Diagnosis and Genetic Variance in Familial Hypercholesterolemia

Also in this issue:
Diabetes Optimal Care and Cardiovascular Risk Reduction (DOC-CARE)
Pediatric FH Guidelines for the Adult Lipidologist

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From the NLA President:
Momentum and Milestones

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Over the past several months, the NLA has made significant progress on a number of initiatives that reflect our commitment to advancing the science and practice of Clinical Lipidology. These initiatives also reflect the NLA’s ambitions to see advances in our field manifest in new and innovative ways.

This year, we opened the inaugural enrollment period for the Lifetime Membership program, which will ensure continuous membership in the association while helping to establish the first dedicated training programs in lipidology. In addition to supporting the development of young professionals in lipidology, the establishment of a fellowship program is a crucial component of our long-term efforts toward subspecialty recognition.

A limited-time offer, Lifetime Membership enrollment is available now through December 2013 for a one-time payment that includes a generous $1,000 donation to the Foundation’s dedicated fund for training programs. Lifetime Membership is an area in which we can make a distinctive and important contribution. I ask that you review the program details and strongly consider signing up at lipid.org/lifemember to play a role in creating a legacy for lipidology.

This past year was also an important one for building on the specialized knowledge and practice of pediatric lipidology. NLA members Donnie Wilson, MD, Catherine McNeal, MD, PhD, Piers Blackett, MD, and Stephen Daniels, MD, PhD, have helped us look at pediatric dyslipidemia and cardiovascular risk factors in childhood. The initial output of their work includes a presentation by Dr. McNeal at the NLA Board meeting in November, as well as the recent Roundtable on pediatric screening featuring Dr. McNeal along with Sam Gidding, MD, and W. Virgil Brown, MD, which will be published in the *Journal of Clinical Lipidology* this spring. The Pediatric Section will constitute a new and important group for the NLA. We will also add a lecture on pediatric dyslipidemia to the NLA Masters in Lipidology course.

There are many other important topics that also engender discussion. NLA expert panels have been convened to develop consensus statements on adiposity, statin safety, and a comprehensive review of HDL. We look forward to publishing these statements in the *Journal of Clinical Lipidology* in 2013.

Looking ahead, we continue to plan for the association in the short- and long-run. Considerable effort has been devoted to preparing for our biannual strategic planning session, to be held this February in Miami Beach. We look forward to sharing the 2013-2015 strategic plan with you once it is finalized and approved this May.

Robert Wild, MD, PhD, and Carl Orringer, MD, are working with a number of members to update the lipidology core curriculum. Numerous NLA members are working closely with the ABCL in an effort to achieve subspecialty recognition for Clinical Lipidology.

I hope these endeavors will encourage you to remain engaged with the NLA as we continue to build on the field in ways that make a positive impact on the way lipidology is practiced throughout the world. ■
From the MWLA President: Making an Impact

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I am very grateful for the opportunity to be President of the Midwest Chapter of the National Lipid Association. During this year, the Midwest Chapter made a commitment to support the activities of both the NLA and the Foundation of the NLA. Because of that commitment, we have chosen topics for the Lipid Spin that align with the great work of the Foundation and address the timely topic of familial hypercholesterolemia. This common disorder is frequently undiagnosed, and therefore appropriate family screening is not undertaken, putting many young individuals at risk for premature heart disease. This issue of the Lipid Spin has been authored by several members of the Midwest Chapter, and I think you will find the articles enlightening and helpful to your practice. I am extremely grateful to all of the authors for their commitment to the NLA as well as their high quality submissions for articles in the Lipid Spin.

We are striving to have many other local practitioners who are interested in Clinical Lipidology enhance their professional satisfaction and experience by encouraging them to become members of the Midwest Chapter. I would like to express my sincere gratitude to James Underberg, MD, and Robert Wild, MD, PhD, for the immense amount of time and effort they put into reviewing all of the submissions for the Lipid Spin to make sure that the articles are appropriate and scientifically correct.

I would like to take this opportunity to discuss a couple of other initiatives beyond the Lipid Spin that hopefully will be completed this year through the Midwest Chapter. The first is an idea that was brought forth by Carl Orringer, MD, who suggested a quarterly newsletter that could be sent to referring physicians by members of our organization. The newsletter would be an update or a review of a recent trial or lipid topic, which would be sent out by chapter members to their referring physicians. The newsletter would serve to educate and to increase visibility for members of the NLA to their referring doctors. This will establish the expertise of NLA members within their local communities in addition to disseminating important information that will translate into better patient care. We are very excited about this initiative and appreciate Dr. Orringer’s input regarding authorship and distribution. Secondly, in order to enhance our membership, reward those who have worked hard within the chapter, and support the Foundation, we are planning to have our first annual awards evening in Spring 2013. This event will be open to all members of the NLA and will include dinner on the Odyssey cruise ship on Lake Michigan. We expect this to be a very enjoyable event that will allow our colleagues to mingle as well as to generate contributions to the Foundation. It will also allow us to recognize those members of the chapter who have committed a great deal of time to the NLA but may not have received the recognition they so greatly deserve. We would like to invite all members of the NLA to join us for this fun evening, and further details on the exact date of the Odyssey cruise will be forthcoming. I am grateful, again, for the privilege of being President of the Midwest Chapter during this year, and I look forward with great anticipation to our upcoming meeting in New Orleans in February 2013.
Editor’s Corner: A Time to Reflect

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With the end of the Thanksgiving weekend, I must reflect on recent events in New York City, and the impact they had on our medical infrastructure. I was finally filling my car up with gasoline and in front of me was a large pickup truck filling up a huge tank of gas. I asked what it was for and was told “fuel” for hospital generators in Staten Island, New York, that are still without electricity. It reminded me that while much in New York City has returned to normal, much has not. Hospitals and physician practices have been impacted all throughout our tri-state area of New York, New Jersey and Connecticut, in areas that many of our NELA members call home.

On a more personal basis, Superstorm Sandy has shut down our three hospitals for the foreseeable future. The New York University, Bellevue, and Manhattan VA facilities sit empty for the first time. While outpatient facilities at NYU and Bellevue are slowly restoring, my colleagues at the VA have been sent to other facilities in the Bronx and Brooklyn. Our surgeons are at many different sites around New York, and our emergency room and medical services remain shut. Patients have been directed to other institutions; however they often prefer closer facilities rather than our alternative offerings. While many of our full-time faculty have simply been relocated, others, both part-time and voluntary, have not been as fortunate. The other day, on the way to our weekly journal club, I ran into a good friend and nephrologist, who reminded me that most of his income is generated in the hospital. With no hospital at which to see patients, he was worried about what the next few months would bring.

The research costs have also been numerous. Loss of animal models, samples and facilities was countless. Time will restore some, but not all, of these losses, and the concern about funding withdrawal lingers for many. Despite this, our spirit remains strong. NYU has a tradition of rising above disaster, and the community is strong. Many of us trained here, and while the administration has changed, the direction and leadership of our dean has been wonderful. The shadow of Saul Farber looms large, and he would—I am sure—tell us all to push forward, as we plan to do.

Three days before the holiday weekend our lipid clinic reopened at Bellevue. With the opening of our outpatient radiology facilities this week, much is returning to normal for some. For others, it will be a long process. The personal calls, e-mails and concern voiced by friends and colleagues were numerous and sincere. We thank you all. We will persevere. I am proud to have trained here and to be part of a wonderful institution that will rebuild and continue its tradition of excellence. ■

Discuss this article at www.lipid.org/lipidspin

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The 1985 Nobel Prize in Physiology for Medicine was awarded to two physicians from Southwestern Medical Center in Dallas, Texas. Michael Brown, MD, and Joseph Goldstein, MD, received this honor “for their discoveries concerning the regulation of cholesterol metabolism.”

They postulated that regulatory abnormalities of 3-hydroxy 3-methylglutaryl coenzyme A reductase were the cause of familial hypercholesterolemia (FH). This disorder had been known for many years, given the known clustering of tendon xanthomas (TX), vascular atheromas and premature onset of coronary artery disease. Many other individuals including Frederickson and Levy in the 1960’s advanced the concept that FH involves the apoprotein and cholesterol components of LDL. Goldstein and Brown discovered the hepatic cell surface LDL receptor (LDLR) and later demonstrated that FH was due to mutations in gene coding.

FH is a co-dominantly inherited disorder of lipid metabolism characterized by a defective allele (or alleles) in the gene coding for LDLR. It is highly penetrant and has a gene dosage effect (i.e., homozygotes are affected to a greater extent than heterozygotes). This results in dysfunction or structural abnormalities of the LDLR which reduce the catabolism of LDL particles and increase LDL plasma concentration.

The LDLR gene resides on the short arm of chromosome 19 and is comprised of 18 exons, spanning 45 kb. The gene codes for an 839 amino acid single chain glycoprotein which binds LDL particles and allows their delivery to the lysosomes for degradation.

Five classes of mutations have been identified, ranging from null alleles which fail to produce the protein, to defects which uniquely block multiple steps in the process of transport, binding and recycling. When LDLR is abnormal, the removal rate of LDL-C declines, and the plasma level increases. Excess LDL is deposited in scavenger cells and forms TX and atheromas. There are more than 1,600 mutations of LDLR known to cause FH.

The prevalence of FH is well-defined: it is one of the most common genetic disorders. Heterozygotes number about 1:500 persons in the general population, increasing to 1:50 when a founder effect is present, such as in French Canadian, Finnish, Christian Lebanese and South African populations.

The disease provides a model system for other treatable genetic disorders, especially given the clinical consequences of premature myocardial infarction. Of concern is that an estimated 80% of FH in Western countries remains undetected, in spite of advancing knowledge of the disease. This is undoubtedly influenced by the substantial variability in the phenotypes associated with FH.

Mean LDL-C concentration at all ages in heterozygotes is 2-3x that of normal subjects. That number is doubled or tripled in homozygotes. Minor structural alterations in some particles result in a decreased triglyceride (TG) content, and an increase in the cholesterol:phospholipid ratio.
ratio. However, when LDL from an FH homozygote is injected into a normal subject, the LDL is normally metabolized, suggesting that the structural variances are not clinically significant. HDL-C levels in FH patients are slightly lower than in normals, and TG levels are also lower or similar depending on environmental factors.\(^2\)

FH has traditionally been diagnosed when elevated plasma TC and LDL-C is combined with family or individual history of premature heart disease. Two sets of criteria logically are used in screening for this disease given a known bimodal probability distribution of LDL-C: one for the general population and one for subjects in whom a 1\(^{st}\) or 2\(^{nd}\) degree relative is known. Using LDL-C alone as a criterion therefore is prone to underdiagnosis.\(^{10,14,15}\)

The “gold standard” for unequivocal diagnosis is DNA testing for genetically identified mutations, although the Dutch Lipid Clinic Network requires one additional clinical criterion. There is relatively weak concordance between phenotype and genotype. Testing for the genetic defect is a complex, expensive process with limited availability. Careful choice of appropriate candidates is advisable.\(^2,11\)

A widely used genetic diagnostic platform in Europe and the U.S., includes a microarray for the detection of common point mutations and small deletions in LDLR and apolipoprotein B (ApoB) genes. If this is negative, then full LDLR coding sequence analysis is done to diagnose large rearrangements by quantitative fluorescence based multiplex polymerase chain reaction analysis. The presence of new disease causing mutations is ascertained by sequencing the promoter region of the 18 exons and flanking intronic regions of the LDLR.\(^18\)

### Worldwide, there are three diagnostic tools for FH:\(^15\)

1) Simon Broome Register Group (SBRG) in the UK
   a. Results are classified as “definite” or “possible”:
      i. TC(LDL) >290(>190) in the index patient or 1\(^{st}\)2\(^{nd}\) degree relative + TX is considered definite FH
      ii. Above criteria + family history myocardial infarction or TC>290 is considered possible FH

2) Make Early Diagnosis Prevent Early Death (MEDPED) in the U.S.
   a. Utilizes age-related cutoffs for TC (LDL) which are further delineated by whether results pertain to general population or to patient with 1\(^{st}\), 2\(^{nd}\) or 3\(^{rd}\) relative with FH
      i. <20 yrs age TC(LDL) 270 (200)mg/dL; 20-29 yrs 290(220); 30-39 yrs 340(240); >40 yrs 360 (260)
      ii. Lowered strata in the setting of positive family history

3) Dutch Lipid Clinic Network (DLCN)
   a. Definite, probable, or possible categories
   b. Score derived from family history of LDL>95\(^{th}\) percentile; family history premature vascular disease; 1\(^{st}\) degree relative with TX or arcus cornealis (AC); LDL >95\(^{th}\) percentile in child <18 yrs age; TX or AC present at <45 yrs; elevated LDL-C; positive DNA testing for LDLR
   c. >8 points is definite; 6-8 points probable; 3-5 points possible\(^17\)

The clinical utility of DNA testing has been validated in many Western populations. Generally speaking, approximately 55% of patients over 14 years of age with a clinical suspicion of FH evaluated with genetic testing were found to have functional mutations in LDLR or ApoB gene loci.\(^19\)

Among those patients the presence of TX either in the proband, or a 1\(^{st}\) or 2\(^{nd}\) degree relative was strongly correlated with identification of a genetic abnormality. This appears to be the most significant predictor of molecular defect when coupled with LDL-C >190 mg/dL.

Mutation positive patients were more often female with higher levels of TC and LDLr, and lower TG.

HDL and high levels of Lp(a) appear to be less predictive of identifiable mutations. In the 45% of patients in whom mutations were not identified, the prevalence of type 2 diabetes mellitus and body mass index was higher.

Using a set of criteria which included LDL>190 mg/dL (with family history, or >220 mg/dL without), combined with TX created a significant correlation (p < 0.0001) with the presence of molecular defects. With these criteria, 9/10 subjects with LDLR or ApoB mutations will be detected. Using the same criteria, when TX were either absent or unknown, the frequency of the FH mutation carrier decreased to 46%, but retained acceptable statistical sensitivity and specificity.\(^12,19\)

Conclusions can be drawn from the above discussion.

1) TX are highly specific for FH in the setting of elevated TC and/or premature coronary artery disease in the family. They should be carefully looked for on physical examination, including the use of tools such as x-ray or ultrasound of the Achilles tendon.
2) MEDPED has emerged as the most
utilitarian diagnostic tool with its simplicity and good accuracy. When patients or family members do not have TX, the use of age adjusted LDL cutoffs is very important diagnostically.

3) Utilizing the approach outlined maximizes the likelihood of genetic confirmation of molecular defects. This can be used to facilitate genetic counsel, and cascade screening. The detection of a mutation also reinforces adherence to diet and drug therapy.

Phenotypically, FH is also known to be caused by mutations in ApoB, gain of function mutations involving paraprotein convertase subtilin/kexin 9 (PCSK9) and several other rare inherited disorders. Study of PCSK9 also represents promising therapeutic opportunities.5,6,20

Familial defective ApoB 100 (FDB) and classic FH are often clinically indistinguishable. ApoB is a non-exchangeable lipoprotein, containing over 4,500 amino acids, which is required for the synthesis of TG-rich lipoproteins in the liver (VLDL) and intestine (chylomicrons). All atherogenic lipoproteins contain ApoB as key architectural component.21

The ApoB gene is located on chromosome 2 and contains 29 exons and 28 introns. ApoB is the ligand required for clearance of LDL-C by the LDLR. It was identified during study of patients with normal LDLR function, who exhibited delayed clearance of LDL.

FDB (aka FLDB—familial ligand defective ApoB), also inherited in an autosomal dominant fashion, is characterized by elevated TC and LDL-C, premature heart disease and frequently with TX. At least four mutations are known, the most prevalent of which is an arginine/glutamine substitution resulting from a missense mutation at the 3500 codon. Often the levels of LDL-C are not as high as in heterozygous FH, and this is one feature which reduces the utility of the MEDPED criteria for diagnosis. In these patients the remnant lipoproteins which depend on ApoE rather than ApoB are still cleared appropriately, or even to a greater extent than in normals which may account for the lower level of LDL-C.22,23

FH has traditionally been diagnosed when elevated plasma TC and LDL-C is combined with family or individual history of premature heart disease.

Finally, the FH phenotype formerly known as Autosomal Dominant FH3 was mapped in France in 1999. Kindred have since been identified in Utah, Sardinia, and Spain. This gene is located on the short arm of chromosome 1 and codes for PCSK9. Several mutations have been discovered. Patients are often clinically indistinguishable from FH although typically LDL is lower, and there is greater responsiveness to statin therapy.

PCSK9 activity correlates with LDLR activity, possibly in a modulatory fashion, and promotes LDLR degradation. Hence, inhibition of PCSK9 increases the clearance of LDL particles, because the LDLR density and activity is enhanced and potentiates statin activity.2,3

Phenotypic variation in FH may also be modulated by ApoE polymorphisms, and variable alleles of this apoprotein (E2,E3, orE4) may have different penetrance in FH subjects versus normal.24,25 Gene-gene and gene-environment interactions play a prominent role in phenotypic expression of the disease.

Clinicians are also often called upon to differentiate between FH and familial combined hyperlipidemia. Clinical tips are easily accessible in the literature to assist with this challenge.14,16

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

References listed on page 31.
According to the 2011 National Diabetes fact sheet, 25.8 million adults and children in the United States (8.3%) have diabetes and 79 million have pre-diabetes. In 2010 alone, 1.9 million new cases of diabetes were diagnosed. In 2007, the total cost of diagnosed diabetes was $174 billion and contributed to more than 231,000 deaths in the U.S.\(^1\)

**Diabetes Means Cardiovascular Disease and More**

Diabetes mellitus (DM) leads to two-four times greater risk for stroke and CVD deaths. Two-thirds of them have hypertension (blood pressure >140/90 or taking medications). It is the leading cause of new cases of blindness; 28.5% (4.2 million) had retinopathy.

DM is the leading cause of kidney failure, accounting for 44% of new cases in 2008.

Sixty to seventy percent of people with diabetes have some form of neuropathy. Sixty percent of non-traumatic lower limb amputations occur in people with diabetes.\(^1\)

How can we tackle this problem? We are in the 21\(^{st}\) Century with EHR (electronic health records) at our fingertips. What works the best? What evidence do we have? How do we approach it? In a recent *Annals of Internal Medicine* article, the authors concluded that the use of a commercially available certified EHR was associated with improved drug treatment intensification, monitoring, and significant improvements in A1C and LDL cholesterol. Greater improvements were seen among patients with worse control of HbA1C (> 9%) and LDL (> 130).\(^2\)

A multifactorial approach to diabetes care that includes an emphasis on blood pressure, lipids, glucose, aspirin use and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains.\(^1,3-6\) The benefits of a multifactorial approach to diabetes care are supported by the results of the Steno 2 Study of 160 patients with type 2 diabetes and microalbuminuria. Multifactorial interventions achieved a 50% reduction in mortality and significant reduction in microvascular complications five years after the end of a 7.8-year study. Multifactorial intervention achieved A1c of 7.8%, LDL of 83 mg/dL, and blood pressure of 131/73, compared to a conventional group that achieved A1c 9%, LDL 126 mg/dL and blood pressure 146/78.\(^5\)

In Minnesota, Community Health Measures report D5 scores of participating clinics (“D5”= A1C <8, LDL <100, blood pressure <140/90, aspirin use, non-use of tobacco). Reaching all five goals (D5) greatly reduces a patient’s risk for the microvascular and cardiovascular problems associated with diabetes.\(^7\)

Optimal glycemic control, blood pressure, aspirin use and management of diabetic dyslipidemia are still evolving and moving targets.

**Glycemic Control**

A new position statement in October 2012 from European Association for the Study of Diabetes and American Diabetes Association...
Association for the treatment of type 2 diabetes takes an approach much more focused on the individual patient compared with the “one number fits all” target of glycated hemoglobin (HbA1c) used up to now. Diet, exercise and education are the foundation of the treatment program. Metformin is used as the optimal first line drug unless contraindicated. Lowering HbA1c to below or around 7% has been shown to reduce microvascular complications, and if implemented soon after the diagnosis of diabetes, is associated with a long term reduction in macrovascular disease. Therefore, a reasonable HbA1c goal for many non-pregnant adults is <7%. Less stringent A1c goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the lower goal is difficult to attain despite appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.1,3

**Diabetic Dyslipidemia**

Seventy to seventy-five percent of adult patients with diabetes die of macrovascular disease. They develop more atherosclerosis than patients without diabetes with the same quantitative lipoprotein profiles. For diabetic dyslipidemia, achieving an LDL goal of less than 100 alone is not optimal. More focus and attention towards shifting the atherogenic dyslipidemia of pattern B to pattern A, as well as aggressive reduction of LDL particle number or achieving optimal apoB levels, is ideal but not yet the standard of care, and performing these tests in every patient is not cost effective. A reasonable approach would be achieving both LDL and non-HDL goal for all diabetic patients along with the other four measures of D5. The beneficial effects of statins on cardiovascular risk reduction may go beyond their effects on lipid levels.1-3 TLC (therapeutic lifestyle changes) and effective doses of statins for all patients is a minimum. If patients cannot tolerate trials of multiple statins to achieve at least a 30-40% reduction of both LDL and non-HDL from baseline, one should individualize the choice of non-statin medications based on patients’ comorbidities and DDIs (drug-drug interactions).

High triglycerides and low HDL cholesterol levels are independent risk factors for cardiovascular disease in the patient with diabetes. Individuals with elevated triglycerides may achieve significant cardiovascular risk reduction with the use of fibrates8 or statins.9 Current evidence does not support the use of combination therapy with statins and other lipid-lowering drugs for most patients with type 2 diabetes. The combination of a statin plus ezetimibe versus statin monotherapy has not yet been shown to be advantageous.10

The ACCORD study showed no significant reduction in myocardial infarction, stroke or cardiovascular death with a fibrate-statin combination compared to statin monotherapy. However, a subgroup analysis suggested a possible benefit for men and women with both low HDL (< 34 mg/dL) and elevated triglycerides (> 204 mg/dL). In AIM-HIGH, niacin/statin combination therapy did not show benefit and was stopped early due to futility. Upcoming ATP IV guidelines, pending major clinical trials data, and new classes of drugs/novel therapies may influence future management of diabetic dyslipidemia.

**Blood Pressure Control**

In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2 diabetes it usually coexists with other cardiometabolic risk factors. There is no definitive evidence for any particular general blood pressure goal for patients with diabetes. Epidemiologic analyses have shown that blood pressures > 115/75 mmHg are associated with increased cardiovascular event rates and mortality in individuals with diabetes.13,14 RCT’s have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to < 140/80 mmHg in individuals with diabetes.13,15-17 The UKPDS, HOT, and ADVANCE trials compared more stringent versus less stringent blood pressure goals and showed reduced major cardiovascular events. However, none of these trials achieved average SBP below 130 mmHg (Table 1). The ACCORD trial found no difference in major cardiovascular outcomes between a more intensive blood pressure < 120 mmHg (achieved 119/69) compared to standard intervention targeting systolic blood pressure between 130 and 139 mmHg (achieved 133/70).

<table>
<thead>
<tr>
<th>UKPDS</th>
<th>HOT</th>
<th>ADVANCE</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>Control</td>
<td>DBP</td>
<td>Treat</td>
</tr>
<tr>
<td>Goal</td>
<td>&lt; 150/85</td>
<td>&lt; 180/105</td>
<td>&lt; = 80</td>
</tr>
<tr>
<td>Achieved</td>
<td>144/82</td>
<td>154/87</td>
<td>140/81</td>
</tr>
</tbody>
</table>

Table 1. Goal vs. mean achieved blood pressure in randomized controlled trials in people with type 2 diabetes.7 (Courtesy of the Institute for Clinical Systems Improvement.)
### Personalized Patient Centered Goals (D5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Current</th>
<th>3 Months Ago</th>
<th>6 Months Ago</th>
<th>9 Months Ago</th>
<th>12 Months Ago</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1C</strong></td>
<td>&lt; 8 or &lt;7 (uncomplicated DM)</td>
<td>patient-centered approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>&lt;70 (for very high risk) or &lt;100 (for all)</td>
<td>Non-HDL &lt;100 or &lt;130 very high risk or all respectively</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt;140/90 for all</td>
<td>&lt;130/80 may be optimal</td>
<td>Minimum is more than 12 mm of SBP reduction from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td>If Yes, Ask/Assess/Assist/Arrange</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aspirin Use</strong></td>
<td>Optional for primary prevention</td>
<td>Essential for secondary prevention if not contraindicated.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight/BMI/Waist Circumference</strong></td>
<td></td>
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</table>

- Diabetes lab protocol Q3-6 months A1c, FLP every year or more (point of care A1c, lipids will be helpful) BMP, LFTs, TSH, Vitamin D level, etc.
- Urine for microalbumin (if elevated, look for other causes, treat and repeat)
- Monofilament Foot Exam (SEMME-Weistein 5.07/10gms), Tuning fork 128-cps to assess vibration Q1 year
- Dilated Eye Exam Q1 year
- Dental Exam Yearly
- Diabetes Medical Nutrition by RD Q1 Year or More
- Diabetes Medical Education by Teaching Nurse Q1 Year or More
- Immunizations (Influenza, Hep B series, update Tdap, and Pneumovax)

Table 2. Created by Dr. Godishala.
Intensive blood pressure regimens were associated with a small reduction in the rate of stroke, greater medication use (3.4 vs 2.1) and more serious adverse events. A post hoc analysis of the INVEST (International Verapamil/Trandolapril) Study of blood pressure control (6,400 patients with diabetes and CAD) demonstrated that “tight control” (<130 mmHg) was not associated with improved cardiovascular outcomes compared with “usual care” (130–140 mmHg).18

SBP targets <130 or <140 mmHg may be appropriate for individual patients, based on response to therapy, medication tolerance, and individual characteristics. Based on pooled data from RCT’s, an average reduction of SBP by 12-13 mm Hg over four years was associated with 21% reduction in CHD, a 37% reduction in stroke, a 25% reduction in total cardiovascular mortality and a 13% reduction in all-cause mortality.19 Urinary albumin excretion should be tested annually and treated if abnormal. RAAS (ACE or ARB) blockers with or without diuretics or calcium channel blockers are appropriate first line agents if not contraindicated. JNC VII and ADA recommended a blood pressure goal of less than 130/80 in diabetics. Upcoming JNC VIII guidelines and future ADA&NKF guidelines may shed more light on targeting blood pressure goals for diabetic patients. For now, the goal for all diabetic patients is less than 140/90, with an optional goal of less than 130/80, with a minimum 12 mm of SBP reduction from baseline.

**Aspirin Use**

There is insufficient evidence to recommend for or against aspirin use in the primary prevention of cardiovascular events in patients with type 2 diabetes. There is sufficient evidence to support the use of aspirin for secondary prevention (i.e., EDTRS, HOT, HARP, et. al, and other systematic and narrative reviews by Sirois, et. al).1,3 In Steno-2 it was difficult to assess if aspirin use was beneficial. However, aspirin is no longer recommended for those at low CVD risk (women under age 60 years and men under age 50 years with no major CVD risk factors or a 10-year CVD risk <5%), as the benefit is likely to be outweighed by the risk of significant bleeding. Clinical judgment should be used for those at intermediate risk (10-year CVD risk of 5–10%) until further research is available.1,3 Recent trials of aspirin use in diabetes have shown less benefit than older trials (perhaps due to better background A1c, blood pressure, and LDL control and lower smoking rates in recent trials).3,11 There are significant limitations identified in all of these studies, and more definitive studies would be helpful.12 Therefore, based on current evidence, low-dose aspirin is considered optional for primary prevention.

**Smoking Cessation**

Tobacco cessation is very likely to be the single most beneficial intervention that is available. Ask, Advise, Assess and Arrange follow-up referral to special programs or pharmacotherapy. A meta-analysis of 20 prospective cohort studies demonstrated a 36% relative risk reduction in mortality for coronary heart disease patients among individuals who quit smoking as compared to those who continued to smoke.20 Much of the documented impact of smoking on health does not separately address patients with diabetes, but suggests that the benefits are at least equivalent to those found in the general population. **Tobacco telephone quit lines**: HHS National Quit line (1-800-QUITNOW) or 1-800-784-8669 connect to counseling and information about quitting smoking in your state.

Disclosures statement: Dr. Godishala has no disclosures to report.

References listed on page 31.
As an Internist who specialized in adult medicine, I had not seen many pediatric patients since my days in medical school. Now, however, as a Clinical Lipidologist, I have had the opportunity on a few occasions to evaluate a child or young adolescent with markedly elevated LDL cholesterol referred by pediatric and family medicine colleagues. Despite the increase prevalence of childhood obesity, diabetes, and dyslipidemia, these problems are still best treated by lifestyle changes of healthier diet, more exercise, and in many cases do not require pharmacologic intervention.

This review focuses on the screening and diagnosis of heterozygous familial hypercholesterolemia (HeFH), including appropriate cardiovascular risk assessment with current treatment recommendations. Guidelines reviewed include the 2008 policy statement by the American Academy of Pediatrics (AAP)—Lipid Screening and Cardiovascular Health in Children, the 2008 National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines—Identification & Management of Familial Hypercholesterolemia, the June 2011 National Lipid Association (NLA) Expert Panel on FH—Familial Hypercholesterolemia: Screening, Diagnosis, and Management of Pediatric and Adult Patients, and the NHLBI Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reductions in Children and Adolescents: Summary Report.1,2,3

Screening: Universal lipid screening for all children is recommended between ages 9 to 11.1,2,3 Previous guidelines had recommended only screening for cholesterol if there was a clear family history of FH or premature CHD.

This recommendation of selective screening based on family history, however, misses about 30-60% of children and adolescents with HeFH, with the greatest risk for premature CHD. The age of 9-11 for routine, universal screening was selected because cholesterol values later, during the age of puberty (especially ages 14-16), tend to be lower than pre-pubescent age, are more variable (less reproducible), and are less sensitive to detect patients at higher cardiovascular risk from FH.

Initial screening is recommended with either a fasting lipid panel or nonfasting non-HDL cholesterol (total cholesterol minus HDL cholesterol) If the non-HDL cholesterol is 145 mg/dL, then a traditional lipid panel is advised. Results are considered elevated when they are over the 95th percentile (LDL cholesterol greater than 130 and total cholesterol greater than 200—see Table 1). Screening should be performed earlier (after two years of age) in the presence of other major CHD risk factors, or if there is a high index of suspicion for FH based upon positive family history of FH or premature coronary heart disease (CHD). In addition to cholesterol testing, evaluation for secondary causes of dyslipidemia should include a focused history, physical exam, and select testing for diseases like hypothyroidism, nephrotic syndrome, and liver disease.

Diagnosis of FH: For children, adolescents, and young adults (< 20
years) FH may be suspected when the LDL cholesterol is 160 mg/dL or non-HDL cholesterol is 190 mg/dL. A follow-up lipid profile should be obtained after appropriate dietary changes, especially in borderline cases, to more accurately assess the mean result. Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria [U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry]. It should be noted that LDL cholesterol cut points usually vary with age (Table 1).

Cardiovascular Risk Assessment:
The presence of multiple cardiovascular risk factors amplifies potential risk of atherosclerosis including smoking, impaired fasting glucose/diabetes, hypertension, chronic kidney disease, presence of elevated Lipoprotein (a), metabolic syndrome, Kawasaki disease with coronary aneurysms, and possibly other chronic inflammatory conditions such as lupus are at risk for coronary artery disease as young adults. Results from autopsy studies of children and young adults (2 to 39 years of age), including the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, and the Bogalusa Heart Study, show that the process of atherosclerosis begins in childhood with the development of the fatty streak.

Treatment: Lifestyle changes of diet and physical activity are always the first step in treating any patient with hypercholesterolemia; however, these steps are not likely to achieve the target LDL cholesterol goals in patients with HeFH. According to the AAP Guidelines, treatment is advisable in children 10 and older with no other CHD risk when the LDL cholesterol is consistently over 190. If other risks are present, then treatment should be considered for LDL cholesterol at 160. With the presence of diabetes, LDL cholesterol of 130 should be considered for lipid lowering therapy. The target goal for patients with FH is at least 50% reduction of LDL cholesterol or LDL cholesterol 130. Like adults, statin is the preferred initial pharmacologic treatment in children after lifestyle intervention. A number of statins have been studied for use in children ages 8 and older demonstrating good efficacy in lowering LDL cholesterol, with reasonable safety for normal pubertal development. Despite the absence of data in children demonstrating morbidity and mortality reduction by aggressive treatment of lipid disorders, the overwhelming data in adults (e.g., decreasing LDL cholesterol, improved morbidity and mortality) and evidence of atherosclerotic lesions developing in childhood support the argument for early treatment. In addition to statin therapy, coleselam is also approved for use children to lower LDL-cholesterol, but clinical data is lacking for use of niacin, fibrates, or ezetimibe in the pediatric population.

Clinical studies which examine vascular structure and function in children with statin therapy have shown improvement in endothelial function. Recent clinical trials demonstrate early initiation of statin therapy in children with FH can delay the progression of carotid IMT in adolescents and young adults, and may also be beneficial in the prevention of atherosclerosis in adolescence.

Homozygous FH: Children with homozygous FH have profoundly elevated LDL cholesterol levels (> 500 mg/dL) with early onset of premature CHD. It is recommended to start lipid-lowering treatment younger than age 8 in homozygous FH children to reduce their marked morbidity. Even with higher doses of the more potent statins, most will require treatment with LDL apheresis in

<table>
<thead>
<tr>
<th>LDL cholesterol categories often used for FH diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

| **Category** | **Description** | **LDL cholesterol (mg/dL)† by age** |
| 1 | General population 95th percentile | 240 | 260 | 300 |

*These LDL cholesterol cut points were derived from analyses of Gaussian (normal) distributions in FH and general populations given the conditions in the descriptions. Fasting lipid levels are assumed. For diagnostic criteria, specifying one category implies all higher categories as well.
† To convert mg/dL to SI units, divide the results by 38.6.
‡ This category is relevant for diagnosis of FH patients who are first-degree relatives of a known FH case. At the LDL cholesterol level shown, approximately 80% of first-degree relatives can be expected to have FH.

an attempt to reduce LDL cholesterol to target goals. Liver transplantation and gene therapy are potential new treatment in development. Referral to a pediatric lipid specialist is highly recommended.1,2,3

Author’s Note: Special thanks are extended to Patrick McBride, MD, MPH, FACC (Faculty, University of Wisconsin School of Medicine and Public Health) for his assistance and thoughtful review of this article.

Screening by Primary Care Clinicians
- Universal screening of all children before puberty (ages 9 to 11 years)
- Screen earlier (2 years of age) if other CHD risks present or family history of premature CAD or FH
- Screen with a fasting lipid profile or nonfasting non-HDL cholesterol measurement
- If non-HDL cholesterol is 145 mg/dL, then obtain a fasting lipid profile
- Evaluate for possible secondary causes of dyslipidemia (hypothyroidism, nephrotic syndrome, and liver disease)

Diagnosis of Familial Hypercholesterolemia
- Suspect diagnosis when LDL cholesterol 160 mg/dL or non-HDL cholesterol 190 mg/dL
- Suggested repeat lipid panel after dietary changes to more accurately reflect true mean
- Confirm diagnosis using validated sets of criteria: U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry

Treatment by Pediatric Lipid Specialist
- Diet and physical activity management first
- Statins are preferred pharmacologic treatment in children
- Start treatment at the age of 8 years or older for LDL cholesterol 190 mg/dL
- The treatment goal in pediatric FH patients is a 50% reduction in LDL cholesterol or LDL cholesterol <130 mg/dL
- More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors

Homozygous FH
- Initiation of therapy early in life and ongoing monitoring of homozygous FH is vital
- High dose statins may be effective in some homozygous FH patients
- Majority will likely require LDL apheresis or liver transplantation

Table 2. Summary of Pediatric FH Recommendations.
The primary health care of women is a complex world of “Hearts, Hormones, Ovaries, Breasts and Bones.” Over the past year women have expressed concern when reading articles and listening to media reports that suggest taking calcium supplements may help prevent fractures but at the same time may increase their risk for cardiovascular events. The Nurses’ Health Study reported calcium supplement intake increased from 30% in 1984 to 72% in 2004. What is the evidence to bring to bear on this conundrum?

The calcium subcommittee of the Professional Practice Committee of the American Society of Bone and Mineral Research (ASBMR) suggested a potential link between calcium supplements and an increase in endpoints of MI, stroke and sudden death. Does this mean we must evaluate a patient’s calcium intake as a risk factor for CVD? The prospective studies, thus far, have been of short duration. Many senior citizens share a number of risk factors for both CVD and osteoporosis. So what’s a woman, and confused public, to do—break a bone or have a broken heart?

Calcium is an essential mineral for cell physiology. It is the fifth most abundant element in our body and impacts cardiac function, vascular tone, the coagulation system, and the nervous system. It is also a key structural component of our bones and teeth. Current daily recommendations for bone health include calcium intake of 1200 mg and vitamin D intakes of 600-800 IU for women over 50. There are no guidelines related to calcium supplements specific to vascular diseases. It has been suggested that a link between calcium supplements and CVD could be related to if the calcified plaques are the response to injury of the vascular walls. The assessment of patients’ cardiovascular risks and evaluation of their bone status are both essential for comprehensive healthcare. We must review our patients’ nutritional status to coordinate health care guidelines.

There are dietary guidelines to reduce cardiac risk, but the American diet is also a major risk for osteoporosis. Typical food choices produce a metabolic imbalance that decreases absorption and retention of minerals like calcium. Diets that include excess protein, high-fat dairy products, sugars, carbonated soft drinks, alcohol, caffeine, and fried foods all produce an acidifying effect that causes calcium to leave the bones in an attempt to buffer this acidity. Soft drinks and caffeine can result in high phosphorus levels, causing calcium to be drawn from the bones. Tobacco decreases estrogen effects, which in turn reduces the f bone mineralization. Progesterone in the presence of adequate estrogen stimulates bone formation. All menopausal and premenopausal women undergoing extreme endurance may have reduced estrogen production leading to decreased protective effects on bone metabolism. Alcohol can decrease healthy nutrition choices. Scoliosis, many endocrine diseases, exogenous glucocorticoids, other hypogonadal states and heavy metal exposure all can affect...
bone and increase fracture risk. Many women have lifestyles characterized by low dietary calcium and Vitamin D intake, low BM < 21, inactivity and/or no weight-bearing activities.

The American Heart Association publishes evidence-based guidelines regarding the burden of vascular disease. Every 25 seconds an American has a coronary event and approximately every minute someone will die of an event. This is one of every six deaths in the United States! Mortality from stroke is one of every 18 deaths in the U.S. That translates into a stroke every 40 seconds. While rates of CVD death have declined, the burden of the CVD disease remains very high.

The National Osteoporosis Foundation (NOF) likewise reports that 25 million Americans have osteoporosis. American Society of Bone and Mineral Research and the NOF have guidelines for the screening, prevention and treatment of this silent disease. One in two women and one in three men will eventually have a fragility fracture. One in three women over age 50 has osteoporosis and one in twelve men has it. Eighty percent of fragility fractures however, happen to women, 250,000 hip fractures are reported annually, and there are 700,000 vertebral fractures and 250,000 wrist fractures. The FRAX (Fracture Risk Assessment Tool) designed by the World Health Organization and the National Osteoporosis Foundation provides a 10-year risk score. This screening is supported by the U.S. Preventive Safety Task Force. We encourage all practitioners to use it, just as we encourage all practitioners to use Framingham risk scoring and Reynolds risk scoring for women.

The risks factors for cardiovascular diseases are hypertension, high blood pressure, diabetes, cigarette smoking, overweight and obesity, poor diet, physical inactivity, alcohol use, family history, gender and age. Osteoporosis has many common risk factors similar to risk factors for cardiovascular disease. Both osteoporosis and heart disease are silent killers without signs or symptoms. A patient’s first symptom is often a dramatic event, a fracture or a vascular event. Almost two-thirds of women who die suddenly of coronary heart disease have no symptoms. The challenge is to identify who is at risk and to screen, diagnose and treat in order to prevent additional disease burden.

Many Americans overdose with supplements under the misperception that this is a prescription for better health. The potential for side effects is often ignored.

Until evidence is solid, it is our belief that calcium supplements should be taken only with caution and according to professional guidelines.

Medline Plus and Consumer Reports are excellent evidence-based references with consumer information readily understood for the use of common supplements. The information is frequently updated. Impaired renal function, kidney stones, and gut and abdominal symptoms are common calcium usage concerns. Taking calcium throughout the day enhances absorption, and not taking a large dose will prevent a calcium spike. Calcium supplements do not reproduce the same metabolic effects as calcium-rich foods.

The U.S. Food and Drug Administration is conducting a safety analysis on calcium supplements.

Julie Paik, MD, of Harvard Medical School reported on an analysis from the Nurses’ Health Study at the recent annual meeting of the American Society for Bone and Mineral Research. Their analysis was based on outcomes for 74,272 women who completed a food questionnaire in 1984. The participants were free of cardiovascular disease and cancer at the baseline. Dr. Paik reported that, in looking at outcomes for women who took more than 1000 mg calcium each day (the common dose that has been used in many of the trials included in the meta-analysis), no significant risks were identified, nor were any associations seen for stroke subtypes.

My current advice to women is to ingest 1000-1200 mg calcium daily, in a balanced nutritional diet. I suggest they take in adequate Vitamin D, and that they participate in weight-bearing exercises. The goal is to empower women to improve their lifestyles and to recognize and modify risk factors for both of these prevalent conditions. Vascular disease and osteoporosis are, for the most part, entirely preventable.

Disclosure statement: Dr. Maxson has no disclosures to report.
Over 26 million Americans have chronic kidney disease (CKD). At risk for CKD include 65 million Americans with hypertension and 20 million patients with diabetes mellitus. The risk of cardiovascular disease (CVD), including coronary, cerebrovascular, peripheral vascular disease, and congestive heart failure increases by 3-to-20-fold as CKD progresses.

The staging of CKD, and slowing (or potentially halting) the progression of CKD through its five stages (Table 1) are paramount, but require recognition of CKD from the outset.1-3

There is a developing epidemic of obesity, diabetes mellitus, metabolic syndrome, aging of the population, and an associated increasing prevalence of CKD and CVD of enormous proportions and costs which are unsustainable.

The kidneys receive 25% of cardiac output and are a major vascular organ. Risk factors for CVD and CKD are similar and include hypertension, dyslipidemia, diabetes mellitus, tobacco abuse, advancing age, obesity, physical inactivity, positive family history, and ethnicity. Treatment modalities that benefit patients with normal renal function have not provided the expected CV event reduction in CKD, as other metabolic and inflammatory factors are inherent in CKD patients1 including:

- Reduced glomerular filtration rate (GFR) which can be present despite apparently normal serum creatinine levels
- Elevated Cystatin C
- Elevated microalbuminuria or proteinuria
- Renin-angiotensin system over activity
- Left ventricular hypertrophy
- Anemia
- Abnormal calcium and phosphorus metabolism, which are linked to bone disease and vascular calcification
- Elevated lipoprotein(a) and homocysteine
- Hypovitaminosis D
- Thrombogenic factors
- Oxidative stress and inflammation

Patients with CKD usually die of CVD. The National Kidney Foundation considers CKD a coronary risk equivalent, and that all patients with CKD, especially stages 3-5, should be considered in the highest risk group irrespective of traditional CVD risk factors4 (see NKF Kidney Disease Outcome Quality Initiative, at www.kdoqi.org). However, early CKD is often not recognized, and there often is “therapeutic nihilism” in patients with CKD, including under-use of aspirin, statins, beta blockers, and suboptimal blockade of the renin-angiotensin system, even in the setting of acute coronary syndrome or CHF.

Only 35% of patients who are within 1 to 6 months of requiring renal replacement therapy for end stage renal disease (dialysis) have ever received a nephrology consultation. Patients referred late (<4
months before ESRD) have a 72% greater mortality during the first year.

**How to Identify CKD**

1. Measure serum creatinine and calculate estimated GFR (eGFR) using the modified Modification of Diet in Renal Disease (MDRD) equation that can be performed quickly at www.kdoqi.org. In all patients at risk for CKD, especially patients with known CVD, diabetes mellitus, hypertension, dyslipidemia, the elderly, or in those with a family history of kidney disease. Calculated eGFR using this formula is very accurate for levels <60 ml/min/1.73m² and requires only age, sex, race and serum creatinine as pertinent variables. An eGFR <60 (stage 3 CKD) is associated with an increased risk for CVD and accelerated decline of renal function. Serum creatinine may appear “normal,” particularly in older patients and women of Caucasian ethnicity who may have decreased muscle mass, a normal creatinine but an abnormal eGFR.

2. Random (“spot”) urine sample for albumin/creatinine ratio (abnormal: >30 mg albumin/g creatinine).

A newer and apparently more accurate assessment of renal dysfunction and likely presence of microalbuminuria and a potential CVD risk indicator is derived from measurement of Cystatin C. Cystatin C is a cysteine protease inhibitor that is produced by all nucleated cells, filtered by the kidney, and degraded by the proximal tubule. Its levels are not dependent on muscle mass.

Microalbuminuria (> 30-300 mg albumin/g creatinine) is strongly associated with endothelial damage and susceptibility to atherosogenesis; and its presence more than doubles the predicted risk of atherosclerotic disease, especially in patients with hypertension and diabetes mellitus.

Microalbuminuria or macroalbuminuria (clinical proteinuria >300 mg/g creatinine) is associated with progression of CKD and CVD, and is also associated with dyslipidemia and elevated lipoprotein(a), even without a reduction in eGFR.

Renin angiotensin system blockade with an angiotensin converting enzyme inhibitor (ACEI) and/or an angiotensin receptor blocker (ARB) reduces proteinuria and may reduce progression of renal disease, but has not yet been shown to consistently reduce CVD events.

The renin inhibitor aliskerin should not be used in combination with an ACE inhibitor or ARB in patients with diabetes or in patients with moderate to severe renal impairment. The ALTITUDE trial which studied aliskerin was stopped because of an increased risk of fatal strokes, acute renal failure, hyperkalemia, and hypotension in the active arm. (Drug Safety Communication, www.fda.gov, posted on 4/20/2012).

**Oxidative Stress and Inflammation**

Oxidative stress can provoke inflammation by activating transcription factor nuclear factor-kappa B (NF-kB), the master regulator of proinflammatory cytokines, chemotactic and profibrotic factors. Oxidative stress also creates oxidized low-density lipoprotein and advanced glycation end products and oxidized phospholipids, all of which are extremely pro-oxidant and pro-inflammatory.

Increased activation of the renin-angiotensin system in renal tissue, irrespective of systemic levels, leads to formation of reactive oxygen species (ROS). That is mechanistically why blocking this system may potentially retard progression of CKD.

Retarding Progression of CKD and Reducing CV Risk (for complete discussion, see www.kdoqi.org and references) The staging of CKD is shown in Table 1. Seek specialty consultation with a nephrologist for stage 3 CKD and microalbuminuria!

Lifestyle modifications are essential for controlling CVD risk factors. Dietary salt restriction is vital, because dietary sodium excess reduces the effectiveness of antihypertensive drugs and treatment of proteinuria. A lower protein diet and low phosphate diet are important in patients with proteinuria and calcium-phosphate imbalance.

Control of hypertension is critical. Often with advanced CKD (especially dialysis patients) we find underuse of beta blockers. This is unfortunate because CKD patients on dialysis often die of arrhythmias or heart failure. Inhibiting the renin-angiotensin-aldosterone system with ACE inhibition or angiotensin receptor blockade may be renoprotective, and their anti-proteinuric effects go beyond lowering of BP.

Do not withhold these agents solely on the basis of renal function! This deprives patients of potential CVD prevention benefits. A modest (20-25%) increase in serum creatinine is to be expected with the use of an ACE inhibitor or ARB. Modest dietary potassium restriction usually is adequate to maintain normal serum potassium when ACE or ARBs are used.

Control of dyslipidemia is often overlooked or substandard in patients with CKD. Lipoprotein changes are very similar to those seen in the metabolic syndrome. They include elevated triglycerides and atherogenic remnants, low HDL-

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**Table 1: Staging of CKD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Risk of Death</th>
<th>Risk of Progression</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>eGFR ≥ 90 ml/min/1.73m²</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>60 ml/min/1.73m² ≤ eGFR &lt; 90 ml/min/1.73m²</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>30 ml/min/1.73m² ≤ eGFR &lt; 60 ml/min/1.73m²</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>4</td>
<td>eGFR &lt; 30 ml/min/1.73m²</td>
<td>Very high</td>
<td>Very high</td>
</tr>
</tbody>
</table>

**References**

1. C is a cysteine protease inhibitor that is produced by all nucleated cells, filtered by the kidney, and degraded by the proximal tubule. Its levels are not dependent on muscle mass.
2. Random (“spot”) urine sample for albumin/creatinine ratio (abnormal: >30 mg albumin/g creatinine).
C, increased small LDL particles, and elevated lipoprotein(a). While LDL-C may not be exceptionally elevated, the number of LDL particles invariably is. In this population, we believe that non-HDL-C (total cholesterol minus HDL-C) better predicts CVD risk than LDL-C. ATP III supports this as a secondary goal for therapy when triglycerides are >200 mg/dL. LDL-C target level is <100 mg/dL (non-HDL-C <130 mg/dL) in patients with CKD, and < 70 mg/dL (non-HDL-C <100 mg/dL) in renal patients with established CVD. 1,8,9 LDL particle number by NMR Lipoprofile, or an apoB level, may improve risk prediction and determination of therapeutic goals and should be considered.

Statins appear to be reno-protective and may reduce proteinuria. They are an essential component of lipid-lowering therapy to reduce atherosclerotic risk present in patients with CKD.

Statins appeared to reduce CV events in the few patients with stage 3 and 4 CKD in early trials (however please note that such patients were often excluded from these trials). 8 Reduction in mortality with statins has not been shown in patients on dialysis (stage 5) likely due to the high death rate from arrhythmias and heart failure and sudden cardiac death in patients with stage 5 CKD, which likely masks any benefit of reduced myocardial infarction when statins are used.

The recent SHARP trial showed clear benefit in CVD risk reduction in patients with advanced CKD using simvastatin/ezetimibe therapy.

Control of diabetes mellitus reduces progression of CKD. Strict glycemic control prevents or delays the onset of diabetic kidney disease. Data is inconclusive with regard to progression of established disease. We believe that control of BP and lipids is of paramount importance in these patients.

Smoking cessation reduces the rate of progression of CKD.

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The recent SHARP trial showed clear benefit in CVD risk reduction in patients with advanced CKD using simvastatin/ezetimibe therapy. There was a trend toward benefit in stage 5 dialysis patients. This large trial looked at 9270 patients with predominantly stage 3 and 4 CKD, focusing on patients with eGFR below 60 and especially between 15 and 45. The combination low dose simvastatin and ezetimibe reduced CV events after a median of 4.9 years follow-up. There was no effect on progression of CKD. There were very few side effects of therapy reported.10

Control of diabetes mellitus reduces progression of CKD. Strict glycemic control prevents or delays the onset of diabetic kidney disease. Data is inconclusive with regard to progression of established disease. We believe that control of BP and lipids is of paramount importance in these patients.

Smoking cessation reduces the rate of progression of CKD.
Lipid, behaves like a bile acid binding resin to lower apoB/LDL-P. Colesevelam can be used as a bile acid binding drug to lower apoB/LDP. These agents may raise triglycerides but may be of use especially when intolerance to statin or niacin therapy is encountered.

Omega-3 fatty acid fish oil therapy may offer benefits to lower very high triglycerides.

Of the above mentioned therapies, only statins have clinical trial evidence for reduced CVD events in CKD.

**Key Issues and Summary**
Suspect CKD in any patient with CVD risk factors. Determine eGFR and check for microalbuminuria in patients at risk for CVD.

The presence of CKD should be considered a coronary risk equivalent, with the need for a global CVD risk reduction program. Treatment of dyslipidemia is paramount generally with a statin, and other therapy as needed to deal with mixed dyslipidemia often found in patients with CKD.

Proteinuria is a marker for CKD; it contributes to the progression of CKD, and it is an independent predictor of increased risk for CVD and death in patients with CKD.

An angiotensin converting enzyme inhibitor or an angiotensin receptor blocker should be strongly considered for therapy in the face of CKD and/or significant proteinuria.

Patients with CKD and an eGFR below 60 mL/min/1.73m² nephrologists believe should be assessed for LVH, anemia, parathyroid, mineral, and vitamin D abnormalities, and lipoproteins including apoB or LDL-P, and insulin resistance.

Primary care physicians and nephrologists need to share responsibility for care of CKD patients. See detailed information from the National Kidney Foundation at [www.kdoqi.org](http://www.kdoqi.org).

**Disclosure statement:** Dr. Ferguson has no disclosures to report.

References listed on page 32.

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<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR Range (mL/min/1.73m²)</th>
<th>Clinical Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>&gt;90 (without markers of damage)</td>
<td>CKD risk factors</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with ↓ GFR</td>
<td>60-89</td>
<td>Mild complications</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>Moderate complications</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>Severe complications</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
<td>Uremia, cardiovascular disease</td>
</tr>
</tbody>
</table>

**Table 1. Stages of Chronic Kidney Disease: Clinical Presentations.**

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73m² for >3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

From the National Kidney Foundation KDOQI Guidelines, public domain online, part 4: [www.kdoqi.org](http://www.kdoqi.org).
Familial hypercholesterolemia (FH) is a disease caused by autosomal dominant defects in the genes coding for the low-density lipoprotein (LDL) receptor, apolipoprotein (Apo) B, or proprotein convertase subtilisin/kexin type 9 (PCSK9). It is the most common single gene lipid disorder. FH is characterized by severely elevated blood cholesterol concentrations. Xanthelasmas, tendon xanthomas, tuberous xanthomas, and corneal arcus may be evident upon physical examination of FH patients. Homozygous FH is rare, occurring in about one of every million persons. Heterozygous FH is more common, occurring in one of every 300-500 people, and in some founder communities the incidence may be as high as one in 50 to 100 persons. More than 10 million people worldwide have some form of FH. Homozygotes have much higher cholesterol levels [total cholesterol (TC) typically in the range of 650-1000 mg/dL] and earlier onset of coronary artery disease than heterozygotes, who typically have total-C in the range of 350-550 mg/dL. Although many patients with heterozygous FH respond well to high-dose statins, ezetimibe, and bile acid sequestrants, management of homozygous FH patients is especially difficult due to the magnitude of LDL-C reduction that is needed, and because many homozygotes are refractory to statins, the mechanism of action of which depends mainly on up-regulation of hepatic LDL receptors. Several therapies are available, or in development, for the treatment of FH. In this article, we will briefly describe LDL-apheresis, PCSK9 inhibitors, mipomersen, and lomitapide, largely reflecting a summary of presentations given in a session on emerging therapies for LDL-C at the 2012 National Lipid Association Annual Scientific Sessions.

**LDL-apheresis.** LDL-apheresis is a Food and Drug Administration (FDA)-approved therapy for patients with homozygous FH and severe heterozygous FH. LDL-apheresis is a process which selectively removes apoB-containing lipoproteins from the circulation, including LDL, lipoprotein (a), and very-low-density lipoprotein (VLDL) particles, through Heparin-induced Extracorporal LDL Precipitation (HELP®) or extracorporal precipitation with dextran sulfate (Liposorber®). LDL-apheresis produces an acute fall in LDL-C levels of 70-80%, but there is a rapid rebound effect, and concentrations return to initial levels by −2 weeks. When repeated once-a-week in patients with homozygous FH and every-other-week in patients with heterozygous FH, LDL-apheresis typically produces a time-average LDL-C reduction of −40-60% (Table 1). Studies of LDL-apheresis have been small and non-randomized, but the results have been
consistent with those from statin trials. Although data from randomized, controlled clinical trials are not available, homozygous and severe heterozygous FH patients treated with LDL-apheresis have shown significant reductions in cardiac morbidity compared to those who have not received the treatment. 5-7 LDL-apheresis has been approved for use in the United States for ~15 years.

**PCSK9 Inhibition.** An emerging therapy for FH is a monoclonal antibody to PCSK9. PCSK9 is a protein secreted by the hepatocyte which “chaperones” the LDL receptor from the cell surface, into the clathrin-coated pit, and into the cell for lysosomal degradation. 8 Gain-of-function and loss-of-function mutations in the gene for PCSK9 have been described. Gain-of-function mutations are rare and result in fewer LDL receptors and increased LDL-C levels. Loss-of-function mutations lead to reduced LDL receptor degradation, resulting in more LDL receptors on the surface of the liver, life-long decreased LDL-C concentrations, and reduced cardiovascular risk. In loss-of-function mutation carriers, LDL-C levels have been shown to be 15 to 28% lower and incident coronary heart disease was reduced by 47 to 88% compared with individuals lacking PCSK9 gene mutations. 9

Monoclonal antibodies to PCSK9 mimic the effects of genetic mutations. In the monoclonal antibody approach, an antibody to PCSK9 binds to the PCSK9 protein, thereby inhibiting its effect on the LDL receptor. 10 Results from phase 1 trials have demonstrated that an injectable monoclonal antibody to PCSK9 was capable of lowering LDL-C by up to 70% above the level achieved by statin therapy, and was well-tolerated with few instances of elevated liver enzymes and injection site skin reactions. 10,11 Patients with statin intolerance, those who cannot achieve an adequate LDL-C level with existing therapy, who have refractory hypercholesterolemia, or who may otherwise require LDL-apheresis, would all be expected to respond favorably to PCSK9 inhibition. However, because PCSK9 acts on the LDL receptor, the effects of PCSK9 inhibition in patients with homozygous FH who lack functioning LDL receptors may be limited. Clinical outcome trials of PCSK9 monoclonal antibodies are highly anticipated. Other methods that target PCSK9 are also in development, including antisense oligonucleotide technology. 12

**Antisense therapy.** Mipomersen is an antisense oligonucleotide injectable drug which is under evaluation for the treatment of homozygous FH and severe heterozygous FH. 13 Mipomersen is complementary in sequence to a segment of the human apoB-100 messenger ribonucleic acid (mRNA). 14 It specifically binds to the mRNA and blocks translation of the gene product. 15 Decreasing the production of apoB-100 reduces the production of VLDL in the liver, which consequently reduces circulating levels of atherogenic VLDL remnants, intermediate density lipoproteins, LDL and lipoprotein (a) particles. Results from phase 3 trials conducted in patients with homozygous FH, severe hypercholesterolemia, heterozygous FH with coronary artery disease, and hypercholesterolemia at high risk for coronary artery disease have indicated that, when added to maximally tolerated lipid-lowering drug therapy, mipomersen reduced concentrations of all apoB-containing atherogenic lipoproteins. 16-19 The average LDL-C reduction was >100 mg/dL in homozygous FH and severe hypercholesterolemia populations, and the effects were consistent across all patient populations. The most frequently observed adverse events occurring on-treatment were mild-to-moderate injection site reactions and flu-like symptoms. To date, the safety and tolerability of mipomersen has been examined up to 104 weeks, and the results appear to support the suitability of mipomersen for the treatment of FH, although longer term studies will be needed to more fully evaluate the benefits and risks, particularly if use is to be extended beyond homozygous FH. 20 Additionally, a potential safety concern was raised during a recent FDA review, an increased frequency of cancer in subjects treated with mipomersen in clinical trials, although it is uncertain whether this association is causal. 21

**Microsomal triglyceride transfer protein inhibition.** Another drug currently under evaluation as an adjunct to a low-fat diet and other lipid-lowering therapies for reducing LDL-C in patients with homozygous

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<th>Therapy</th>
<th>LDL-C</th>
<th>apoB</th>
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<tr>
<td>LDL-apheresis</td>
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<tr>
<td>PCSK9 inhibitor</td>
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<tr>
<td>Mipomersen</td>
<td>25-37</td>
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<td>Lomitapide</td>
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Abbreviations: Apo = apolipoprotein, FH = familial hypercholesterolemia, LDL-C = low-density lipoprotein cholesterol, Lp(a) = lipoprotein (a), PCSK9 = proprotein convertase subtilisin/kexin type 9

Table 1. Summary of ranges of approximate LDL-C, apoB, and Lp(a) reductions observed in studies of emerging therapies for FH.
FH and severe hypertriglyceridemias is the orphan drug lomitapide. Lomitapide is a small molecule microsomal triglyceride transfer protein (MTP) inhibitor. MTP is located in the endoplasmic reticulum of enterocytes and hepatocytes, and is necessary for the formation of chylomicron and VLDL particles. Results from recent phase 2 and 3 studies of lomitapide (formerly BMS-201038 and AEGR-733) demonstrate its efficacy as add-on therapy to substantially reduce atherogenic lipoprotein concentrations in FH patients. Total-C, LDL-C, and apoB declined from baseline by >40% at 26 weeks and reductions were maintained for another 52 weeks. Gastrointestinal disorders were the most frequent side effects and the most common reason for failure to tolerate lomitapide dose escalation. However, a concern regarding the use of lomitapide is its tendency to increase hepatic fat dose-dependently, although the effect varies considerably between patients and hepatic fat declined during a washout period. It is anticipated that long-term safety and cardiovascular benefit studies will be required by the FDA. In addition to treating adult patients with homozygous FH, other populations in which MTP inhibitors may be considered are severe heterozygous FH, hypercholesterolemic patients who are statin intolerant, and individuals with severe hypertriglyceridemia caused by lipoprotein lipase deficiency. Initial approval of lomitapide (and mipomersen) is being sought for adult patients, however, children with homozygous FH represent a particularly important group to which the indication could eventually be extended since they often develop coronary heart disease in their 20s or earlier.

In summary, the emergence of new lipid-altering therapies that act in series and in parallel with available agents may provide more effective LDL-C lowering in patients with FH who do not tolerate high-dose statins, or for whom the magnitude of LDL-C lowering needed is beyond the degree which can be achieved with current regimens.

Disclosure statement: Dr. Maki has received research grants from Abbott Laboratories, BioSante Pharmaceuticals, Omthera, Trygg Pharmaceuticals, Amarin Corp., Pharmavite, Coca-Cola, Ocean Spray Cranberries, PepsiCo Beverages and Foods, Shaklee, Solae, Welch’s, Ingredion Inc., Atherotech Inc., Cargill Inc., Dairy Research Institute, Fermenich, GlaxoSmitKline, Kellogg Co. and Monsanto. Dr. Maki has received consulting fees or speaking honoraria from Abbott Laboratories, Kowa Pharmaceuticals, Omthera, Trygg Pharmaceuticals, Pharmavite, PepsiCo Beverages and Foods, Cargill Inc., Dairy Research Institute, General Mills, GlaxoSmithKline, and Kao Corp. Dr. Wild has received honoraria from the U.S. Food and Drug Administration, the National Institutes of Health, and Atherotech Inc.

Dr. Dicklin has no disclosures to report.

References listed on page 32.

Accreditation Council for Clinical Lipidology

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The ACCL Offers Two Pathways to Recognition:

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Julie Bolick, RD, MS, CD, CLS
Salt Lake City, Utah

Learn more at
www.lipidspecialist.org
Phone: 904.309.6250
This 58-year-old patient was referred to the lipid clinic for statin intolerance and a history of “genetic hypercholesterolemia.” The patient has had tendon xanthomas on the extensor surface of his hands and on his Achilles tendons since childhood just like his brother and sister. Both siblings have expired prematurely due to coronary artery disease. He states that he has had a biopsy of his Achilles tendon that revealed “cholesterol” deposition by pathology per his surgeon. The patient was not able to take simvastatin, atorvastatin, pravastatin, or rosuvasatin due to significant myalgias and, hence, was referred for initiation of lipid-lowering therapy. He was not on lipid-lowering drugs at the time of his initial visit.

His past medical history was remarkable. His father died at 85-years-old of CAD. Two brothers died of MI’s at ages 59 and 53 respectively. A sister died of CAD at age 56. At least two of his siblings had similar xanthomas. Social history is remarkable for an 82 packs-per-year smoking history and rare alcohol. He works as a highway maintenance worker. Allergies include cephalosporins, quinolones, and sulfa. Home medications at the time of his initial visit included fexofenadine and clindamycin. Vital signs were blood pressure 120/72, pulse 84, respirations 18, and afebrile height 66 inches, weight 189 lbs., BMI 30.6.

His physical exam was remarkable for xanthomas on the extensor surface of his hands and on his Achilles tendons as shown in the photos. The remainder of his physical was unremarkable.

Lab results were as follows:
- Cholesterol 231; HDL 35 mg/dL, LDL 169 mg/dL;
- Triglycerides 137 mg/dL;
- Fasting Glucose 80 mg; TSH 0.96 IU

CBC and remainder of his chemistry testing was normal

The differential diagnosis included functional Familial Hypercholesterolemia (FH), CTX (cerebrotendinous xanthomatosis), and hereditary beta sitosterolemia.

FH was ruled out due to the relatively low serum cholesterol levels. CTX was ruled out due to the absence of any neurologic symptoms, diarrhea, cataracts or seizures. A presumptive diagnosis of Hereditary Sitosterolemia was made.

Serum sitosterol levels were drawn and the results were as follows (note that patient had already been started on ezetemibe before blood draw):
- Lathosterol 9.8 (Normal range 0.0-5.0) mg/dL
- Campesterol 9.1 (Normal range 0.0-7.0) mg/dL
- Sitosterol 6.6 (Normal range 0.0-5.0) mg/dL

These elevations in plasma sterols despite initiation of ezetemibe as well as the clinical presentation were strongly suggestive of a diagnosis of Hereditary Sitosterolemia.
Hereditary beta sitosterolemia is a very rare autosomal recessive disorder. As of the year 2000, only 40 cases had been reported. It is likely that the disorder is underreported due to missed diagnosis. The clinical manifestations include xanthomatosis and premature coronary artery disease. The disorder can superficially mimic FH on physical exam with extensor tendon xanthomas on the hands and Achilles tendons leading to misdiagnosis, as in the case of our patient. The cholesterol levels can be mildly elevated or low in contrast to FH, providing a clue to the diagnosis.

Patients may also have painful and inflamed joints, particularly in the knees and ankles. Hemolysis and platelet abnormalities such as thrombocytopenia have also been reported. It is thought that incorporation of plant sterols into erythrocytes makes them more rigid and more susceptible to hemolysis. The pathophysiology of this disorder stems from a mutation in the ABCG5 or ABCG8 transporter proteins in the intestinal mucosal cell. Sterols (including cholesterol and plant sterols) are transported from the intestinal lumen into the mucosal cell via the NP1L1 (Neimann Pick 1L1) protein. The absorbed cholesterol and usually minimal amounts of plant sterol are then packaged into chylomicrons which are secreted from the mucosal cell into the lymphatic system. The majority of potentially toxic plant sterols are pumped out of the intestinal mucosal cell and back into the intestinal lumen by the ABC G5/G8 proteins to avoid their absorption into the circulation. In patients with sitosterolemia, a mutation in the ABCG5 or ABCG8 proteins causes inability to pump plant sterols back into the intestinal lumen for disposal and hence high levels are incorporated into the chylomicrons and absorbed into the bloodstream. These high levels of circulating plant sterols lead to a marked increase in atherosclerosis, likely due to the incorporation of increased levels of plant sterols into VLDL and increase deposition into the arterial wall.

The definitive diagnosis is made by the finding of elevated levels of plant sterols in the serum as analyzed using chromatography:

- Treatment includes ezetemibe which blocks absorption of plant sterols into the intestinal mucosal cell by inhibiting the activity of the NP1L1 sterol transporter protein. In addition, bile acid resins can be used and in rare cases, ileal bypass surgery has been utilized.
- Patients should be placed on a diet low in plant sterols. Dietary recommendations include an attempt to eliminate vegetable fat in the diet. Olives and avocados should be avoided due to high levels of vegetable fat. Nuts, seeds, and chocolate as well as vegetable oils, margarine and shortening should be avoided. Shellfish should also be avoided. A consult with a dietitian is recommended to help instruct patients on a low plant sterol diet.
- Appropriate consultations would include cardiology for evaluation of atherosclerosis, hematology for hemolysis, and possibly rheumatology for arthritis. A lipidology consult would also obviously be recommended. A geneticist evaluation, if available, would also be optimal and screening of extended family members for xanthomas is appropriate.

Disclosure statement: Dr. Brown has received honoraria for serving on the advisory board of Kowa Pharmaceuticals.
When Tara Dall, MD, began her medical career, it was in 2001, after she graduated from medical school and completed her residency at the University of Wisconsin at Madison. She started as a family practice physician with no specialization in lipidology. That changed quickly, however, when she saw how much lipid management impacted her patients’ everyday lives.

“I began using advanced biomarkers, such as NMR and apoB, in most patients from the day I started my primary care practice,” Dr. Dall said.

In January 2006, Dr. Dall opened an independent lipid clinic practice, Advanced Lipidology, in Delafield, Wisc., and has been its president ever since. Around that time, she also began lecturing about utilizing advanced testing to guide practitioners’ risk management and assessment.

In early 2012, Dr. Dall also accepted the position of Chief Medical Officer for Health Diagnostic Laboratory in Richmond. She frequently commutes between Wisconsin and Virginia and continues to lecture at educational events both abroad and throughout the U.S.

“The chief medical officer position was a natural fit for me as I have been using advanced biomarkers in every patient I have seen for more than a decade now,” Dr. Dall said. “I also realize there is a great need for education and research in this area and feel I will be able to do so in my new position in ways I was not able to do independently.”

She takes particular interest in furthering education and research about biomarkers, and wants to help increase acceptance of their utilization in primary care and specialist communities as well as among patients worldwide. This interest also inspired her to cofound Lecturepad.org, a non-profit web portal that provides the medical community with educational resources about biomarker testing.

Outside the office, Dr. Dall is married with two beautiful children and dreams of participating in church mission work abroad.

Her family and the community inspire her because she believes that, with the help of many passionate clinicians, the statistics for diabetes and heart disease can really improve within the next decade.

“My children and the world’s children are my real motivation,” Dr. Dall said. “I don’t want them to have to fight this pandemic of obesity, diabetes, and heart disease. I want to someday tell them that we have found a way to beat it.”

TARA L. DALL, MD, FNLA
Medical Director/President
Advanced Lipidology
Delafield, WI
Diplomate, American Board of Clinical Lipidology

Discuss this article at www.lipid.org/lipidspin
Lifetime Membership
For the first time, the NLA is offering a Lifetime Membership program with rates based on the duration of your involvement with the NLA. All Lifetime Memberships include a $1,000 donation to the Foundation of the NLA, which will be set aside to establish training programs and fellowships in Clinical Lipidology. To learn more, please visit www.lipid.org/lifemember.

Recognize Your Colleagues
To honor the exceptional professionals in our ranks, the NLA has established several types of recognition. We are currently seeking nominations for the following awards, to be presented at the 2013 Annual Scientific Sessions in Las Vegas, Nevada:

Fellow of the NLA: Fellowship in the National Lipid Association recognizes the excellence, innovation, and leadership of health professionals in the NLA with respect to Clinical Lipidology in private practice or academic settings. Fellowship is reserved for NLA members who have made significant regional and/or national contributions to the science and practice of Clinical Lipidology.

NLA Distinguished Achievement Award: The highest honor conferred by the NLA recognizes a member who has made a major contribution to Clinical Lipidology (research, teaching, publishing, or service), whether as a single accomplishment or through lengthy career work.

NLA Honorary Lifetime Membership Award: Presented to a scientist or clinician who would not normally be a member of the NLA to recognize his or her unusual expertise and contributions to Clinical Lipidology. The NLA national and chapter boards will each be requested to make one nomination per year. In addition, Fellows of the NLA may also submit a nomination for this award, through the NLA Awards Committee.

Awards nominations are due by February 21. To view the qualifications or to submit a nomination, please visit www.lipid.org/awards.

Call for Board Nominations
The Nominating Committees of the NLA Board of Directors and the five regional Boards of Directors are seeking nominations for board and officer positions. Several positions are open on each Board. New Board members are elected each May at the NLA Annual Scientific Sessions. Materials needed for Board applications include letters of support from 1-2 Board or other NLA members, a current CV, a personal statement, and a current disclosure of any industry relationships. Board nominations are due by Thursday, February 21. For more information, please go to www.lipid.org/boardnominations.

Member Updates
Spencer Kroll, MD, PhD, and Gina Chadwick Kroll married after they met at the 2011 NLA Annual Scientific Sessions in New York City. After becoming engaged at the 2012 NLA Annual Scientific Sessions in Scottsdale, the couple married this past October. The happy newlyweds reside in Morganville, New Jersey.

Kim Birtcher, PharmD, was promoted to Clinical Professor for the University of Houston College of Pharmacy this past September. Congratulations, Dr. Birtcher!

Lindsey Howard, Esq. joined the NLA staff as Policy Coordinator in December. She brings fresh expertise on current legal issues to her position’s responsibilities of legal research, policy analysis, contract review, compliance, legislative affairs, and committee management. Lindsey interned at the Florida Coastal School of Law’s Housing Rights clinic, and is an active volunteer with the Florida Guardian ad Litem program, helping to represent abused and neglected children in the legal system. Lindsey can be reached at lhoward@lipid.org.

Krista Wessel signed on in the event planning department as Meeting Coordinator. She graduated from the University of North Florida after studying Communications. Krista interned with the March of Dimes in meeting planning and fundraising, and her background in hotel convention sales gives her an insider perspective on conference planning. Krista’s e-mail address is kwessel@lipid.org.

News and Notes
Education and Meeting Update

It’s Not Too Late to Register: Spring CLU in New Orleans

Jointly hosted by the Southwest and Midwest Chapters, this CLU will be held February 22-24 at the city’s famous Roosevelt Hotel. The program, “Lipids Throughout the Lifetime,” features world-renowned speakers discussing treatment of cardiovascular disease through the various stages of life. For more information, please visit www.lipid.org/clu.

2013 Call for Abstracts

On behalf of the Scientific Sessions Program Committee, the NLA invites you and your colleagues to submit abstracts of your latest research to the 2013 Annual Scientific Sessions scheduled to take place May 30–June 2 at the Red Rock Hotel in Las Vegas, Nevada. The Abstract Submission Deadline is March 1, 2013, at 5 p.m. PDT. If you, your junior faculty members, or fellows are working in areas that fall within lipidology but are not limited to the abstract categories, we still hope to see submission of your best work to be considered for the poster session. Please visit www.lipid.org/abstracts for more information.

Managing Residual CVD Risk: The Role of HDL

The goal of this three-part Continuing Medical Education/continuing education (CME/CE)-certified interactive newsletter series is to help clinicians successfully manage and treat residual risk in cardiovascular disease (CVD) due to abnormally low or dysfunctional HDL. Issue 1 reviews the emerging evidence, which suggests that certain subsets of high-density lipoprotein (HDL) particles may be more protective against CVD than others. Although clinical trials have not demonstrated that increasing HDL-cholesterol directly translates into a reduction in hard CVD events, emerging research can help to clarify and elucidate the complicated relationship between HDL-cholesterol and atherosclerotic vascular disease. Please visit www.lipid.org/nla/new-hdl-cmece-online-activity for access.

HDL Web Resources

The NLA is pleased to announce two HDL-related programs available online. The “Advancing HDL Science” program consists of three self-study slide libraries and two interview series on HDL nomenclature, HDL functionality, cholesterol efflux, and atheroprotective effects. Each module is individually accredited and can be completed at one’s own pace. The second program is the first slide module in the NLA’s HDL Resource Center, “CETP as a Therapeutic Target,” and addresses cholesterol ester transport protein: history, metabolism, and therapeutic development as well as cholesterol ester transport protein Inhibitors. All programs are available at www.lipid.org/advancinghdlscience.

Improving Outcomes in Patients with Severe Familial Hypercholesterolemia eCME Activity

The NLA partnered with Elsevier to create an open access, journal-indexed eCME program, based on the live NLA Special Session on Improving Outcomes in Patients with Severe Familial Hypercholesterolemia, which was held at the NLA Annual Scientific Sessions in May 2012. This web activity addresses current knowledge, practice gaps, and challenges in the identification and management of with severe familial hypercholesterolemia and offers therapeutic strategies for optimizing patient outcomes. Participants are able to view slides, hear audio, watch a patient video, and claim CME/CE at http://multimedia.lipidjournal.com/2012/SevereFH.

ATP IV Guidelines Update

The NLA is still waiting for the release of the ATP IV Guidelines but has no new information about the release date. However, interested members can track the status of the documents at the following site: http://www.nhlbi.nih.gov/guidelines/develop.htm. As the page shows, the lifestyle and cholesterol guidelines are closest to complete, followed by the risk assessment guidelines. The hypertension and obesity guidelines have a number of stages pending. We will continue to keep you posted.

Train the Trainer Program in Ukraine

Thomas Bersot, MD, PhD, and William Cromwell, MD, participated in a “Train the Trainer” program in Ukraine this past September. The event was sponsored by AstraZeneca Ukraine.

Lipid Spin Review

Thanks to Wayne Warren, MD, for reviewing articles for this issue.
2013 Scientific Meetings

2013 National Lipid Association
Clinical Lipid Update—Spring
Hosted by the Southwest Lipid Association and the Midwest Lipid Association
February 22–24, 2013
The Roosevelt Hotel
New Orleans, Louisiana

2013 National Lipid Association
Scientific Sessions
Hosted by the Pacific Lipid Association
May 30–June 2, 2013
Red Rock Hotel
Las Vegas, Nevada

2013 National Lipid Association
Clinical Lipid Update—Fall
Hosted by the Southeast Lipid Association and the Northeast Lipid Association
September 20–22, 2013
Hyatt Regency Baltimore Hotel
Baltimore, Maryland

Other 2013 Meetings

SCAN Annual Meeting
April 26–28, 2013
Westin Michigan Avenue
Chicago, Illinois
www.scandpg.org

PCNA Annual Meeting
May 2–4, 2013
Paris Hotel
Las Vegas, Nevada
www.pcna.net

2014 Scientific Meetings

2014 National Lipid Association
Clinical Lipid Update—Spring
Hosted by the Pacific Lipid Association and the Southwest Lipid Association
March 14–16, 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

Other 2013 Meetings

SCAN Annual Meeting
April 26–28, 2013
Westin Michigan Avenue
Chicago, Illinois
www.scandpg.org

PCNA Annual Meeting
May 2–4, 2013
Paris Hotel
Las Vegas, Nevada
www.pcna.net
Foundation Update

The Foundation of the National Lipid Association has accomplished much since its creation four years ago, but we want to continue to grow. Over the past year, I have been engaged in conversations with leadership, members, staff and patients about the future of our charitable organization. As we look ahead to the way the Foundation will define its agenda in the coming years, several themes consistently emerge.

The Foundation continues to build on the inaugural public awareness campaign, “FH: It’s Relative—Know Your Family Cholesterol History,” which was launched in May 2011. Earlier this year, the International Guidelines Center published an FH pocket guide based on the NLA’s expert panel consensus statement. More than 2,000 copies were sold this year. For National Cholesterol Education Month in September, the NLA staff distributed several news releases, including one focusing on the importance of checking the cholesterol levels of patients who may have a family history of FH.

Also this past September, the Foundation hosted a “Strike Out FH!” bowling fundraiser during the Fall Clinical Update to a sold-out crowd of 40 participants. We look forward to another terrific turnout for our cooking and jazz fundraiser at the Spring Clinical Lipid Update in New Orleans this February.

In November, we enjoyed a presentation by the FH Foundation at our biannual Board meeting. We look forward to working with them in the future, particularly in regard to supporting the group’s efforts to establish an FH patient registry.

Thanks to many generous individuals, the Foundation has received more than $26,000 in donations this past year. Thank you to everyone who has made a gift to the Foundation.

Looking ahead, NLA President Peter Toth, MD, PhD, and I are asking you to support an initiative of great importance to the Foundation. The NLA recently unveiled a limited-time offer of Lifetime Membership in the NLA, which would charge members a one-time fee that would include a generous donation of $1,000 to the Foundation for the purpose of funding lipidology fellowships. Applications to participate in this offer will be accepted through December 2013. To learn more, please visit www.lipid.org/lifemember.

Please continue to support our FH outreach and our fundraising initiatives. Soon, the Foundation will be making changes in several important areas. Subcommittees have been established to review fundraising and development, criteria for Foundation grants, refinement of our mission. I look forward to sharing details of our progress with you in the coming months.

As always, thanks for your support and dedication to the Foundation. Together, we will continue to accomplish great things.

ANNE C. GOLDBERG, MD, FNLA
President, Foundation of the National Lipid Association
Associate Professor of Medicine
Washington University School of Medicine
St. Louis, MO
Diplomate, American Board of Clinical Lipidology

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connect - collaborate - contribute

LipidSpin
Clinical Feature References

7. Leen T, Fishorod T, Mandhau T, Oue G. Diagnosis of familial hypercholesterolemia in general practice using clinical diagnostic criteria or genetic testing as part of cascade genetics screening; Community Genetics (2008);11:26-35.

EBM Tools for Practice References


References

4. Kavey R, Allada V, Daniels S, et al. American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young, American Heart Association Council on Epidemiology and Prevention, American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism; High Blood Pressure Research; Cardiovascular Nursing, and the Kidney and Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research; Cardiovascular Risk Reduction in high-risk pediatric patients: a Scientific Statement from the American Heart Association Expert Panel on Population and Prevention Science: the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney and Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research endorsed by the American Academy of Pediatrics. Circulation. 2006;114:2701-2738.


Lipid Spin References


The National Lipid Association now offers the 2011 Update of the NLA-SAP series—a one-of-a-kind comprehensive, clinical problem-solving program and self-assessment exam. Designed for physicians, physician assistants, nurses, pharmacists, and dietitians managing patients with dyslipidemia, the NLA-SAP serves as an invaluable resource to ensure mastery of this critical content and to prepare you for certification, maintenance of certification, and/or state licensure.

The four-volume NLA-SAP series provides over 750 multiple-choice questions with robust, evidence-based critiques:

- **Volume I** Basic Lipid and Lipoprotein Metabolism, Diagnosis and Treatment of Dyslipidemia
- **Volume II** Management of Cardiometabolic Risk, Biomarkers of Atherosclerosis, Epidemiology and Statistics, Clinical Trials
- **Volume III** Complex Case Management and Advanced Pharmacology
- **Volume IV** Vascular Biology, Advanced Lipid Metabolism and Lipoprotein Biochemistry

Each Volume of the NLA-SAP consists of a board exam-style Question Book and a separate, referenced Critique Book, providing comprehensive explanations for the correct answers.

**Benefits of Participation in the NLA-SAP**

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