Theme:
Statin Intolerance—Facing Adversity

Also in this issue:
Evidence-Based Approach to the Use of CoQ10 to Deal with Statin Intolerance
Vitamin D Deficiency and Statin Intolerance

This issue sponsored by the Southeast Lipid Association
Join us for the opening session of the 2014 Clinical Lipid Update Meeting as world renowned thought leaders discuss Lipid Management and Metabolic Syndrome in various populations from around the world.

W. Virgil Brown, MD, FNLNA
Yuji Matsuzawa, MD, PhD

Cesare R. Sirtori, MD, PhD
Gerald Watts, DSc, MB, BS, PhD

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A debate from John Brunzell, MD and Sekar Kathiresan, MD
How Close are we to Personalizing CVD Prevention with Genetics?

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Benjamin Ansell, MD, FNLNA

**Cardiovascular Risk in Asians and Pacific Islanders**
Beatriz Rodriguez, MD, PhD
Keawe’a mia’moku Kaholokula, PhD
Nathan Wong, PhD
Latha Palaniappan, MD, MPH

**Debate: Is it time to Stop using Fibrates Combined with Statins?**
Jocelyne R. Benatar, MD, MBChB
Eliot Brinton, MD, FNLNA

**Dietary Issues and Supplements**
Kathleen Wyne, MD, PhD, FNLNA
Terry Jacobson, MD, FNLNA
Forrest Batz, PharmD
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*indicates ABCL Diplomate status
From the NLA President: Spreading the Word

As a Doctor of Pharmacy and President of the National Lipid Association (NLA) this year, I am committed to raising awareness about this disorder. I want both patients and health care providers to know exactly how important early diagnosis and aggressive treatment is—from my personal—and life-threatening—experience.

I encourage you to continue to educate your patients about FH through the many resources the National Lipid Association offers, including lipid.org, lipidfoundation.org and learnyourlipids.com.

It is important to know that although not curable, FH and other dyslipidemias are treatable. The aim of treatment is to reduce your cholesterol to an acceptable level, thereby preventing or delaying ischemic vascular disease. As a lipidologist, you can implement cascade screening in all first-degree relatives of the FH index case to help facilitate early detection and treatment, develop the best treatment plan between you and your patient, provide optimal patient education to ensure patient adherence and persistence to therapeutic lifestyle changes and pharmacotherapy, and continue to assess for subclinical atherosclerosis to further guide the intensity of therapy. In the near future, if emergent therapies in clinical trials are approved, these therapies added to maximum tolerated statin combination therapy could provide important reductions in cardiovascular risk to our FH patients.

In addition, please spread the word about the FH Foundation’s new patient registry. You can find more information at www.thefhfoundation.org.

I hope to see you at one of our upcoming meetings. Best wishes to you and your families this holiday season.
From the Chapter President and Immediate Past-President:

Statin Intolerance

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President, Southeast Lipid Association
Durham, NC
Diplomate, Accreditation Council for Clinical Lipidology

PAUL E. ZIAJKA, MD, PhD, FNLA
Immediate Past-President, Southeast Lipid Association
Director, Florida Lipid Institute
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Diplomate, American Board of Clinical Lipidology

The SELA board decided to devote this issue of *Lipid Spin* to the problem of statin intolerance. In formal clinical trials statin intolerance is reported in 2 to 3 percent of study subjects, but longer term follow up studies report a more realistic rate of 15 to 20 percent. In an informal survey of the past-president’s (PZ) private practice lipid clinic 24 of the most recent 30 new patients were referred because of statin intolerance.

The most common problems reported by statin intolerant patients are muscle complaints (about 80%), but the full spectrum of statin intolerance includes increased liver enzymes, allergic reaction, headache, neuropathy, alopecia, memory disturbances, glucose intolerance, gastrointestinal disturbances, insomnia, arthralgias, exercise intolerance, depression and dizziness.

Also, patients with statin intolerance are at a clinical and economic disadvantage. In patients with a history of coronary heart disease statin intolerance is associated with an 80 percent relative risk increase for myocardial infarctions and a 53 percent relative risk increase for all cause mortality compared to similar patients able to tolerate statins. Dyslipidemic patients unable to take statins have been reported to incur a $400 to $900 greater total health care cost over an 18 month observation period compared to similar patients able to tolerate statin therapy.

This issue of *Lipid Spin* will examine some of the clinical strategies used to deal with statin intolerance, including switching to statins with a better tolerability profile, use of very low dose - low frequency statin administration, vitamin D supplementation, CoQ10 supplementation and the use of non-statin lipid lowering regimens.

Discuss this article at www.lipid.org/lipidspin
Letter From the Lipid Spin Editors:
NLA CME: A Culture of Policing Ourselves

ROBERT A. WILD, MD, PhD, MPH, FNLA
Clinical Epidemiology and Biostatistics and
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Oklahoma University Health Sciences Center
Oklahoma City, OK
Diplomate, American Board of Clinical Lipidology

Lipid Spin is but one NLA educational offering. As editors we are pleased to bring these issues to clinicians on a regular basis. Lipid Spin is peer reviewed. The subject matter is always trying to address how we can better take care of the patients/clients we serve. Our focus is prevention. Because we are always trying to prevent ravages of CVD for everyone, by definition some of what we offer will always be useful for some and not useful for others. We need to remind everyone from time to time that many of the articles here provide clinical opinions. Peer review is not a perfect process. There is always an element of subjectivity involved. However it is the best way we have to try to avoid conflicts of interest. We strive to bring you useful information from a clinical perspective. Always be aware that articles presented are opinions of the authors and as such do not imply NLA endorsement. One of my favorite maxims is that strong opinion is the lowest form of evidence. Often the stronger the opinion the least amount of data behind the opinion!

The educational efforts of the NLA are undergoing a massive structural change for peer review to deal with issues of subjectivity and/or potential conflicts of interest. We recognize that all of us have ‘bias’. We all have our likes, dislikes and each of us has a relatively limited view of the world of science around us given the massive differences, experiences and individuality as we apply the information we learn about.

As a professional educational organization we are guided by governing bodies that try to assure that all professional organizations do their best to avoid conflicts of interest. In short we have national guidelines that we adhere to as we strive to make our educational efforts second to none. The NLA has many educational offerings and the process of peer review requires our own policing. Fortunately, we have unanimous opinions amongst the leadership that this is a priority for the NLA. As you attend the regional and national meetings please be aware that presenters are given guidance as to acceptable content and their presentations are reviewed for compliance. We ask that everyone help in this effort. If a potential conflict of interest arises, real or perceived, for any of our educational offerings, let us know so that we can look into it.

We feel strongly as an educational organization that we all benefit from this effort to strive to be the premier organization for the clinician in the practice of Clinical Lipidology. Help us all by doing your part. Help us move to clarity and give us feedback. Not until we know how we can help you can we learn how best to provide what is useful and meaningful to each of you. We welcome your input. Be part of this culture. Let your regional president know if you have any concerns, and most importantly, you have suggestions regarding how best to improve our efforts. There are a number of considerations that we have to deal with: logistics, costs, feasibility, relevance, timeliness, etc. Rest assured however that our hearts are in the right place. Help us move to excellence.

We hope that you enjoy this publication and recognize that it has a place. Also recognize that helping us by giving us feedback in the long run will allow us to serve you better.
Clinical Feature:
An Update on Statin Safety with an Emphasis on Differences

DEMIr BAYKAL, MD, FACC, FASE, CCT
Gwinnett Consultants in Cardiology
Medical Software LLC
Diplomate, American Board of Clinical Lipidology

Statin drugs have been studied in numerous controlled trials involving hundreds of thousands of study participants. Their use has resulted in reduced coronary artery disease (CAD) mortality, morbidity and, in several studies, all-cause mortality. Even though clinical trial evidence and clinical practice experience have demonstrated extremely low incidence of adverse effects, safety concerns have existed, mostly on the basis of case reports and data from clinical trials. The U.S. Food and Drug Administration (FDA) provided updates on statin labels regarding side effects in 2011 and 2012.

Clinical trial assessment of muscle adversities

No conclusive comparative evidence exists to indicate that currently available statins differ in regard to their risks of myopathy, defined as otherwise unexplained marked creatine kinase (CK) elevation >x10

Abbreviations
ULN = upper-limit normal
CAD = coronary artery disease
MMSE = Mini-Mental State Examination
LFT = liver function test

the upper-limit normal (ULN) associated with myalgia or rhabdomyolysis. The incidence of myopathy was (0.1%) for lovastatin 40mg/day and (0.2%) for lovastatin 80mg/day in the Evaluation of Xience Prime™ versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial.¹
There were no cases of myopathy or rhabdomyolysis in three major pravastatin trials.² None of the three cases of rhabdomyolysis in patients on 10mg/day dose or the two cases on 80mg/day dose of atorvastatin in the Treating to New Targets (TNT) trial was felt by investigators to be casually related to atorvastatin.³ In an analysis of 27 Phase 2/3 controlled clinical trials of rosuvastatin, CK elevation >10X ULN occurred in 0.02% to 0.04% in a dose-independent manner. No cases of rhabdomyolysis was reported.⁴

The incidence of CK elevations is reported as 0.03% on 40mg/day fluvastatin and 0.00% on fluvastatin 80mg/day and there have been no reported cases of rhabdomyolysis. Therefore, fluvastatin may have the least propensity to cause myotoxicity.⁵ On the other hand, 10 patients – nine of them on simvastatin 80mg/day – developed myopathy in the high-risk-CAD A to Z trial.⁷ The highest incidence of statin-related myopathy was encountered in the seven-year, randomized, double-blind SEARCH study. Fifty-two patients (0.9%) in the 80mg group versus one patient (0.02%) in the 20mg group developed myopathy, defined as unexplained muscle weakness or pain with a serum CK >10 times ULN.⁸ This was higher than the labeled risk (based on clinical trial data) of 0.53%. Twenty-two patients (0.4%) in the 80mg group versus no patient in the 20mg group developed rhabdomyolysis. The risks for myopathy and rhabdomyolysis with simvastatin 80mg were highest in the first 12 months of treatment; older age and female gender both increased the risk of myopathy.

In SEARCH, the risk of myopathy was approximately doubled in patients taking
a calcium channel blocker, in particular diltiazem.8

The findings from the SEARCH trial are supported by analyses of the FDA’s Adverse Event Reporting System (AERS) database, which show that the level of reporting of fatal rhabdomyolysis associated with the 80mg dose of simvastatin has been higher in comparison with lower doses of simvastatin or most other statins, leading to a recommendation to limit the initiation of an 80mg/day dose.

The incidence of statin-related myopathy varies little between different statins, except the highest incidence is seen with the initiation of simvastatin 80mg daily and lowest (none reported) with fluvastatin 80mg daily.

Drug interactions and metabolic pathways are major considerations. Because they are not metabolized significantly via the cytochrome P450 (CYP) pathway, pravastatin and rosuvastatin may be administered in a safer fashion if given concomitantly with drugs known to be CYP inhibitors.

Potential liver adversities
Overall, statin trials have demonstrated that the incidence of significant elevations1 in liver injury tests (defined as > 3 X ULN) is between 0.5% and 5%; and liver enzyme elevations are dose dependent. There is little relationship between the magnitude of low-density lipoprotein (LDL) reduction and the degree of enzyme elevation at lower doses; in other words, there are no differences between more potent statins and less potent ones. Instead, when a statin dose is doubled from the second highest to maximum allowed dose, blood transaminase levels increase. In one comparative head-to-head, six-week study involving 2,431 participants, there were only five cases of two consecutive-visit aspartate transaminase (AST) elevations on atorvastatin 80mg (n=1), atorvastatin 20mg (n=2), simvastatin 40mg (n=1), simvastatin 80mg (n=1), and none on rosuvastatin 40mg daily dose.6 The clinical significance of these often transient, self-limited elevations is unclear. The baseline measurements of liver function tests are useful for future comparisons. Pretreatment liver enzyme levels have not been predictive of clinically meaningful acute hepatocellular reactions. Therefore, routine continued monitoring of liver enzymes at lower doses of statins is not necessary except for patients on concomitant medications, with co-morbid conditions or otherwise felt to be at high risk. On Feb. 28, 2012, the FDA approved crucial changes to the safety label for statins, removing the recommendation for periodic monitoring of liver enzymes. According to the new labels, the FDA recommends that such tests be conducted before starting therapy and as clinically indicated thereafter.

Adverse renal experiences
Preclinical animal studies have demonstrated renal tubular toxicities related to high-dose statin intake. Mild proteinuria seen clinically is the result of impairment of renal tubular protein absorption by receptor-mediated endocytosis and is physiological because of HMG-CoA reductase inhibition. Hematuria seen with statin use in clinical trials commonly has other explanations. To address the question of whether urinary abnormalities with statin use are detrimental to long-term renal function, an open-label atorvastatin study was conducted. It was concluded that atorvastatin reduced the proteinuria and progression of chronic kidney disease (CKD) additive to angiotensin-converting enzyme (ACE) Is or angiotensin-receptor blockers (ARBs). This particular beneficial or safety profile of atorvastatin may be contributed by minimal renal excretion, <2% as opposed to 10% with rosuvastatin, 13% with simvastatin and 20% with pravastatin. In the atorvastatin-based Die Deutsche Diabetes Dialyse (4D) study, no case of rhabdomyolysis was reported in 619 hemodialysis patients.11

Potential neurological adverse experiences
The level of evidence supporting potential neurological adverse effects of statins is listed in Table 1.

Case reports and clinical trials have suggested that statins may impair cognitive function, which may be of safety concern,
particularly in older individuals.

In a double-blind study of 209 generally healthy hypercholesterolemic adults, randomly assigned to six-month treatment with lovastatin 20 mg or a placebo, lovastatin did not cause psychological distress or substantially alter cognitive function, but it did result in small performance decrements on neuropsychological tests of attention and psychomotor speed, which were concluded to be of uncertain clinical importance. In a similar follow-up study of 308 adults with hypercholesterolemia, a randomized, double-blind, placebo-controlled trial of simvastatin 10mg or 40mg for six months provided partial support for minor decrements in cognitive functioning with statins. In the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial, the largest statin trial conducted specifically in older study participants, 5,804 men and women ages 70 to 82 years with a history of or risk factors for vascular disease were evaluated for mental changes. After an average of 3.2 years, pravastatin 40mg/day was found to have no significant effect on cognitive function or disability compared with a placebo, as assessed by diagnostic instruments such as the Mini-Mental State Examination (MMSE). With specific regard to dementia (which may include Alzheimer’s disease), nested case-control designed studies revealed that individuals who were prescribed statins actually had a substantially lowered risk of developing dementia. However, a meta-analysis based on the Cochrane database review (pooling the studies providing a change in MMSE from baseline) of the effect of statins on dementia concluded that, while there was insufficient evidence to recommend statins for the treatment of dementia, statins were not detrimental to cognitive function.

An FDA review concluded that data from the observational studies and clinical trials did not suggest that cognitive changes associated with statin use were common or led to clinically significant cognitive decline, but information about the potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) was added to the statin labels.

Peripheral nervous system
In case reports, and in a small number of case-control and cohort studies it is suggested that statins may be associated with peripheral nervous system adverse experiences. However, from a review of the literature, it is reasonable to conclude that any potential risk of peripheral neuropathy with statin use is very small. A stepwise approach to the patient with a potential statin-related peripheral neuropathy adverse experience may be to, first, ensure that other secondary causes have been evaluated; second, to perform a neurologic physical examination and attempt to objectively quantify abnormal neurologic physical findings; and third, to obtain appropriate diagnostic neurologic studies; and, fourth, to stop administering the statin. If objective abnormalities are found on physical examination and diagnostic neurologic testing, and if the neuropathic symptoms resolve upon discontinuing the statin, then it may be useful to repeat the objective evaluations to see whether the resolution of symptoms correlates with the resolution of objective neurologic findings. If resolution of symptoms or objective neurologic testing does not occur after withdrawal of statin therapy, then the diagnosis of idiopathic peripheral neuropathy unrelated to statin use should be considered. Conversely, if symptoms and objective neurologic testing resolve, then the clinician can best decide

### Table 1.

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Potential Statin-Adverse Experience</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Statins reduce the risk of ischemic stroke&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>B</td>
<td>A decrease in cognition or memory&lt;sup&gt;13,14,15&lt;/sup&gt;</td>
</tr>
<tr>
<td>F</td>
<td>Statins may worsen dementia, Alzheimer’s disease&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>B</td>
<td>Statins may improve dementia, Alzheimer’s disease&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>U</td>
<td>Some statins are safer than others in regard to adverse neurological events</td>
</tr>
<tr>
<td>C</td>
<td>Peripheral neuropathy is a potential adverse effect&lt;sup&gt;18,19&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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The incidence of new diabetes development appears to be a class effect and appears to be more common with moderate or higher doses, but a causal relationship is unproven.
whether the benefits of a re-challenge of a statin drug exceeds the potential risks.

**Increases in glycosylated hemoglobin (HbA1c) and fasting plasma glucose**

In the FDA’s review of the results from the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, it was reported that there was a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients. High-dose atorvastatin also has been associated with worsening glycemic control in the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators (PROVE-IT TIMI 22) substudy. A meta-analysis by Sattar, et al., reported that statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09[1.02-1.17]), with little heterogeneity (I² = 11%) between trials. A meta-analysis by Rajpathak also reported a small increase in diabetes risk (relative risk [RR] 1.13[1.03-1.23]) with no evidence of heterogeneity across trials. A recent study by Culver, et al., using data from the Women’s Health Initiative, reported that statin use conveys an increased risk of new-onset diabetes in postmenopausal women and noted that the effect appears to be a medication-class effect, unrelated to potency or to individual statin type contrary to the findings of Carter. In this 14-year observational study, a relationship between the potency (and duration) of statin therapy and the incidence of diabetes development was observed. However, the selection bias of a higher-risk population requiring more intense statin therapy could not be excluded.

Based on clinical trial meta-analyses and epidemiological data from the published literature, information concerning an effect of statins on incident diabetes and increases in HbA1c and/or fasting plasma glucose was added to statin labels.

Disclosure statement: Dr. Baykal has received consulting fees from Actelion Pharmaceuticals Ltd.

References are listed on page 29.
A patient recently told me the story of her statin-intolerant sister, who was referred to a cardiologist she had seen for chest pain a few years earlier. When he entered the room, she explained that she could hardly walk or even get out of bed on atorvastatin. The doctor simply stated there was nothing he could do for her and walked out, leaving her confused and hurt. We can do something for these patients and it starts with listening.

Statin clinical trials suggest an incidence of adverse muscular events of ~1.5 - 3%, but the true incidence of statin intolerance (SI) is likely between 10% and 15%.1,2 In a recent one-month chart review of 393 patients seen in our lipid clinic, 185 (47%) were originally seen for statin-related adverse events, and 145 (37%) of these had a history of SI related solely to musculoskeletal complaints.

So, what can we do for these patients? Of the 145 SI patients from our review, 90% (129 patients) are actually on a statin today – 14% on a statin alone and 83% on statins dosed at very low doses and/or dosed 2-4 times weekly, in combination with other lipid lowering medications. The average low-density lipoprotein (LDL) reduction in these patients was 50.8%. So the crux of therapy for our statin-intolerant patients is STATIN, but often dosed in an unconventional manner in unusual combinations with other lipid-lowering agents.

Following is our approach to the SI patient.

First, listen to the patient. Just listening with a compassionate ear will make the patient more receptive to at least try another statin at a very low dose.

Second, educate the patient on the benefits of statin therapy. The patient’s perception of these drugs often comes from the evening news, a friend’s report of some statin horror story or the hungry lawyer ads on T.V. They rarely hear the good news. A favorite “one-liner” for this purpose: “For every one high-risk person on statin who has died from an adverse muscle event, 1,188 people DIDN’T DIE because they took their statin,” a calculation based on the incidence of fatal rhabdomyolysis of 0.3/100,000 person-years of statin therapy3 compared to the 360 lives saved per 100,000 person-years of statin therapy in 17 secondary prevention trials. A little pain is worth a lot of gain.

Third, rule out other causes of myopathy and evaluate potential exacerbating factors by checking a TSH, B12, vitamin D level. A baseline CK should be established and monitored with symptoms as recommended by the National Lipid Association Statin Safety Task Force.3

Finally, we initiate drug therapy by:
(1) Switching to another statin, one with a different metabolism or to an extended-release preparation (fluvastatinXL or lovastatin XR-Altoprev).

(2) Initiating very low doses (Ld) of
long half-life statins at a low frequency (Lf), i.e. once a week to every other day (QOD), using primarily rosuvastatin (19 hours) and atorvastatin (14 hours) or pitavastatin (11 hours) QOD.

(3) Combining very low daily doses of weaker statins or alternate-day dosing of long half-life statins with ezetimibe – also used at a low-dose/low-frequency (5-10mg daily, QOD or 3 times weekly) – for reduced symptoms, lower cost or if full doses cause a reduction in high-density lipoprotein (HDL).

(4) Combining the above (statin +/- ezetimibe) or ezetimibe alone with other non-statin lipid-lowering medications (BAS, niacin, fibrates) with an intense effort to choose a drug that has some clinical trial evidence of benefit for that individual patient, i.e. fibrate for triglycerides >200mg/dl and HDL <40mg/dl, colesuevelam for diabetics with close triglyceride monitoring, niacin for LDLS not at goal and NOT for those with severe expressions of metabolic syndrome, monitoring platelets and symptoms of ulcers and gout.

Since most patients referred to lipid clinics have already failed multiple attempts with multiple statins, proceeding directly to options 2 and 3 above is reasonable. We almost always start with rosuvastatin 2.5mg -5mg, taken on Mondays, Wednesdays and Fridays (MWF), with directions to add ezetimibe 5mg (1/2 10mg pill) on Tuesdays, Thursdays and Saturdays (TuThSa). Providing samples for this first cycle definitely improves compliance. A normal week’s supply lasts a month with the pill splitting and QOD dosing. We repeat labs after six weeks. Once the patients see the usually significant improvements, they are encouraged enough to continue and even increase the medications. We advance the statin very gradually, as tolerated, by increasing the dose first, not the frequency. For insurance purposes, we often switch to atorvastatin 5-10mg dosed at the same frequency or<br> change to very low doses of weaker statins (i.e. pravastatin 10-20mg) daily. From there, it’s a slow process of tweaking, determined by other lipid abnormalities, comorbidities and cost.

Following is a summary of studies evaluating the efficacy and tolerability of low-dose/low-frequency (Ld/Lf) dosing strategies with statins:

(1) Piamsomboon et al. — In 61 patients treated with atorvastatin 10mg QOD, LDL was reduced 30%.

(2) Juszczyk et al. — In 25 patients treated with atorvastatin QoD (mean dose 18.8mg) or rosuvastatin QOD (mean dose 9.7mg), LDL reductions were 43% and 28%, respectively.

(3) Wongwiwatthanaukit et al. — In 81 patients treated with rosuvastatin 10mg
qd vs. QOD, LDLs were reduced 48% and 39%, respectively, and 85% vs 70% achieved NCEP targets, neither statistically significantly different.

(4) Jafari et al.7—In 54 patients, there were no statistically significant differences in LDL reductions between atorvastatin dosed at 10mg qd, 10mg QOD or 20mg QOD after 6 weeks of treatment; all tolerated treatment.

(5) Keles et al.8—In 61 patients treated with atorvastatin 20mg qd vs QOD, there was no significant differences in the reductions of LDL or hsCRP after 3 months.

**Similar trials performed in STATIN INTOLERANT patients include:**

(1) Backes, et al.9—In 51 patients treated with rosvastatin 2.5-10mg QOD, (mean dose 5.6mg), LDL was reduced 34.5%, 50% achieved National Cholesterol Education Program goals and 72.5% tolerated therapy.

(2) Gardala, et al.10—In 40 lipid patients receiving rosvastatin 5-10mg twice weekly (Mondays and Thursdays); LDLs were reduced 26% and 80% tolerated treatment.

(3) Rusinger, et al.11—50 patients receiving rosvastatin 2.5-20mg once a week; LDLs were reduced 23%, 74% tolerated treatment, but only 27% reached their NCEP goal.

(2) Reddy, et al.13—In 23 patients intolerant of atorvastatin or rosvastatin receiving the same drug dosed twice weekly plus ezetimibe twice weekly plus colesvealam 6 pills a day, LDLs were maintained at the level produced by daily dosing, but 87% of patients tolerated treatment, and HDLs went up in the rosvastatin patients.

(3) Stein, et al.14—In patients receiving daily fluvastatin XL 80mg, ezetimibe 10mg or both, LDLs were reduced 33%, 16% and 41%, NCEP targets were achieved in 59%, 20% and 84%, and muscle-related side effects occurred in 17%, 24% and 14%, respectively.

Results from our chart review are consistent with the above reports: 29 of 140 SI patients were on non-daily doses of statins, and 44 were on statin in combination with ezetimibe alone with an average LDL reduction of 52%. Many of these were on non-daily low doses of ezetimibe (5mg 2-4 times per week). An additional 33 patients were on statin+ezetimibe + other non-statin drugs and had an average LDL reduction of 62%. Coincidentally, 62% of the patients were below the more aggressive NCEP targets; 79% of those not at goal had >40% LDL reductions.

Following statins and ezetimibe, fibrates were the drugs used at the next highest frequency. This is not surprising, because 295 of 393 (75%) of our patients had TGs >200, and 22% were referred with severe hypertriglyceridemia ([TG]>500). Even so, less than half of these patients were on full-dose fenofibrate. Fenofibrate can help

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**Table 1. Usage of Lipid-Lowering Medications in 140 Patients with Myalgia-Related Statin Intolerance; A One-Month Chart Review.**

<table>
<thead>
<tr>
<th>Lipid-Lowering Agent</th>
<th>No. of patients on medications</th>
<th>%</th>
<th>a</th>
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<th>d</th>
<th>e</th>
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<td>Statins b</td>
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<td>Single-agent</td>
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<tr>
<td>+ ezetimibe alone</td>
<td>129</td>
<td>90</td>
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<tr>
<td>+ other agents (below)</td>
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| a | 145 of 393 patients were SI; 2 had stopped all medications, 3 had no results following initial visits; the denominator used to calculate percentages was 140. |
| b | Statins used: rosvastatin 48% (average dose: 7.4mg/d); atorvastatin 27% (average dose: 13.5mg/d); pravastatin 14% (average dose: 35mg/d); pitavastatin 3% (average dose: 2mg/d); fluvastatin XL 2% (average dose: 80mg/d); simvastatin 3.5% (average dose: 24mg/d); lovastatin 0.7% (average dose: 40mg/d). |
| c | Statins used for non-daily dosing: rosvastatin 2.5mg (7pts), 5mg (13pts), 10mg (4pts) and 20mg (2pts) dosed twice weekly (M&W), MF, MF+ p.m. + Sun a.m.; atorvastatin 5mg (5pts), 10mg (1pt), 20mg (4pts) dosed M:F, MWF or QOD. |
| d | Ezetimibe was used at 5-10mg, dosed 2-4 times/week (Tues/Sat, Tues/Thurs/Sat or Tues/Thurs/Sat/Sun) usually alternating with statin MF. |
| e | 75% of 393 lipid patients reviewed had TGs>200; 22% had TGs>500mg/dl. Gemfibrozil was used only with very low doses of rosvastatin and pravastatin in very carefully selected patients who were educated extensively on the signs/symptoms of rhabdomyolysis. |
lower the LDL further and often results in a dramatic LDL reduction when combined with ezetimibe alone, a very consistent finding in the completely statin-intolerant patient. If fenofibrate lowers HDL and increases creatinine, especially enough to preclude the use of metformin, we reduce the dose or stop it. Table 1 summarizes the drugs used and Table 2 the lipid values achieved with various drug combinations. Only 20% of the patients were on a Ld/Lf statin-dosing schedule, but most were originally started on rosuvastatin (2.5mg) three days a week. Most patients tolerate a very gradual increase in the statin dose—to a point. **The art is knowing when to stop.**

While all of these results of alternate-day statin dosing, especially in combination with other lipid drugs, are quite remarkable and encouraging, these are non-approved strategies and no clinical trial evidence for cardiovascular risk reduction exists. Therefore, these strategies should be reserved for those patients who have failed recurrent attempts of conventionally dosed statins. Designing a clinical trial to evaluate these kinds of treatments in SI patients would be a monumental task. However, if one were designed so medications were meticulously tailored for the individual patient—the way most of us treat these SI patients—compared to those treated with statin alone, these patients just might come out ahead—or at least they could get out of a chair! ■

**Disclosure statement:** Dr. Honkanen is on the speaker’s bureau for Merck & Co., Inc., Astra-Zeneca and Amarin Pharma, Inc.

**References are listed on page 29.**

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Table 2. Efficacy of Various Treatment Regimens Used in Statin-Intolerant Patients; A Chart Review of 140 Patients **a**

| **a** Results were calculated by comparing the most recent lipid values to the worst corresponding lipid value on record. For example, LDLs were compared to the highest LDL observed after correcting chylomicronemia. Some baseline values were not available, because patients often were referred while on some lipid therapy. **b** 62% of patients achieved the more aggressive NCEP/ADA LDL target, i.e. <70mg/dl with documented disease or DM + 1 risk factor. Of the 38% not at goal, 79% had LDL reductions > 40%. **c** Triglyceride and HDL responses were likely confounded by changes in other medications (i.e. addition of pioglitazone, other diabetic agents and omega-3 fatty acids [10 pts] or discontinuation of thiazides, atenolol etc.) and significant lifestyle modifications. **d** BAS bile acid sequestrant. **e** 4 of 8 patients also were started on high-dose omega-3 fatty acids in the fenofibrate group, none in the gemfibrozill group. |
Statins reportedly are the most effective of the lipid-modifying drugs in primary and secondary prevention of coronary heart disease.1-6 Yet, many patients are deprived of the benefits of statins because of their associated complications. The most common statin-related complication is myopathy, which was underreported in clinical trials because of the exclusion of patients with a previous history of myalgia.1,7,8 Studies specifically designed to assess the rate of statin-related myalgia have estimated muscle-related complications occur in between 9% and 22% of patients – or 1.5 million people – each year.9-12 This ultimately leads to the discontinuation of statins in between 5% and 10% of patients.11 Practitioners have been searching for strategies capable of alleviating statin-induced myopathy to facilitate the continued use of statins. The most prevalent of these strategies is CoQ10 supplementation.9

Statins, CoQ10 and Myopathies
CoQ10 is essential in cellular bioenergetics, because it participates in the electron transport chain during oxidative phosphorylation, leading to adenosine triphosphate (ATP) production.13 Depletion of CoQ10 is known to result in mitochondrial dysfunction, which is theorized to result in myopathy.10,14 The theory of CoQ10 depletion involvement in statin-induced myopathy was first proposed in the late 1980s.14 CoQ10 is an end-product of the mevalonate pathway. Statins are believed to reduce CoQ10 biosynthesis and cause myopathy by interfering with this pathway via the inhibition 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA].7,10,14,16

CoQ10 Depletion Studies
The theory of statin-induced CoQ10 depletion was supported by Ghirlandaio et al., who published the first double-blind study assessing the effect of statins on plasma CoQ10 levels. Since then, the relationship of statins and reduced CoQ10 plasma levels has been well documented.8,10,12,17,36

Conventional wisdom would suggest that, given the role of CoQ10 in muscle-energy production, reversing CoQ10 depletion via supplementation would resolve cases of statin-induced myopathy. The evidence to date has been, at best, controversial.10

EBM Tools for Practice: Evidence-Based Approach to the Use of CoQ10 to Deal with Statin Intolerance

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**CoQ10 Outcomes**

The two most widely cited studies, by Young et al. and Caso et al., have produced equivocal results. In a double-blind placebo-controlled pilot study, Young et al. concluded that, despite a significant increase in plasma CoQ10 levels, supplementation with 200mg/day CoQ10 did not improve statin tolerance and myalgia after 12 weeks in patients with prior statin-induced myalgia.37

Caso et al. performed a double-blind, randomized pilot study assessing the effect of 100mg/day CoQ10 versus 400IU/day Vitamin E on the degree of muscle pain and its interference with daily activities. After 30 days, pain intensity decreased significantly from baseline in the CoQ10 group. Those in the Vitamin E group did not experience a significant difference in pain.38

Adding to the dilemma, more recent studies – such as those by Bookstaver et al., Zlatohlavk et al., and Fedacko et al. – also failed to produce consistent results.39-41 Several clinical reviews have assessed these studies and have been unable to definitively conclude that CoQ10 improves statin-induced myopathy.8,9,42-44

**Rethinking Plasma CoQ10**

Inconsistencies in the research data have led some to call into question the significance of reduced plasma CoQ10 levels on myalgia.

Researchers suggest that, rather than indicating a true inhibition of CoQ10 synthesis, a reduction in plasma CoQ10 levels should be expected because of the statin-induced reduction of low-density lipoprotein (LDL) particles, the primary transporter of CoQ10 in plasma.8 Additionally, while the statin-induced depletion of CoQ10 is well documented, research has not established a firm association between statin use and mitochondrial myopathy, because intramuscular CoQ10 levels have not consistently decreased with statins.7,10,42,45 Two studies observed intramuscular CoQ10 increases of 46% and 9% in statin-treated patients.46,47

---

**CoQ10 should be considered in statin-intolerant patients, even if only to induce a placebo effect, arguing minimal risk with possible benefit.**

---

**Where do we go from here?**

Because of inconsistent results, the National Lipid Association (NLA) has not endorsed the use of CoQ10 for prophylaxis to reduce statin-induced myalgias.48 However, some researchers have suggested that CoQ10 may still have a place in treating statin-induced myalgia, particularly in the setting of CoQ10-depleting conditions such as advanced age, multisystem diseases, multisystem inherited metabolic disease, mitochondrial encephalomyopathies and certain movement disorders, including Parkinson’s disease and some cerebellar ataxias.7,45 There also is research to suggest the benefits of CoQ10 in patients with cancer.49,50

Additionally, CoQ10 may be beneficial in patients who have a genetic or neuromuscular predisposition to statin-induced myopathies.51,52

The use of CoQ10 may be considered because of its remarkable safety record, because there are no known risks in doses up to 600mg/day.8,10,12,45,54 There is strong evidence based on the observed safety level of CoQ10 that doses up to 1,200mg/dl are very safe.53 Based on the safety data alone, several authors have suggested CoQ10 should be considered in statin-intolerant patients, even if only to induce a placebo effect, arguing minimal risk with possible benefit.10,12,45

**Conclusion**

To date, there is inconclusive evidence to prove if CoQ10 can reduce statin-induced myopathy in all patients. Some research, however, suggests that it may provide some benefit in certain patients who have CoQ10-depleting conditions. Additionally, the remarkable safety profile makes CoQ10 an attractive low-risk option for practitioners who are aggressively trying to maintain statin use in their patients. More data are needed to determine if CoQ10 is an effective treatment in statin-induced myopathy. Many are eagerly anticipating the release of the Parker et al. trial later this year in the *Journal of Clinical Lipidology*, hoping it will shed more light on this ongoing debate.55

Disclosure statement: Dr. Welding has no disclosures to report. Dr. Ragheb has no disclosures to report.

References are listed on page 29-30.
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Lipid Luminations:
Lowering LDL Using Non-Statin Regimens

Although statin therapy is a cornerstone of cardiovascular disease prevention, and although it achieves the largest reduction of low-density lipoprotein (LDL-C),¹ and has one of the safest overall side-effect profiles among lipid-lowering medications, some patients are unable to tolerate statins because of one or more side effects. When this clinical scenario is present, alternative risk-reduction strategies are needed to achieve target LDL-C goals. Clinicians should be familiar with alternative pharmacological therapies, non-pharmacologic therapy and intensive therapeutic lifestyle modifications that reduce atherosclerosis progression when statin therapy is not an option.

**Bile acid Sequestrants**

Bile acid sequestrants — colestipol, cholestyramine and colesevelam — bind to bile acid in the intestines and prevent recirculation of cholesterol-decreasing LDL-C by 15%-26%,²,³ achieving maximal LDL-C reductions within two weeks. Colesevelam has a higher specificity for bile acids than the two older bile acid sequestrants, and consequently there are fewer gastrointestinal side effects and drug interactions.² Colesevelam has been noted to decrease hemoglobin A1C by about 0.5%,³,⁴ and is more frequently being used in diabetic patients. Because bile acid sequestrants are not absorbed systemically, large doses are required. They do not have any systemic drug interactions but they can interfere with drug absorption.²,⁵ This requires constant vigilance, monitoring and adjustments to ensure therapeutic levels of concomitant medications are maintained to improve outcomes.

**Nicotinic acid**

Although recent clinical trials have shown no benefit from nicotinic acid when LDL cholesterol is therapeutically low, there are many research studies demonstrating LDL-C reduction.⁵ The Coronary Drug Project found significantly fewer cardiovascular events and decreased mortality with niacin, and these benefits persisted for up to 15 years after induction or therapy.⁶ Niacin reduces LDL-C by 25%, increases high-density lipoprotein (HDL-C) by 15%-30% and decreases triglycerides by 35%-50% with more pronounced benefits in patients with metabolic syndrome. Some clinicians erroneously eliminate niacin from dyslipidemia treatment options because of results of several recent randomized clinical trials without an overall understanding of aggregate literature. In addition to the lipoprotein changes associated with niacin administration, there are several other pleotropic effects, including associated anti-oxidative and anti-inflammatory properties, improved endothelial function, reduced high-sensitivity C-reactive protein, and regression of carotid intima-media thickness. This makes niacin a more compelling option.¹,⁷

**Cholesterol-absorption inhibitors**

Ezetimibe, a cholesterol-absorption inhibitor, can be used alone or in combination with other medications to
reduce LDL-C (by 15%-20%). This amount of reduction in LDL-C does not meet the 30% reduction proven to reduce cardiovascular events, and routinely clinicians use ezetimibe in combination with other medications. Based on the available data, ezetimibe appears to be safe but has not been proven to provide significant long-term cardiovascular benefit. Ezetimibe and colesevelam combination therapy has been noted to provide a 30%-40% reduction in LDL-C.

**Alternative therapies**

Red yeast rice is a traditional Chinese supplement that is procured after red yeast is grown on rice. It combines monounsaturated fatty acids, sterols, isoflavones, Monacolin K (a form of lovastatin) and other ingredients, whereby it is reported to lower LDL-C by 10%-20% in several small population studies. This level of LDL-C reduction does not equal the potency of the weakest statin, and long-term safety and decreased cardiovascular mortality are not clearly documented, leading some clinicians to object to its use. It has been used for centuries in China and it does lower LDL-C to some degree, and therefore remains non-statin option to reduce LDL-C, primarily in combination with other therapies.

Plant sterols occur naturally and have a similar structure to cholesterol. Plant stanols are “saturated sterols” and do not have double bonds. Between 150-400 mg/d of sterols and stanols are provided by the typical Western diet. However, much higher intakes (1-3 g/d) are needed to decrease atherogenic lipoprotein properties. Plant sterols and stanols are underutilized in the treatment of dyslipidemia. At doses of 2 grams per day, they can lower LDL-C by about 10%-15%; and these benefits are often additive to lifestyle modifications.

**Lifestyle modifications**

All patients receiving lipid-lowering medications should be counseled on the benefits and importance of aggressive therapeutic lifestyle modifications.

**Conclusion**

Statin therapy is first line pharmacologic interventions for patients with increased LDL-C; however, some patients experience untoward side effects and are unable to continually adhere to this therapy. As clinicians we need to be familiar with effective strategies that lead to better lifestyle modifications and we need to be able to employ alternative pharmacologic and non-pharmacologic therapies to reduce cardiovascular risk and to improve healthcare outcomes in our patients in need of CVD risk reduction.
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The National Heart, Lung and Blood Institute (NHLBI) recommends universal pediatric lipid screening to identify and treat children with serious genetic dyslipidemias. Primary care providers should certainly identify children who will be candidates for statin therapy. One in 500 people are heterozygous for the autosomal co-dominant mutations causing familial hypercholesterolemia (FH), making it one of the most common genetic diseases in Western populations. Still, a very low number of the children tested will reach the threshold for treatment. Statin therapy is recommended for otherwise healthy children older than 10 years with low-density lipoprotein cholesterol (LDL-C) > 190 mg/dL; this high cutpoint include only those with severe dyslipidemias such as FH. Regardless of the low number of children who will require treatment, obstacles remain for these pediatric patients. Medications commonly associated with grandparents and secondary prevention of further cardiovascular disease may seem out of place in a child’s medicine cabinet. Even for willing prescribers, pediatricians historically have had little training in the management of lipid disorders, particularly pharmacotherapy.

Hesitation to use this class of drugs is unfortunate, because statins have proven highly effective and safe in adult primary and secondary prevention trials and improve carotid medial thickness in children with FH. Furthermore, a recent meta-analysis of 135 studies involving ~250,000 adult patients showed that side effects of statins were rare. They are far more palatable and more effective at lowering LDL-C than the prior mainstay of pediatric treatment, bile-acid-binding resins.

Regardless of the agent used, reducing cholesterol in the pediatric population has caused concerns about decreasing the available substrate to form hormones that orchestrate pubertal development, and initiating a low-fat diet in at-risk children has been questioned because of the necessity of fats for healthy brain development. These concerns remain theoretical; a well-designed meta-analysis of six studies examining a total of 798 children showed no pubertal or growth concerns in children treated with statins. Smaller studies showed efficacy and safety of other agents, though none was powered to detect rare events. Reversible elevations in transaminases were reported.

Statins are well tolerated in children when prescribed by specialists as recommended by the conservative guidelines given by the NHLBI.
in from 1% to 5% of children in trials of simvastatin or atorvastatin, but none had clinical signs of liver injury.\textsuperscript{11,12}

Infrequent but significant adverse effects of statin therapy have been reported, including severe muscle injury leading to rhabdomyolysis. However, the more common issue in practice is statin intolerance, an inability to stay on the medication because of muscle complaints without objective signs or blood marker changes. Furthermore, recent studies showing a slight but statistically significant increase in risk for new onset diabetes have given many prescribers pause about statin use in patients of all ages.\textsuperscript{7,13} Acute kidney injury with high doses,\textsuperscript{14} increased muscle injury and strains,\textsuperscript{15} reversible memory problems\textsuperscript{16} and decreased exercise tolerance\textsuperscript{17} also have been reported. Furthermore, the possible cumulative effect of statins is unknown. Young patients who start statin therapy for FH will likely take a pill for the rest of their lives. Statins are classified as a Category X medication for their potential teratogenic effects\textsuperscript{18} and should be used carefully in women of childbearing age, including teenage girls.

One potential explanation for low rates of adverse effects in young patients is that children are generally healthy, without concomitant kidney or muscle disease. Furthermore, children are not usually taking other medications known to cause serious interactions, including gemfibrozil and digoxin.\textsuperscript{19} Polypharmacy increases the risk of toxicity because of competition with other cytochrome P450 isoform 3A4-metabolized substances.\textsuperscript{19} Lipid specialists also treat to less aggressive goals in children and use lower doses than for high-risk adult patients, and lower doses are associated with fewer adverse effects.\textsuperscript{7}

In summary, statins are well tolerated in children when prescribed by specialists as recommended by the conservative guidelines given by the NHLBI. Early identification and treatment of serious dyslipidemias provide an important opportunity to prevent atherosclerotic disease later in life. Routine clinic visits with appropriate screening and counseling regarding adverse drug effects are necessary, but the knowledge of these potential rare complications should not limit the use of these powerful and effective lipid-lowering agents in appropriate patients. ■

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

References are listed on page 30-31.
Studies specifically designed to evaluate prevalence of statin-related myalgia have shown that approximately 22% of patients on statins have some degree of musculoskeletal pain.1 As clinicians, we know it is difficult for patients to discern between pain related to statin intolerance and that associated with aging, osteoarthritis or autoimmune disorders. Many patients with these symptoms discontinue their statin medication without consulting their primary care provider. This likely leads to increased cardiovascular disease (CVD) risk related to medication non-compliance.

Low serum concentrations of 25-hydroxyvitamin D (< 20 ng/ml) are independently associated with myalgia2,3 and there is a possible connection between statin intolerance and vitamin D deficiency. Bioactive vitamin D, or calcitriol (1, 25-(OH) 2D3), is a steroid hormone that has an essential role in bone mineralization. However, recent data shows that vitamin D receptors have been identified in a wide variety of cells, demonstrating that this hormone’s biological involvement may well extend beyond mineral metabolism.4 The function of vitamin D at the cellular and genomic levels may explain the hormone’s possible role in diseases such as multiple sclerosis, depression, tuberculosis, CVD, asthma and cancer.5,6 It is reported that vitamin D deficiency is more prevalent than previously recognized and may be present in 50% of the adult population.7

In my own clinical practice dealing with lipid disorder patients, I began seeing an association between vitamin D deficiency and reported intolerance to statins. Vitamin D levels were measured as part of a retrospective chart review of lipid outcomes in patients seen in my lipid clinic. This allowed me to track my presumption that an association may exist between a deficiency in vitamin D and intolerance to statin medications. This association led to a review of the literature and a closer look of patients already enrolled in a six-month pilot study within my practice.

From this literature review there appears to be different concepts related to the potential mechanisms by which vitamin D and statins may be connected to patient intolerance. Vitamin D insufficiency may potentiate statin-induced myalgia and/or statins themselves may contribute to vitamin D deficiency. As of this review, there have been several non-blinded studies that support the concept that vitamin D deficiency may be directly

Practical Pearls:
Vitamin D Deficiency and Statin Intolerance

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Diplomate, Accreditation Council for Clinical Lipidology

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related to statin-induced myalgia. Ahmed et al.\textsuperscript{8} reported in 2009 the resolution of statin-induced myalgia in 92\% of vitamin D-deficient patients after vitamin D supplementation. In a small case series published in 2010 by Dr. David Bell,\textsuperscript{9} four of six patients with statin-induced myalgia and vitamin D deficiency who were re-challenged with the same statin dosage after the correction of vitamin D levels tolerated the statin for at least six months. In a review, Lee et al.\textsuperscript{10} also highlighted the association of vitamin D insufficiency with statin-induced myalgia, demonstrating successful re-introduction of statin therapy in a subgroup of patients following appropriate repletion of vitamin D levels. Literature also reports that insufficient cytochrome P450 (CYP) enzyme activity related to vitamin D deficiency may be responsible for inactivity and increased toxicity of CYP-metabolized statins in some patients, leading to the need for possible statin dose adjustments.\textsuperscript{11}

Reviewing the data from my own six-month pilot study (Figure 1), I found that 106 (70\%) of 151 lipid patients had vitamin D levels assessed as part of their initial workup. Of these patients, 47 (44\%) had vitamin D levels of less than 30 ng/dl. The number of vitamin D-insufficient patients intolerant to statins was 28 (59\%). Most notably, the number of vitamin D-deficient and -intolerant patients who — after achieving normal vitamin D levels with supplementation — were able to tolerate the re-challenge of a statin for at least six months was 18 (64\%).

The data are certainly evolving related to vitamin D deficiency and its relationship to CVD risk as a whole. Vitamin D deficiency potentially is associated with hypertension, diabetes and the metabolic syndrome, left ventricular hypertrophy, congestive heart failure and chronic vascular inflammation.\textsuperscript{12,13} In a recent meta-analysis of 18 randomized controlled trials of 57,000 subjects, a vitamin D intake of > 500 IU/day was associated with lower all-cause mortality, in part by association with fewer CV deaths.\textsuperscript{14}

This information, along with the small non-blinded studies and anecdotal observations that repletion of 25 (OH)D levels predictably improves or resolves statin-related myalgia, certainly warrants a further look at how we treat our lipid patients who are already at increased CVD risk. Statins are the cornerstone for the prevention and treatment of coronary heart disease. Strategies to improve tolerance of and compliance with these medications are essential; thus, supporting the suggestion that vitamin D may be an excellent option for this statin intolerant patients with inadequate Vitamin D, thus, supporting the suggestion that vitamin D may be an excellent option for statin intolerant patients with inadequate vitamin D.

Disclosure statement: Debra Friedrich has received honoraria from Amarin Corporation.

References are listed on page 31.
Our patient is a 67-year-old African American female referred to the Duke Lipid Clinic for hypercholesterolemia and elevated creatine kinase (CK). She has a history of coronary heart disease with a prior non ST-elevation myocardial infarction (NSTEMI) and stent placement. She has a former 40-packs-a-year smoking history, hypertension, lumbar degenerative disk disease and constipation. She had lower extremity muscle pain with atorvastatin with elevated CK in the low 300s (reference 20-200 U/L). Her mild CK elevation persisted when she was off of statin therapy. She was unable to tolerate a statin re-challenge with pravastatin because of lower extremity muscle cramping that started within a few weeks of beginning statin therapy and stopped after statin discontinuation. CK levels never rose above her baseline of 290-330 U/L on statin therapy. However, her quality of life was impaired to the point of being unable to perform her activities of daily living (ADLs). At her initial visit, when she was off all lipid medications, her lipid profile results were: total cholesterol 287 mg/dL, low-density lipoprotein cholesterol (LDL-C) 209 mg/dL, triglycerides 108 mg/dL; her high-density lipoprotein (HDL) was 56 mg/dL.

How common are statin-related muscle complaints?
There is little doubt that Statins are highly effective for cholesterol lowering. Clinical trials have demonstrated that they reduce the risk of ischemic heart disease events, coronary procedures and stroke by about one third. Clinical trials and experience have demonstrated that statin therapy is generally safe and well tolerated. However, muscle symptoms and associated myopathy can limit their use in clinical practice. While the incidence of severe myopathy is low, occurring in less than 0.1% of patients who receive statin therapy, mild to moderate muscular symptoms are quite common. The Prediction of Muscular Risk in Observational conditions (PRIMO) study, a large observational study of primary care patients on high-dose statin therapy, demonstrated that 10.5% of study patients had mild to moderate muscular symptoms.

What are risk factors for muscular symptoms?
The PRIMO study highlights certain patient characteristics that are likely to be associated with muscle side effects from statin therapy. In PRIMO, the strongest
independent risk factor for muscular symptoms was a personal history of muscle pain with another lipid-lowering therapy (statins or fibrates). This prior history was associated with a 10-fold increase in the risk of muscular symptoms. Other significant, independent risk factors in the PRIMO study were unexplained cramps (odds ratio [OR] 4.14), a history of CK elevation (OR 2.04), a family history of muscular symptoms (OR 1.89) and hypothyroidism (OR 1.71). Treatment with statins for more than three months and concomitant antidepressant medication use were associated with a significantly lower prevalence of muscular symptoms (OR 0.28 and 0.51, respectively). Importantly, no greater prevalence was found amongst patients with impaired kidney function or older age. Patients with muscle symptoms were more physically active and the incidence of muscle pain increased with the level of physical activity.

Clinical features of statin-induced myalgia

Usual Statin-related muscular pains are proximal, symmetric muscle weaknesses and soreness. In the PRIMO study, pains were most commonly described as heaviness, stiffness or cramps. However, weakness, loss of strength during exertion and tendon-associated pain were also frequently reported. Symptoms were most commonly in the lower extremities; however, upper extremity, truncal and diffused pain also were also found. On physical exam, patients may have muscle tenderness and impairment in motor function, such as difficulty rising from a seated position or raising arms above the head. Most patients have no elevation — or only minor elevation — in serum CK.

How do you evaluate a patient with statin intolerance?

Our approach to patients with statin intolerance because of muscle side effects consists of a detailed history, physical exam, medicine reconciliation and focused laboratory evaluation. Our history focuses on the timing of muscle effects related to statin initiation or dose titration, unusual physical activity or concurrent illness, as well as historical features that would point to a secondary cause of muscle pain (hypothyroidism, vitamin D deficiency, and family history of autoimmune or neuromuscular disease, symptoms of systemic illness). Medication reconciliation particularly focuses on drugs that inhibit cytochrome P450 3A4, fibrate therapy, drugs independently considered a risk factor for myopathy (i.e. glucocorticoids, cyclosporine, daptomycin, zidovudine) and diet history (daily consumption of grapefruit juice). During physical examination, we look for signs of systemic illness or inflammatory myositis (rash, joint effusions, fever, muscle redness or edema) as well as muscle weakness and pain. In a younger person, the ability to do six deep knee bends without using arms and hands to assist the legs is reassuring that proximal motor weakness is absent; in an older person, the ability to rise from a chair without using arms and hands is reassuring. A standard laboratory workup includes renal and liver function tests, and measurement of CK and thyroid-stimulating hormone (TSH). Based on the history and physical examination, serum calcium, albumin, phosphorus, 25-hydroxyvitamin D, CBC, erythrocyte sedimentation rate (ESR), autoantibodies (such as antinuclear antibodies [ANA] for suspected lupus, rheumatoid factor [RF] for suspected rheumatoid arthritis, etc.), electromyogram or possibly muscle biopsy may be obtained.

Let’s get back to our patient. At her initial appointment, off statin therapy for several months, she had intermittent, chronic low back pain. She denied systemic complaints other than severe constipation. She rode a stationary bike for 30 minutes three times weekly without difficulty. She ate a low-fat, low-glycemic-index diet. Her medications consisted of Tylenol, tramadol, aspirin, carvedilol, lisinopril and a bowel regimen. Her blood pressure was 133/58, her body mass index (BMI) was 27 kg/m² and her physical examination was within normal limits, including the ability to rise from a chair without using her arms. There was no other muscle weakness or pain. Her basic metabolic profile, albumin, phosphorus, liver function and TSH were all within normal limits. She had an erythrocyte sedimentation rate (ESR) of 22 mm/h and CK 305 U/L off of statin therapy.

Rosuvastatin 2.5 mg twice weekly was prescribed but, within three weeks, she developed crampy lower-extremity pain and weakness that made it difficult for her to walk up the stairs in her home and take care of her other ADLs. Symptoms resolved several weeks after discontinuing rosuvastatin.

Based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), our patient’s LDL-C goal is less than 100 mg/dL. Given her intolerance of low-dose pravastatin and even low-dose rosuvastatin twice weekly with symptoms that interfered with her ability to carry out ADLs, she was felt to be statin intolerant. Other medication possibilities include fibrates, bile acid sequestrants, niacin and cholesterol absorption inhibitors. Given her severe constipation, bile acid sequestrants were not an option. She was counseled on therapeutic lifestyle changes and started on ezetimibe 10 mg daily with immediate-release niacin titrated up to 1,000 mg twice daily. A mortality benefit from niacin was suggested from the follow-up of the Coronary Drug Project which demonstrated an 11% decrease in mortality in patients who received niacin after a myocardial infarction. Ezetimibe has been demonstrated to reduce LDL-C by 25% when added to niacin therapy.
Over a period of about nine months, our patient lost weight, reaching a BMI of 25 kg/m² and increasing her exercise to an hour five times weekly. She tolerated her medications and had no medical event. She recently had the following lipid profile: total cholesterol, 198; LDL-C, 102; HDL-C, 89; triglyceride, 36 mg/dL. The decrement in her LDL-C is surprisingly large for niacin-ezetimibe combination therapy; however, individual patient responses are variable. During a period of active weight loss, LDL-C can drop transiently for several months, and we warned her that long-term results may not sustained at this level. She is not at her NCEP ATP III goal; nevertheless, she has had vast improvement and, for the next six months, we will continue current medications. We suggest that adding psyllium to her bowel regimen may reduce LDL-C further. Disclosure statement: Dr. Greyshock has no disclosures to report. Dr. Guyton has received consulting fees from Merck & Co. Inc. and research grants from Merck & Co. Inc., Abbott Laboratories, GlaxoSmithKline, Amarin Corporation, Regeneron Pharmaceuticals, Inc., Amgen Inc., and Genzyme Corporation, A Sanofi Company. He is a stockholder in Eli Lilly and Company. References are listed on page 31.
Member Spotlight:
Barbara S. Wiggins, PharmD

For Barbara Wiggins, PharmD, a typical work day involves working up patients, managing medication reconciliation, verifying doses, compliance, and completing rounds as a member of an interdisciplinary health care team. Her spare time is divided into providing input on patient management, counseling and teaching.

Before she became a clinical pharmacy specialist in cardiology, Dr. Wiggins had deferred going into clinical practice and served in the United States Navy for 6 years. She then continued her education by obtaining her PharmD, and made the transition to clinical practice. She enjoys all aspects of patient care.

Dr. Wiggins first became interested in Clinical Lipidology through a colleague who invited her to get involved with the National Lipid Association where she participated in the naming and development of what is now known as the ACCL.

“I think it is easy to just think of lipidology in terms of HDL, LDL, triglycerides, etc.,” Dr. Wiggins said, “through my involvement with the NLA and the ACCL, I have acquired a greater depth of knowledge regarding the various aspects of lipid management that I incorporate into my everyday practice.”

She has gradually become more involved with the NLA, starting first with involvement with the ACCL and then moving on to serve on the NLA and Southeast Lipid Association (SELA) boards.

In the future, Dr. Wiggins would like to see lipid management focus on methods to increase medication compliance, particularly with statin therapy, and she would also like to someday see a breakthrough on HDL-raising agents that show reduced cardiovascular outcomes.

Outside of the office, Dr. Wiggins likes to spend time with her husband, her three children, three dogs, and loves running. Something surprising that most people don’t know about Dr. Wiggins is that she is a former professional runner who

competed in the Olympic trials in the marathon, and was at one time nationally ranked for the 5 and 10 kilometer distances. She continues to race and is looking forward to running in the U.S. Army 10-miler in Washington, D.C., this October. ■
Save the Date! NLA Clinical Lipid Update in Maui: March 13-16, 2014

Save the date for breathtaking Maui! The NLA’s Spring CLU is scheduled for March 13-16, 2014 at the Grand Wailea Hotel in Maui, HI. Be there as world renowned thought leaders discuss lipid management and metabolic syndrome in various populations from around the world. Other sessions include HDL analytics & functionality and cardiovascular risk in Asians in Pacific Islanders. You can earn 18.5 CME/CE credits for attending. Please check www.lipid.org/springclu for the latest details.

Adherence Toolkit Available

This issue of Lipid Spin includes a supplemental Clinician’s Toolkit: A Guide to Medication and Lifestyle Adherence. The goals of the toolkit are to define adherence and the various types of non-adherence, identify common barriers to adherence and predictors of non-adherence, describe the role of all health care professionals in the identification and management of non-adherence, summarize current methods used to assess adherence and review evidence-based, innovative strategies to improve adherence. Access this toolkit online and let us know how it has helped you in your practice: www.lipid.org/practicetools/tools/adherence.

New Patient Registry Available for Patients with High Triglycerides

As a professional organization, the National Lipid Association’s mission has been to reduce the morbidity and mortality from cardiovascular disease by increasing the understanding of the pathophysiology, and detection and optimal treatment of lipid disorders. Developing patient registries is crucial to this mission by pooling patient data concerning more rare dyslipidemias so that epidemiologic and/or clinical research can be more focused. Your participation in this specific patient registry will assist researchers in the planning of clinical trials that will assess the efficacy of new therapies. The NLA and the Foundation of the NLA are pleased to announce the formation of this new registry specific patients with hypertriglyceridemia. For information on the registry and how to get patients added, go to www.connect.patientcrossroads.org/?org=fnl.

Introducing the Clinical Lipidology Resource Center

The Clinical Lipidology Resource Center is now available. This resource center aims to support lipidologists and other health care professionals through its expert provision of peer-reviewed, evidence-based educational content from the Journal of Clinical Lipidology and the National Lipid Association. You can access the resource center directly from the NLA website or by visiting this link: www.nlaresourcecenter.lipidjournal.com

Abstracts now Invited for NLA Annual Scientific Sessions May 1-4, 2014

The National Lipid Association is now accepting abstracts from the Scientific Sessions in Orlando, FL May 1 – 4, 2014. This is your opportunity to submit your science for inclusion in the NLA’s 2014 Poster Hall. Visit lipid.org/abstracts to submit. The NLA Poster Hall will cover a vast array of topics in 16 categories, including clinical applications of biomarkers, epidemiology of cardiovascular disease, management of statin intolerance, and imaging in atherosclerosis. Submit your abstract using the online abstract submission system. All accepted poster abstracts will also be published in the 2014 Annual Scientific Sessions edition of the Journal of Clinical Lipidology.

Thank you Dr. Swartz

The Lipid Spin co-editors wish to thank ToniMarie Swartz, PharmD, for her work supplying keywords so each issue of Lipid Spin is conveniently accessible in the search function on www.lipid.org.

Pediatric Dyslipidemia Questionnaire

As a member of the NLA, your expertise and knowledge of dyslipidemia is a valued opinion for a pediatric dyslipidemia survey. Please follow the link to the questionnaire on the homepage of www.lipid.org. Your participation is voluntary and all responses are anonymous. Even though you may not screen or medically manage pediatric populations, but your participation is still valued.

Research Study Request from University of Pennsylvania

We are looking for patients with HDL-C levels consistent with a confirmed or suspected genetic cause (apoA-I, ABCA1, LCAT, CETP deficiency) interested in participating in a study assessing reverse cholesterol transport using a radiotracer technique developed by our team at the University of Pennsylvania. Subjects are required to have one overnight stay in our research unit. Travel and lodging costs are covered. If you are interested in receiving more information, please contact Marina Cuchel, MD, PhD at 215-746-2834; mcuchel@mail.med.upenn.edu.
September is National Cholesterol Education Month. In recognition of this, the Foundation of the NLA has supported an important campaign called “ARE YOU THE ONE?” To help call attention to familial hypercholesterolemia (FH), the Foundation has provided two copies of a poster and handout to all NLA members and more than 40,000 members of the American Academy of Family Physicians. This campaign furthers one of our priorities: to educate clinicians—especially primary care providers—on FH and other cholesterol disorders to facilitate proper diagnosis and treatment of patients.

Additional FH awareness efforts for National Cholesterol Education Month include a series of FH-themed broadcasts on ReachMD, an FH content area on the newly created Clinical Lipidology Resource Center (http://nlaresourcecenter), FH specialist member highlights on lipid.org, and public relations outreach to local and regional media affiliates.

Other Foundation highlights include:

- Hosting a food tour in the historic Fell’s Point Neighborhood of Baltimore at our Fall Clinical Lipid Update in Baltimore, MD. Thank you to everyone who supported the Foundation of the NLA through this event. Please stay tuned for more information about the Foundation event in Maui, which will be inspired by the traditional luau, perfect for our Pacific location during this meeting!

- Lifetime Membership has been a successful membership campaign and it is not over yet! Remind your colleagues that Lifetime Membership to the NLA is only available through December 2013. To show your support, please visit lipid.org/membership/lifemember and register today!

- Foundation members assisted with a patient survey to launch a new registry for patients with high triglycerides. Go to http://connect.patientcrossroads.org/?org=fnla for more information on the registry.

As always, we are extremely grateful for your support of the Foundation!

Two new patient registries:
- Hypertriglyceridermia patient registry, visit: http://connect.patientcrossroads.org/?org=fnla
- Familial Hypercholesterolemia patient registry, visit: www.thefhfoundation.org
19. 2010;375:735-742

EBM Tools for Practice
Participants From 135 Randomized Controlled Trials. Circulation Cardiovascular quality and outcomes 2013.


Events Calendar

2013 Scientific Meeting
American Heart Association
Scientific Sessions 2013
November 16–20, 2013
Dallas, Texas

2014 Scientific Meetings
2014 National Lipid Association
Clinical Lipid Update—Spring
Hosted by the Pacific Lipid Association and the Southwest Lipid Association
March 13–16, 2014
Grand Wailea Hotel
Maui, Hawaii

2014 National Lipid Association
Scientific Sessions
Hosted by the Southeast Lipid Association
May 1–4, 2014
Hyatt Regency Grand Cypress Hotel
Orlando, Florida

2014 National Lipid Association
Clinical Lipid Update—Fall
Hosted by the Midwest Lipid Association and the Northeast Lipid Association
August 22–24, 2014
JW Marriott Hotel
Indianapolis, Indiana
Strategies to Deal with Muscle-Related Statin Intolerance

1. **Switch statins**
   - if muscle symptoms developed on a lipophyllic statin, switch to a hydrophyllic one (see hydrophyllic vs. lipophyllic listing below)
   - if muscle symptoms developed on CYP3A4 metabolized statin, switch to one metabolized by a different pathway (see metabolic pathways in table below)
   - if muscle symptoms developed on a long half-life statin, switch to a short half-life statin and vice versa (see half lives in table below)
   - if statin therapy is thought to objectively and consistently interfere with exercise tolerance (e.g., compromised exercise capacity, extended recovery and/or muscle pain) consider another statin with different pharmacokinetics

2. **Use a statin at a dose and/or frequency that is below the FDA approved lowest dose**
   - try half of the lowest FDA approved dose every day and then consider every other day or 2 to 3 times a week

3. **Consider checking for 25 (OH) vitamin D deficiency**
   - if the level is less than 30 ng/ml, hold the statin until vitamin D has been replaced to greater than 30 ng/ml, then rechallenge

   **Replacement Protocol #1:**
   - 50,000 IUs of prescription vitamin D2 qweek for 8 weeks, then recheck the 25(OH) vitamin D level
   - repeat as needed until 25(OH) vitamin D is greater than 30 ng/ml
   - then switch to over-the-counter vitamin D3 at 2000 IUs daily

   **Replacement Protocol #2:**
   - 5000 IUs of vitamin D3 for 8 weeks, then recheck the 25(OH) vitamin D level
   - repeat as needed until 25(OH) vitamin D is greater than 30 ng/ml
   - then switch to vitamin D2 at 2000 IUs daily

4. **Consider supplement with 200 mg of CoQ10 daily, although randomized trials haven’t been uniformly supportive**

5. **Lower the LDL to goal using a non-statin treatment regimen**
   - especially in patients with the SLCO1B1 Val/Ala or Ala/Ala variations

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**Definitions:**

**Myalgias:** muscle pain without an increase in CPK levels or with an increase that is less than 10 times the upper limit of normal

**Myositis/myopathy:** muscle pain with a CPK increase equal to or greater than 10 times the upper limit of normal

**Rhabdomyolysis:** myopathy (as defined above) with renal compromise (i.e. increase in serum creatinine)

**Hydrophyllic statin:** a statin that is primarily soluble in water (i.e. the oil/water separation coefficient is less than 1.0). Includes: pravastatin, rosuvastatin and fluvastatin

**Lipophyllic statin:** a statin that is primarily soluble in oil (i.e. the oil/water separation coefficient is greater than 1.0). Includes: simvastatin, atorvastatin, and pitavastatin

**SLCO1B1 174 Ala variant – single nucleotide polymorphism associated with statin induced muscle side effects**

**Cytochrome p450 3A4 (CYP3A4); primary mode of metabolism of lovastatin, simvastatin and atorvastatin**

**Organic Anion Transport Polypeptide 1B1 (OATP1B1):** the main transporter responsible for extracting all statins from the portal circulation into the hepatocyte. Many of muscle statin side effects are related to the concomitant use of drugs that inhibit CYP3A4 and/or OATP1B1

**CYP3A4 inhibitors:** itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, cyclosporine, danazol, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine

**OATB1B1 inhibitors:** rifampin, clarithromycin, indinavir, ritonavir, cyclosporine, neflinavir, erythromycin, atazanir

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**Generic Name**

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(1) per FDA approved package labelling
(2) lists the primary mode of metabolism; most statins have alternate modes as well
(3) lists half life of the active drug, not metabolites

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- HDL Modification, Novel HDL Raising Therapies
- Hypertriglyceridemia
- Imaging in Atherosclerosis
- Lipid Management Best Practices
- Lipid Management in Special Populations
- Management of Statin Intolerance
- Nutrition, Nutrigenomics, Nutraceuticals and Exercise Therapies
- Omega-3 Fatty Acids
- Pathophysiology of Atherosclerosis
- Pharmacological Control of Lipids and Lipoproteins
- Visceral Obesity, Metabolic Syndrome and Atherosclerosis