos, et al., for arguable reasons, decided to set the p-value for significance at 0.006 and claimed, therefore, that the finding was not significant (Figure 1).\(^\text{6}\)

**Summary:** A meta-analysis is only as good as the studies it includes, which gives an idea of the validity of these two recent meta-analyses. Yet, for some reason, they have been accepted by the public and various physicians as evidence that there is no cardiovascular benefit from OM3 use. We need to keep sight of the numerous other reviews and studies that have described the advantages of using OM3 for cardiovascular benefits and continue to use OM3 for cardiovascular risk reduction (see table with citations).

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**Disclosure statement:** Dr. Moran is a speaker for Amgen, Repatha, Sanofi, and Regeneron.

**References are listed on page 46.**

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**Figure 1. Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events: A Systematic Review and Meta-analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Events</th>
<th>Participants</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>17</td>
<td>6295</td>
<td>63279</td>
<td>0.96 (0.91-1.02)</td>
</tr>
<tr>
<td><strong>Cardiac death</strong></td>
<td>13</td>
<td>3480</td>
<td>56407</td>
<td>0.91 (0.85-0.98)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7</td>
<td>1030</td>
<td>41751</td>
<td>0.87 (0.75-1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13</td>
<td>1755</td>
<td>53875</td>
<td>0.89 (0.76-1.04)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>1490</td>
<td>52589</td>
<td>1.05 (0.93-1.18)</td>
</tr>
</tbody>
</table>

**Outcome**

- **All-cause mortality**
- **Cardiac death**
- **Sudden death**
- **Myocardial infarction**
- **Stroke**

**Studies**

- 17
- 13
- 7
- 13
- 9

**Events**

- 6295
- 3480
- 1030
- 1755
- 1490

**Participants**

- 63279
- 56407
- 41751
- 53875
- 52589

**RR (95% CI)**

- 0.96 (0.91-1.02)
- 0.91 (0.85-0.98)
- 0.87 (0.75-1.01)
- 0.89 (0.76-1.04)
- 1.05 (0.93-1.18)
Statin Therapy for the Very Elderly >80 with ASCVD: Balancing the Benefits and Risks

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There is a large population >80 in the U.S., some who have either been advised to or chose to discontinue statin therapy. Randomized clinical trials have typically excluded very elderly subjects or group all elderly into age >65. There are vast differences in this population in terms of frailty vs. vigorousness, comorbidities, motivation, and financial resources. In the rapidly growing 80+ age group, the prevalence of ASCVD exceeds that of younger age groups, affecting 84.7 percent of men and 85.9 percent of women.1 Prescribing patterns for the elderly have been reportedly low,2–5 and patient adherence rates tend to significantly decrease over time.6–7 The evidence base regarding the use of statin specifically in the over 80 age group follows.

Relevant Clinical Research Studies
The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial,8 randomized 5,804 United Kingdom patients age 70 to 82 with a history of, or risk factors for, vascular disease to 40 mg pravastatin or placebo with an average follow-up of 3.2 years. Mean low-density lipoprotein cholesterol (LDL-C) reduction was 34 percent with pravastatin, which was well tolerated with 24 percent coronary heart disease (CHD) mortality reduction and no significant adverse effects on liver function, muscle enzymes, cognition, or disability. Pravastatin treatment was not associated with a decrease in mortality.

The Study Assessing Goals in the Elderly (SAGE) trial,9 a prospective multicenter randomized double-blind international trial, compared treatment with atorvastatin 80 mg to pravastatin 40 mg in 893 coronary artery disease (CAD) patients age 65–85. The primary endpoint was change in ischemia duration on comparison of 48-hour holter monitor studies at baseline, three months, and 12 months. Both arms had significant reduction in ischemia duration. There was no significant difference between the groups, although there was a favorable trend in major coronary events and a post-hoc finding of significant all-cause mortality reduction favoring atorvastatin. Overall treatment-related adverse events were 17.3 percent on atorvastatin, 13.9 percent on pravastatin, but not statistically different.

LDS Hospital/University of Utah2 conducted a prospective observational cohort study of 7,220 CAD patients for an average of 3.3 years. Statin therapy was associated with mortality reductions in all age groups, with greatest mortality benefit found in the >80 group (29.5 percent vs. 8.5 percent, p=0.03).

A prospective observation study by NY Medical College and University of Texas Medical School3 followed 1,410 post-MI patients with a mean age of 81 and LDL-C ≥125 mg/dl in a long-term healthcare facility with a mean follow-up of three years. New coronary event incidence was 46 percent on statin vs. 72 percent on no statin.

A retrospective chart abstraction of 5,500 acute MI patients, found patients <80 who were prescribed a statin at discharge had a significant 16 percent lower
three-year all-cause mortality compared to patients not discharged on a statin (p=.002). Patients ≥80 were not found to have a significant statin-related mortality benefit. An observational Swedish study of 14,907 acute MI patients ≥age 80 with median follow-up of 296 days and a maximum of five years, compared outcomes for patients who had been prescribed statin therapy compared to no statin treatment at discharge. Following exclusion of patients who died within the first year, the remaining patients were found to have a 37 percent reduction in cardiovascular mortality and acute MI mortality (RR 0.64, CI 0.57-0.73).10

The meta-analysis of more vs. less intensive statin therapy by the Cholesterol Treatment Trialists Collaboration11 included five trials of acute coronary syndrome or stable CAD patients. Subjects >75 on more intense statin had a statistically significant reduced risk of major vascular events of 4.8 percent compared to 5.4 percent on less intense statin (p<0.0001).

Statin-prescribing practices are also strongly influenced by the provider’s and patient’s perception of safety concerns. The evidence base specifically regarding the over 80 age group is summarized below.

Potential Statin Safety Concerns
Li et al13 found no significant association between statin use and dementia or Alzheimer disease in their prospective study of 2,356 cognitively intact randomly selected patients ≥65. Brain autopsies of 110 subjects aged 65–79 years with prior statin use found a reduced risk for typical Alzheimer’s pathology. The Cardiovascular Health Study, a longitudinal study of 3,334 patients ≥65, found statin use associated with slight reduction in cognitive decline and lower risk of silent infarcts detected by MRL.14 The FDA found rare post-marketing reports of cognitive impairment have not generally been serious and are reversible on discontinuation.15 In a 2013 systematic review of 57 statin studies, University of Pennsylvania researchers concluded that the evidence does not support an association between statin use and memory loss or dementia.16

The FDA reviewed post-marketing data of clinically serious hepatotoxicity with statin use and noted extremely low incidence of ≤2 per 1 million patient-years.15 A 2008 meta-analysis of seven randomized clinical trials found more intense statin regimens associated with a 1 percent increased drug discontinuation rate due to elevated transaminases.17

These data prompted the FDA to remove routine LFT monitoring for asymptomatic patients from the statin package insert in 2012. PROSPER8 reported a very low 0.03 percent incidence of >3 fold transaminases increase. In contrast, the SAGE investigators,9 reported elevated transaminases on atorvastatin 80 mg were 4.3 percent compared to 0.2 percent on pravastatin 40 mg, however, they normalized on repeat testing or statin discontinuation. Considering these data, clinicians may want to monitor LFTs for the very elderly on high intensity statin.

The risk of myopathy has been associated with advancing age, female gender, and renal or hepatic abnormalities,18 with underrepresentation of these populations in clinical trials. Myalgia incidence was 1 percent in PROSPER, with no rhabdomyolysis cases.8 Terry A. Jacobson, MD, discussed factors associated with muscle injury risk for the elderly, including hypothyroidism, concomitant cytochrome P450 inhibitor, fibrate, or immunosuppressant use, reduced lean body mass, and polypharmacy.19 In 2011, the FDA advised avoidance of the 80 mg simvastatin dose for new patients because of the increased risk of muscle damage, and the avoidance or dose modification of specific medications to reduce rhabdomyolysis risk.20

New cancer diagnosis in PROSPER increased on pravastatin,6 however, extended follow-up of subjects to an average of 8.6 years found no increased cancer risk.21 A Swedish study of MI patients age ≥80 found no statin-related increase in cancer mortality.7 Setoguchi et al found rates of colorectal, lung, and breast cancers in patients ≥65 similar to the general population.22

In conclusion, the decision to implement statin therapy for the high risk very elderly with ASCVD should incorporate a shared decision-making approach with an upfront discussion of benefits and risks, and consideration of patient perceptions, comorbidities, concurrent medications, frailty, and cost concerns. The majority of studies show overall a very favorable cardiovascular benefit with low associated risk that may help preserve quality of life. The decision, however, to prescribe high intensity statin therapy needs to take into account factors that may predispose them to increased risk, with regular monitoring incorporated. Randomized clinical trials with this population are needed. ■

Disclosure statement: Judith Collins has no disclosures to report.

References are listed on page 46.
INDUSTRY COUNCIL

The National Lipid Association would like to acknowledge the following companies for their support of the NLA’s overall mission and goals for 2016. They are honored as Industry Council members:

Akcea Therapeutics, A Subsidiary of Ionis Pharmaceuticals, Inc.
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Merck & Co., Inc.
Novartis Pharmaceuticals Corporation
Pfizer Inc.
Quest Diagnostics
Sanofi-Regeneron
Familial defective apolipoprotein B-100 (FDB) is an autosomal dominant disorder of lipid metabolism considered by international guidelines to be a genetically defined cause of familial hypercholesterolemia (FH).¹⁻³ FDB arises from mutations in apolipoprotein B (apoB) affecting the affinity of apoB-containing low-density lipoprotein particles for the low-density lipoprotein receptor (LDL-R) and, subsequently, their rate of endocytosis and catabolism in hepatocytes.⁴ FDB is associated with both hyperlipidemia and increased risk of atherosclerotic cardiovascular disease (ASCVD), although the hypercholesterolemia caused by FDB is often milder than that because of mutation in LDL-R, the most frequent cause of autosomal dominant FH, and is therefore frequently underdiagnosed by standard diagnostic criteria such as the Dutch Lipid Clinic Network and US MEDPED criteria.⁵⁻⁵ Recent results from the Copenhagen General Population Study report that on average, individuals affected by FDB suffer myocardial infarction nine years earlier than non-carriers, and R3500Q carriers have been reported to display increased coronary artery calcification (CAC) even when compared with non-carriers presenting with equivalent levels of LDL-C.⁹,¹⁰

Compared with LDL-R, relatively few pathogenic mutations have been identified in apoB, and, unlike LDL-R, most fall within a mutation “hotspot” affecting the conformation of the protein.¹¹,¹² Interestingly, of mutations associated with FDB, the two most common, known as R3500Q and R3500W, affect the same site within apoB.¹,¹³ The R3500Q mutation is frequently reported in European cases of clinical heterozygous FH, and is thought to have arisen in a common central European ancestor due to the elevated prevalence reported in the region; its twin mutation, R3500W, was recently reported to comprise a plurality of mutations affecting subjects with clinical FH of Han Chinese background.¹⁴⁻¹⁸ Furthermore, an association study of genetic variants affecting lipid levels in over 50,000 subjects reported R3500Q to be the single variant most strongly associated with elevated LDL-C in Americans of European background, leading to an average increase in LDL-C of 71 mg/dL.¹⁹

In 2010, the Amish Research Clinic in Lancaster, Pa., found that approximately 12 percent of members of the Old Order Amish, an Anabaptist group of Swiss-German origin, carried the R3500Q mutation, roughly 60 times the rate found in the general Caucasian population.¹⁰
The investigators who discovered the high prevalence of FDB among the Amish described the phenomenon as a “founder effect,” wherein a population bottleneck and subsequent endogamy over generations led to a dramatic increase in the prevalence of the R3500Q mutation. Founder effects for mutations causing FH have been reported in several other populations, such as French Canadians and Afrikaners (South African ethnic group descended from predominantly Dutch settlers); however, the reported population prevalence rates of FH mutations within these groups are significantly lower than that of FDB among the Amish, a rapidly growing demographic group.20,21 Furthermore, approximately 10 to 20 percent of the Amish enter the general population each generation, leaving not only present members of the Amish community but also the many individuals of extended Amish background at risk.22

To provide early preventive care and reduce lifelong disease burden in the public, the Pennsylvania Department of Health has undertaken since 1965 a newborn child genetic screening protocol. Last updated in 2014, the Newborn Child Testing Act, also known as P.L. 497, Number 251, established provision for “screening tests of newborn children” for several inherited diseases, including those more common among the Old Order Amish and other Anabaptist groups such as phenylketonuria (PKU) and glutaric acuduria (GA).23 As a disorder of lipid metabolism conferring elevated lifelong risk for atherosclerosis and myocardial infarction, FH due to the R3500Q mutation poses a significant burden on the population health of special groups and the general population in Pennsylvania, however, screening and early treatment for FDB in this region presents a unique opportunity in lipid-focused preventive medicine. In addition to the benefits of lifelong treatment and management of the disorder, identification of newborns with FDB could serve as a starting point for “reverse” cascade screening of parents and other affected relatives.

As a single nucleotide polymorphism (SNP), diagnostic testing for the R3500Q mutation can be completed inexpensively and quickly en masse, and with currently available lipid-lowering treatment, the disease burden of FH due to mutations in apoB can be significantly reduced. As an internationally accepted, frequently reported cause of FH, FDB diagnosed as part of universal screening would also qualify those affected for specialty care, including therapy with monoclonal antibody inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9).24,25 Low rates of correct diagnosis according to standard clinical FH diagnostic criteria further underscore the importance of molecular diagnosis for FDB. The unique population of southern Pennsylvania thus presents an opportunity to implement individualized therapy based on mutational status on a population scale, a generational goal not only for lipid specialists, but for the entire medical field. We therefore call for the addition of the R3500Q mutation to universal genetic screening protocols in Pennsylvania and support for addressing FDB as an issue of public health. ■

Disclosure statement: Dr. Andersen has no disclosures to report. Lars Andersen has no disclosures to report.

References are listed on page 46.
Perceptions of Fish Oil Dietary Supplements (FODS)
According to 2008 national health statistics, fish oil dietary supplements (FODS) are the most commonly used supplements among U.S. adults.¹ There is a general public perception that consumption of fish is a healthy dietary habit.² This perception may be responsible for a greater than threefold increase in the use of FODS among older adults in the U.S. over the past decade.³ Individual perceptions of the benefits of fish and FODS cover a wide spectrum. These perceptions include the idea that FODS may improve general health, reduce atherogenic lipids, and improve brain and heart function, and that fish serves as a good source of protein.²,⁴

Daniel E. Hilleman, PharmD, one of the authors of this article, conducted a survey of 496 patients with known cardiovascular disease who indicated that they were taking either a FODS or a prescription omega-3 fatty acid (OM3FA) product. Of these patients, 40 percent indicated that they were taking the product for general health, while 60 percent reported taking FODS for a specific health benefit.⁴ These specific health benefits typically corresponded to the medical conditions of the individual survey respondents. Myocardial infarction and coronary disease were most commonly mentioned.³ Only 10 percent of cardiology patients indicated they were using the product for lipid disorders.⁴

The same survey also showed that, among the patients known to be using either FODS or a prescription OM3FA product, only 9 percent (45 of 496 patients) indicated that their physician told them to use the product.⁴ About half (n = 22) of those patients said their physician wrote a prescription for omega-3-acid ethyl esters (an OM3FA drug product containing a mixture of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), yet only nine of those patients were actually filling the prescription.⁴ Fewer than one in four of the 496 patients could identify that OM3FAs were the active ingredients in their FODS or prescription OM3FA product, and less than 5 percent knew the actual amount of active ingredient in the product they were using.⁴ The number of pills (capsules or dosage units) taken each day ranged from 1 to 8.

The majority of patients (73 percent) in Hilleman’s survey said they bought the same FODS at each purchase.⁴ However,
only 17 percent of patients indicated that they bought their FODS in a pharmacy. Given that the vast majority of patients are buying their FODS outside of pharmacies, pharmacists and other healthcare providers need to be proactive when taking patient histories and document the use of these products at times other than when they are purchased. A complete history of patient use of prescription and non-prescription products, including dietary supplements, should be taken each time a patient visits his or her pharmacy and/or treating provider. An additional concern is that research shows that some pharmacists have a knowledge gap about the safety and efficacy of common dietary supplements. Pharmacists need additional education and training about commonly used dietary supplements, including FODS, since they are not approved by the Food and Drug Administration (FDA) to treat disease.

**Fish Oil Dietary Supplements (FODS) versus Prescription Omega-3 Fatty Acids (OM3FAs) for Patient Care**

For patients with elevated triglyceride (TG) levels, the American Heart Association has recommended 2–4 g/day of EPA+DHA. To achieve this goal, patients may choose to take FODS on their own instead of taking prescription products indicated as an adjunct to diet to reduce TG levels in adults with severe (≥500 mg/dL) hypertriglyceridemia. Some managed-care plans require patients to fail on FODS before covering prescription products. Although FODS are widely available, dietary supplements are not subject to the strict regulations governing over-the-counter drug approval by the FDA, so their content and chemical integrity are not regulated in a rigorous manner. Additionally, their efficacy and safety are not regulated prior to marketing and are not well documented. Additionally, the low EPA and DHA content of FODS may require patients to take ≥10 capsules/day in an attempt to reach a therapeutic dose of EPA or EPA+DHA equivalent to prescription OM3FA 4 g/day, potentially negating any cost advantage.

Oil extracted from marine animals is a common source of FODS but it also is an extremely unstable product. Fish oil is obtained primarily from processing plants during the manufacturing of fishmeal from whole or filleted fish bodies. To aid in the coagulation of tissue protein and expression of the oils, the harvested fish are cooked at about 100°C. OM3FAs are susceptible to free radical damage during such manufacturing processes, and the damage is accelerated in the presence of light and contaminants. Free radicals contribute to oxidative modification of OM3FAs, which may interfere with the intended biological or potential clinical benefit of FODS.
the OM3FA content and integrity of FODS. A study funded by the U.S. Department of Agriculture found that 74 percent of 47 FODS tested contained less than the amounts of EPA and/or DHA indicated on their labels. A scientific study in New Zealand of 36 FODS demonstrated that more than 80 percent had unacceptably high levels of lipid peroxides, an indication of lipid decomposition. Of those tested, only three (8 percent) met international standards for acceptable peroxide and total oxidation levels. Additionally, FODS sold in North America have been shown to have unacceptably high levels of lipid peroxides. An elevated peroxide value indicates high levels of primary oxidation and hydroperoxides, which can interfere with any intended biological antioxidant activity.

Recently presented data highlighted the fatty acid content issues of leading FODS (by sales) in the U.S. with respect to saturated fat, EPA, and DHA. Also measured were the extent of oxidative damage in the oil compared to a prescription form with respect to purity and the ability to prevent human low-density lipoprotein (LDL) oxidation in vitro. This research was presented by R. Preston Mason, PhD, co-author of this article, at the 2015 meeting of the Academy of Managed Care & Specialty Pharmacy (AMCP). The fatty acid content of six FODS was determined and more than 30 fatty acids were identified in the FODS samples, including 10 to 14 saturated fatty acids in each sample, comprising as much as 36 percent of total fatty acid content (Figure 1). Additionally, OM3FA levels varied widely among the FODS (33 to 79 percent), including levels of EPA (21 to 52 percent) and DHA (9 to 31 percent). This study also measured primary and secondary products of oxidation that are associated with fatty acids containing multiple double bonds, such as OM3FAs. All of the supplements exceeded recommended maxima for most of these oxidation products. By contrast, the prescription product did not produce significant levels of oxidation products under identical test conditions.

"Despite the widespread use of FODS in the U.S., there is substantial confusion about their benefits and appropriate use among both healthcare providers and patients."

Finally, the biological activity of the OM3FAs isolated from a leading FODS was compared to non-oxidized and oxidized preparations of EPA/DHA mixtures to determine their effects on small, dense LDL (sdLDL) oxidation. Oxidation of sdLDL was inhibited by >95 percent (P<0.001) with the non-oxidized OM3FAs but was not inhibited by the oxidized OM3FAs or the FODS isolate, which contained both oxidized and non-oxidized OM3FAs. The clinical translation of the lack of biological effect from oxidized FODS has been reported to include negative therapeutic effects on blood lipid levels and a lack of intended effectiveness on lipid or inflammatory parameter levels.

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**Conclusion**

Despite the widespread use of FODS in the U.S., there is substantial confusion about their benefits and appropriate use among both healthcare providers and patients. There is the perception that FODS produce various health benefits, including a reduction in atherogenic lipids and improvements in brain and heart function, but these have not been clinically proven. FODS are not approved by the FDA to treat or cure disease and are not categorized as over-the-counter drugs, but as dietary supplements, equating to less rigorous regulation regarding efficacy, safety, content, and chemical integrity. While containing varying amounts of desirable OM3FAs, leading FODS also contain more than 30 fatty acids, including significant levels of saturated fat. FODS also contain elevated levels of primary and secondary lipid oxidation products that interfere with their biological activity and may have adverse clinical implications. These data indicate that there is a need for more education about the quality and appropriate use of FODS. As a product without rigorous FDA regulation and with varying levels of fatty acids and oxidation products, FODS are not an appropriate substitute for prescription products in patients diagnosed with certain medical conditions, such as very high TG levels.

**Disclosure statement:** Dr. Mason has no disclosures to report. Dr. Hilleman has no disclosures to report.

**References are listed on page 47.**
Pediatric hypertriglyceridemia (fasting triglycerides ≥ 130 mg/dL) was identified by routine screening in a healthy 14-year-old male. He was subsequently referred to our pediatric lipid clinic for evaluation. A fasting lipid profile confirmed hypertriglyceridemia: total cholesterol (TC): 136 mg/dL, triglyceride (TG): 357 mg/dL, low-density lipoprotein cholesterol (LDL-C): 18 mg/dL, high-density lipoprotein cholesterol (HDL-C): 47 mg/dL, and non-HDL-C: 89 mg/dL.

The patient is an active ninth grader who participates in track and cross country, follows a prudent diet, and does well academically. He denies tobacco, alcohol, and illicit drug use. His medical history is unremarkable and he does not take medications. He was born at full term, without complications.

**Family history:** The patient has a 12-year-old sister, whose lipid profile is not known. His mother (age 45 years) is being treated for hypothyroidism, and is otherwise healthy. His maternal grandparents (ages 72 and 75 years) are healthy, as is his maternal great-grandmother at age 90 years. His father (age 48 years) has a normal lipid profile. The patient’s paternal grandparents are in their mid-80s and healthy. No significant family history of early atherosclerotic cardiovascular disease (ASCVD), hyperlipidemia, or diabetes was reported.

**Physical examination:** His body mass index (BMI) was 16.2 Kg/m² (50th percentile for age and gender). The patient was alert, oriented, and appeared well-nourished. The physical exam was unremarkable.

**Pertinent chemistry results:** Thyroid stimulating hormone: 1.58 mcU/mL; free thyroxine: 1.3 ng/dL; fasting blood glucose: 96 mg/dL; hemoglobin A1c: 5.4 percent; creatinine: 0.9 mg/dL; aspartate aminotransferase: 7 IU tens/L; alanine aminotransferase: 30 units/L.

**Impressions and recommendations:** The elevated fasting triglyceride level, the absence of secondary causes, and the lack of a significant family history of hyperlipidemia suggested the diagnosis of sporadic hypertriglyceridemia. Sporadic hypertriglyceridemia is a primary dyslipidemia that is distinguished from familial hypertriglyceridemia by the lack of a family history of isolated hypertriglyceridemia in 50 percent or more of first- and second-degree relatives.
maternal or paternal family relatives. The triglyceride concentration is generally modestly elevated (250–400 mg/dL), although it can be very high (≥ 500 mg/dL) if associated with secondary causes of hypertriglyceridemia (e.g., unhealthy body weight, hyperglycemia, hydrochlorothiazide, steroids, beta-blocker use, and/or excess alcohol consumption). An over-the-counter (OTC) marine omega-3 fatty acid supplement containing 300 mg of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) per one gram (1 gram capsule, twice daily), along with dietary reduction of refined carbohydrates was recommended. A repeat fasting lipid profile assessment after three months of following these recommendations indicated no significant change in the fasting triglycerides level; TC: 134 mg/dL, TG: 353 mg/dL, LDL-C: 46 mg/dL. The OTC marine omega-3 fatty acid supplement was discontinued and replaced with the prescription omega-3 fatty acid ethyl ester (465 mg EPA and 375 mg DHA per 1 gram capsule), at one gram capsule taken twice daily. This change to the prescription omega-3 fatty acid ethyl ester was instituted to eliminate the potential variability in EPA/DHA content in OTC omega-3 fatty acid supplements. The prescription omega-3 fatty acid ethyl ester has a standard composition of EPA and DHA content. Dietary and adherence recommendations were reinforced.

Follow-up: A clinical chemistry assessment after six weeks of taking the prescription omega-3-fatty acid ethyl ester indicated no reduction in the fasting triglyceride level; TC: 153 mg/dL, TG: 385 mg/dL, LDL-C: 30 mg/dL, HDL-C: 45 mg/dL. This suggested “pseudohypertriglyceridemia.” A subsequent glycerol-blanked triglyceride assessment confirmed pseudohypertriglyceridemia: glycerol-blanked TG: 68 mg/dL, glycerol: 3763 mmol/L. With confirmation of glycerolemia and normal triglycerides, a letter documenting pseudohypertriglyceridemia was provided to the family to accompany subsequent lipid profile analyses.

Pseudohypertriglyceridemia: The American Academy of Pediatrics (AAP) defines fasting triglyceride levels into three categories: acceptable (<90 mg/dL), borderline-high (90–129 mg/dL) and high (≥130 mg/dL). It is recommended that elevated triglycerides initially be treated with lifestyle changes, including dietary modification (i.e. reduced intake of refined carbohydrate), weight reduction, decreased consumption of alcohol, and control of underlying disorders such as diabetes mellitus and hypothyroidism. Pharmacologic therapies including omega-3 fatty acids, niacin, and fibrates can be considered for fasting triglyceride levels greater than 500 mg/dL. Should an elevated fasting triglyceride remain unchanged following lifestyle modification with or without pharmacological therapy, pseudohypertriglyceridemia should be considered.

An elevated plasma concentration of glycerol can cause pseudohypertriglyceridemia. Glycerolemia can be secondary to stress, glycerol-containing intravenous medications, parental nutrition and metabolic disorders such as glycerol kinase deficiency (GKD). This is an X-linked recessive disorder occurring in isolation or in complex form involving adrenal malfunction. The frequency of asymptomatic isolated GKD is unclear, although rare, with only 25 cases reported. Almost all clinical laboratories analyze triglyceride concentrations using enzymatic methods that involve three basic steps. The first step uses lipases for the hydrolysis of triglycerides to glycerol and fatty acids. The second step utilizes glycerol kinase to phosphorylate glycerol. The final step is the formation of a colored phosphorylated glycerol that can be measured spectrophotometrically to provide an estimate of the triglyceride concentration. Since these enzymatic assays measure triglycerides as the quantity of glycerol in a specimen, the elevated plasma glycerol concentration in hyperglycerolemia causes an overestimation of the true triglyceride concentration. Glycerol-blanked triglyceride assays “blank” or subtract the free plasma glycerol from the specimen and assay only the glycerol produced from the enzymatic hydrolysis of the triglycerides.

Summary: The evaluation of hypertriglyceridemia should always include a detailed medical and family history. A 12-hour fast is recommended to optimally assess triglyceride levels. Should lifestyle changes (dietary improvement, physical activity, weight reduction), control of secondary metabolic or pharmacologic causes, and/or triglyceride-lowering therapy fail to reduce the triglyceride level, the presence of pseudohypertriglyceridemia stemming from hyperglycerolemia should be included in the differential diagnosis. A glycerol-blanked triglyceride assay should be performed to confirm this diagnosis.

Disclosure statement: Dr. Maciejko has no disclosures to report. Dr. Anne has no disclosures to report. Manisha Ravi has no disclosures to report. References are listed on page 47.
Atherosclerotic Arteries with Cholesterol Crystals Enhance Bacterial Growth: Risk for Plaque Destabilization

Background

In previous reports we demonstrated that cholesterol occupies greater space when crystallizing from a liquid to a solid state forming sharp tipped crystals that can tear fibrous membranes (1,2). Similar findings have been noted in human coronary arteries of patients dying with acute myocardial infarction (Fig. 1).

![Figure 1](image1.png)

Figure 1. Scanning electron micrograph (SEM) of left anterior descending artery in a patient who died with acute cardiovascular event. Cholesterol crystals are noted perforating the intimal surface just below the plaque rupture site (1).

- Bacteria have been reported present in human atherosclerotic plaques (3). Both gram positive (*Staphylococcus aureus*) and gram negative (*Pseudomonas aeruginosa*) bacteria have been shown to interact with cholesterol crystals.

Objective

In this study we investigate if arteries with atherosclerotic plaque rich in cholesterol crystals will enhance bacterial growth compared to normal non-atherosclerotic arteries in a rabbit model.

Methods

- Ten NZW rabbits were made atherosclerotic by balloon de-endothelialization and feeding a cholesterol enriched diet for six months.
- Arterial tissue was sampled from the aortas after euthanasia and placed in a washer ring to expose only the intimal surface to a broth solution with *Staphylococcus aureus* (Fig. 2).
- The same was repeated for normal control rabbits fed normal rabbit chow without intimal injury.
- Ten samples were obtained from 5 atherosclerotic rabbits and 5 normal controls.
- For each group, five samples were incubated in broth for 1 h and another five samples were incubated for 3 h. Bacterial colony counts were measured at each time interval.
- Bacterial presence on the intimal surface was examined by scanning electron microscopy (SEM) from additional arterial samples exposed to bacteria.

![Figure 2](image2.png)

Figure 2. Washer with exposed arterial intima.
Results

- Arterial samples with atherosclerosis had significantly higher bacterial count compared with the normal controls (Fig. 3).
- Using analysis with Box-Cox transformation of bacterial count there was a significantly higher bacterial count present in atherosclerotic arteries compared with normal controls (p<0.0001), (Fig. 4).
- By SEM *Staphylococcus aureus* bacteria were found attached to cholesterol crystals in the atherosclerotic arteries and appeared to be dissolving them (Fig. 5).

![Figure 3](image1.png)

**Figure 3.** (left) Bacterial growth from normal artery as control inoculum. (right) Bacterial growth from atherosclerotic artery inoculum.

![Figure 4](image2.png)

**Figure 4:** Bacterial colony counts following incubation of normal (gray) and atherosclerotic (black) aorta segments with *Staphylococcus aureus* for 1 or 3 hours. Bars = ± SD.

![Figure 5](image3.png)

**Figure 5:** (left) Control crystals (right) Bacteria attaching to cholesterol crystals on atherosclerotic arterial wall dissolving and pitting the crystals.

Conclusion

- This study demonstrates that bacteria have a high affinity to cholesterol crystals in arterial tissues rich in cholesterol crystals.
- The presence and growth of bacteria in atherosclerotic plaques have the potential of destabilizing the plaque leading it to rupture.
- Further studies on the mechanism of interaction between bacteria and cholesterol crystals need to be performed. However, a plausible explanation for our findings may be related to bacteria utilizing cholesterol as a source of nutrition.

References

Some patients refuse statin therapy or cannot tolerate its side effects. Many of these patients seek alternative therapies, including red yeast rice (RYR), a widely available herbal supplement made by culturing a yeast, *Monascus purpureus*, on rice. This process produces 14 monacolins, compounds that inhibit HMG-CoA reductase, the rate-limiting step in hepatic cholesterol synthesis. One of the monacolins produced is monacolin K, which is chemically identical to lovastatin.

We began our research on RYR a decade ago, after we heard anecdotes from patients about its efficacy and tolerability. Patients who previously had been prescribed statins had, on their own, started taking RYR and seemed to tolerate it well while lowering their low-density lipoprotein cholesterol (LDL-C) to goal levels. Rather than dismiss this supplement as naturopathic “snake oil,” we decided to perform randomized, double-blinded, placebo-controlled trials to formally evaluate its efficacy and safety. A decade after renewed interest in this product, we provide a brief overview of its use, especially in patients who cannot tolerate or refuse statin therapy. We also summarize regulatory and safety issues that continue to make the use of RYR controversial for both practitioners and patients.

Several clinical trials have documented RYR’s efficacy in lowering total cholesterol, LDL-C, and triglycerides. A recent meta-analysis found that RYR lowered LDL-C an average of 21 to 30 percent, depending on dose and formulation used. One secondary prevention trial found significantly fewer deaths, revascularizations, and cardiac events in 4,870 Chinese patients with average LDL-C and a history of myocardial infarction who were randomized to RYR versus placebo.

Red yeast rice may be a useful adjunct to diet and exercise in patients who prefer not to take statin therapy, but it also may have a much bigger role for patients who develop statin-associated myalgias (SAMs). The incidence of SAMs may be as high as 15 percent, and may affect approximately 1.3 million people in the U.S. There is no consensus on optimal therapy for patients with SAM, but there are many approaches for treating hyperlipidemia in this population (Table 1). There has been increased interest in SAM with the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors into clinical practice. The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3 (GAUSS-3) trial recently examined the use of evolocumab in this population and suggested that these agents may present...
with the placebo group at week 12 (P decreases in LDL-C in the RYR compared -21.3 percent at week 24 with significant percentage change in LDL-C in the RYR PA) or placebo for six months. Mean twice daily (Sylvan Bioproducts, Kittanning, PA) or pravastatin, 20 mg/d for 12 weeks, in addition to a lifestyle modification program. LDL-C levels decreased 30 percent in the RYR group and 27 percent in the pravastatin group, and there were no significant differences between groups in other serum lipid levels. There were also no differences in incidence of myalgias (P = 0.99).

The third trial evaluated the combination of RYR and phytosterols in 187 patients with statin-intolerance or statin refusal. All patients took RYR, 1,800 mg twice daily, (Sylvan Bioproducts, Kittanning, PA) and mean LDL-C decreased from 150 mg/dL at baseline to 111 mg/dL at week 12, 110 mg/dL at week 24, and 113 mg/dL at week 52 (all P<0.001). Four participants experienced myalgias necessitating cessation of RYR, with no objective evidence of myositis.

A fourth study, published by Paul Thompson, et al., was a retrospective analysis of 1,400 charts of patients with a history of statin intolerance. The authors found 17 patients with a history of SAMs who were treated with RYR for at least four weeks. In those patients, LDL-C decreased 19 percent and 15/17 tolerated the treatment with no adverse effects.

Most studies noted similar rates of adverse events between RYR and placebo in a population intolerant of statins. Participants in RYR studies took the equivalent of only 5 mg/d to 6 mg/d of lovastatin, with resultant LDL-C reductions of 25 to 40 percent, equivalent to reductions seen with 20 mg/d to 40 mg/d of lovastatin in other trials.

Unfortunately, the major criticism of RYR is its status as an unregulated, over-the-counter supplement and there remain valid concerns about efficacy and safety. In 2010, we found that 12 widely available RYR products had marked variability of monacolin content, corroborating similar results published by Heber, et al. almost a decade earlier. Up to 80 percent of RYR products may contain citrinin, a potentially nephrotoxic mycotoxin produced by several yeast species. Because of these issues, there are no reliable methods for physicians and patients to know the true content of commercial RYR products. Red yeast rice has been reported to have serious side effects, including myopathy, rhabdomyolysis, hepatoxicity, and anaphylaxis.

So the question remains: Should doctors recommend RYR to their patients? In our practice, we advocate a trial of RYR for patients who refuse statins or prefer a “natural” approach to pharmacotherapy, and for patients with a history of statin-associated myalgias, and we provide close monitoring and follow-up. Until there is improved regulation and standardization of RYR, its use will remain controversial, and physicians should remain cautious in recommending this promising and popular alternative therapy for hyperlipidemia.

Table 1. References available on page 47.
The National Lipid Association and the Foundation are thankful once again for another successful year of meetings and fundraising. But we still have much work to do.

If you are onsite at the Fall CLU in Amelia Island, make sure to purchase a ticket to the Foundation Event for an evening of miniature golf on Aug. 27 from 6:30–8:30 p.m. Engage your peers in a friendly competition through 18 holes on the Heron Cove Adventure Golf course located at the Omni Amelia Island Plantation Resort. The winning team will take home prizes and bragging rights, and a portion of your ticket will be donated to the Foundation. For more information, stop by the registration desk onsite.

During the Scientific Sessions in New Orleans last May, more than 80 people attended the event “A Night at the Museum.” The night started off with cocktails, where attendees had a chance to mingle and view the exhibit “Road to Berlin,” which had been opened only for Foundation event guests. After the cocktail hour and exhibit viewing, everyone gathered for dinner and a live showing of the Johnny Cash Experience. It was a fun night, and another successful event for the Foundation.

In addition, the Foundation will once again launch an awareness campaign to coincide with National Cholesterol Education Month this September. The objective of the 2016 Rare Disease Education and Awareness Campaign is to establish a national patient outreach program that will enable the Foundation to address the medical community and educate both healthcare professionals and patients with the latest knowledge and information regarding rare lipid disorders.

Until now, publicly available information has tended to focus on low-density lipoprotein (LDL) cholesterol as the key element of cardiovascular health risk. Rare lipid disorders significantly affect individuals and their families. We hope to improve the physician-patient relationship by using information and education to increase patient awareness of disorders such as familial chyomicronemia syndrome (FCS), lysosomal acid lipase deficiency (LAL-D), lipodystrophy, and...
heterozygous and homozygous familial hypercholesterolemia (HeFH and HoFH, respectively).

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

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

As always, thank you for your continued support to the Foundation and to another successful year!

A Series of Programs Focused on the Field of Lipidology.

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- Scientific and clinical research updates
- New treatment options
- Best practices in patient care

Supported by an educational grant

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The National Lipid Association (NLA) would like to acknowledge and thank our longtime members for their commitment to the NLA and the field of lipidology. The strength and longevity of our organization is only possible because of the dedication and contributions of our members. Below is a list of our committed members who have helped shape the NLA.

5+ YEAR MEMBERS

George Abela, MD
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Mohammad Abnammi, MD
Dominique Adair, MS
James Adams, MD
Jim Ader, PA-C
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Heidi May, PhD
Patrick McBride, MD
Brown McCallum, MD
Bassam Amara, MD
Marvin Matlock, MD
Janet Maxson, PhD
Heidi May, PhD
Patrick McBride, MD

The dedication and contributions of our members. Below is a list of our committed members who have helped shape the NLA.
Save the Date for 2017 NLA Meetings
Make sure you save the date for the NLA’s 2017 meetings. The 2017 Spring Clinical Lipid Update — hosted by the Pacific and Southwest Chapters — will take place Feb. 24–26, 2017, at the Hyatt Regency Phoenix. In addition, the 2017 NLA Scientific Sessions will be held May 18–21, 2017, at the Philadelphia Marriott Downtown. The annual meeting will be hosted by the Northeast Lipid Association. Finally, the 2017 Fall CLU — hosted by the Southeast and Midwest Chapter — will take place Aug. 11–13, 2017, at the JW Marriott Indianapolis. Check lipid.org/conferences for more information and regular updates as they become available.

NLA Meeting Highlights Now Available
Slide presentations and audio recordings from the Spring CLU in San Diego and the Scientific Sessions in New Orleans are now available. To view these highlights, and others, visit lipid.org/education/highlights.

JCL Sees Increase in Impact Factor
The 2015 Impact Factors were recently released and the Journal of Clinical Lipidology (JCL) saw yet another increase — from 3.904 (2014) to 4.906 (2015). The JCL is now ranked 23rd out of 253 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 2013 and 2014.

Check Out the Latest ReachMD Recordings
Lipid Luminations host, Alan Brown, MD, welcomed several guests at the NLA’s 2016 Scientific Sessions in New Orleans this past May. Visit lipid.org/communications/reachmd to hear the lastest from David Cohen, MD; Barbara Wiggins, PharmD; Julie St. Pierre, MD; and much more.

Certification in Lipidology
Preparing to become certified in lipidology through either the American Board of Clinical Lipidology or Accreditation Council for Clinical Lipology? The deadline to apply for the Fall Testing Window is Sept. 16. Applications must be postmarked by this date. For more information, visit lipid.org/education/certification or contact Nicole Woodsmall at nwoodsmall@lipid.org.

Resource Toolbox Available Online
The Clinician’s Lifestyle Modification Toolbox includes patient education material based on the NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. It is a resource designed to assist clinicians and healthcare professionals in beginning a conversation with patients about achieving successful lifestyle changes that promote their lipid health. Visit lipid.org/clmt to view the resources.

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

Patients Needed for Clinical Study
Gemphire Therapeutics Inc., a clinical-stage biotech based in Michigan, is currently recruiting adult patients with homozygous FH for their Phase 2 clinical study. There are currently two investigatory sites in the U.S. accepting new subjects. Funds are available for transportation to investigative sites for qualified patients. If you have patients who could benefit from enrollment in this trial or would like to receive more information, contact Liz Masson at lmasson@gemphire.com or 508-769-9630.

Research Initiative Launched to Characterize Disease Burden of FCS
Akcea Therapeutics has launched an IRB-approved research study to understand the multi-dimensional impact of Familial Chylomicronemia Syndrome (FCS) on adults living with the disease. FCS, also known as lipoprotein lipase deficiency (LPLD) or type I hyperlipoproteinemia, is a rare hereditary condition in which individuals lack properly functioning lipoprotein lipase (LPL), an enzyme that clears triglycerides from plasma. Through this study, called the IVestigation of Findings and Observations Captured in bUrden of Illness Survey in FCS Patients (IN-FOCUS), adults affected by FCS can anonymously share information about their experience living with FCS using a simple Web-based survey. FCS patients may access the survey at fcsinfocus.com.

2016 Young Investigator Competition
Congratulations to Imran Baig, MD, an academic hospitalist at McLaren Hospital in Flint, Mich., who authored the abstract “Atherosclerotic Arteries with Cholesterol Crystals Enhance Bacterial Growth: Risk for Plaque Destabilization” and placed first in the Sanofi Regeneron Young Investigator Award Competition at the 2016 NLA Scientific Sessions in New Orleans, May 19–22. You can view this abstract on Page 34 of this issue of the LipidSpin. In addition, you can view a downloadable version of this abstract online at lipid.org/util/eposters/PDF/177.pdf. The Young Investigator Competition was sponsored by an educational grant from Sanofi U.S. and Regeneron Pharmaceuticals.
NLA Events Calendar

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

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

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

Lipid Academy
February 23–24, 2017
Phoenix, AZ

May 17–18, 2017
Philadelphia, PA

August 10–11, 2017
Indianapolis, IN

Masters in Lipidology
February 23–24, 2017
Phoenix, AZ

May 17–18, 2017
Philadelphia, PA

August 10–11, 2017
Indianapolis, IN

17. Gotto AMC, Cohn JS. Evaluation of lipid, drug concentration, and safety parameters following cessation of treatment with the cholesteryl ester transfer protein inhibitor TMF-001 in patients with familial hypercholesterolemia (FHTP): a randomized, double-blind, placebo-controlled Phase 2 trial. Lancet. 2015;386:452-60.


Healthy Sleep Habits for Your Heart
Advice from the National Lipid Association
Clinician’s Lifestyle Modification Toolbox

Sleep and Your Health
Not sleeping enough hours each night or not sleeping well can cause many health problems. Poor sleep habits may be linked to obesity, high blood pressure, type 2 diabetes, heart disease, atrial fibrillation (irregular heart beat), stroke, and heart failure. Having healthy sleep habits is healthy for your heart!

“How Long Should I Sleep Each Night?” The “<” means less than. The “>” means greater than. The “h” means hours.

<table>
<thead>
<tr>
<th>Age</th>
<th>Newborns (0–3 months)</th>
<th>Infants (4–11 months)</th>
<th>Toddlers (ages 1–2)</th>
<th>Preschoolers (ages 3–5)</th>
<th>Children (ages 6–13)</th>
<th>Teenagers (ages 14–17)</th>
<th>Young Adults (ages 18–25)</th>
<th>Adults (ages 26–64)</th>
<th>Elderly (age ≥65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieve</td>
<td>14–17 h</td>
<td>12–15 h</td>
<td>11–14 h</td>
<td>10–13 h</td>
<td>9–11 h</td>
<td>8–10 h</td>
<td>7–9 h</td>
<td>7–9 h</td>
<td>7–8 h</td>
</tr>
<tr>
<td>Avoid</td>
<td>&lt;11, &gt;19 h</td>
<td>&lt;10, &gt;18 h</td>
<td>&lt;9, &gt;16 h</td>
<td>&lt;8, &gt;14 h</td>
<td>&lt;7, &gt;12 h</td>
<td>&lt;7, &gt;11 h</td>
<td>&lt;6, &gt;11 h</td>
<td>&lt;6, &gt;10 h</td>
<td>&lt;5, &gt;9 h</td>
</tr>
</tbody>
</table>

“What Can I Do for Healthy Sleep Habits?”

DO
• Try to be in bright light during the day.
• Have a daily physical activity routine.
• Exercise in the morning and/or afternoon.
• Set aside a “worry” time during the day so you can relax at bedtime.
• Make the area where you sleep comfortable.
• Enjoy a relaxing activity before bedtime like light reading or listening to calming music.
• Avoid screen time (TV, computer, tablet, smartphone) 2 hours before bedtime.
• Enjoy a warm bath.
• Use bed only for sleeping or intimacy.
• Establish a regular sleep pattern. Go to bed and get up about the same time every day, even on weekends.

DON’T
• Drink alcohol. Drinking too much will make your sleep restless.
• Use products that have caffeine (for example: coffee, soda, energy drinks), nicotine, and other stimulants.
• Have exposure to bright light during the night.
• Exercise within 2–4 hours of bedtime.
• Have heavy meals within 2–3 hours of bedtime. If you are hungry, eat only a light snack.
• Nap, if you are not a shift worker.
• Watch the clock. This can make you more anxious about not sleeping.
• Keep trying to sleep. Instead, get out of bed and do a relaxing activity until you feel tired.
• Have your bedroom too hot or too cold.
• Allow excessive noise.

Signs and Symptoms You May have a Sleep Problem
The symptoms of a condition called “sleep apnea” are listed below. If you or a family member notice any of these symptoms, talk with your healthcare provider.

• Snoring
• Temporarily stop breathing during sleep
• Gasping/choking during sleep
• Unexplained daytime sleepiness
• Large neck size (greater than 17 inches for men, greater than 16 inches for women)
• Middle-of-the-night waking or insomnia
• Non-refreshing sleep

This information is provided as part of the Clinician’s Lifestyle Modification Toolbox courtesy of the National Lipid Association.
The Clinician’s Lifestyle Modification Toolbox (CLMT) is a project created and developed by the NLA Nutrition Task Force in conjunction with the NLA Practice Management Council. The CLMT includes patient education material that is based on the NLA Recommendations for Patient-Centered Management of Dyslipidemia—Part 2.

The CLMT resources are designed to assist clinicians and healthcare professionals in beginning a conversation with their patients about achieving successful lifestyle changes that promote their lipid health. The NLA recommends patient referral to a registered dietitian nutritionist for personalized medical nutrition therapy to enhance and support sustained healthy lifestyle changes.

The NLA would like to make a special thanks and acknowledge all of the CLMT authors and reviewers for their efforts and dedication to creating and developing this resource.

- Carol Kirkpatrick, PhD, RDN, LDN, CLS, FNLA (CLMT Co-Chair)
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- Geeta Sikand, MA, RDN, CDE, CLS, FNLA (CLMT Co-Chair)
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- Kaye-Eileen Willard, MD, FNLA
- Dean Bramlet, MD, FNLA

Visit lipid.org/clmt to view this resource.

Created and developed by the NLA’s Practice Management Council and Nutrition Task Force