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Look for the NLA Community logo to discuss articles online at www.lipid.org
It has been my distinct pleasure to serve as President of the National Lipid Association (NLA) during the 2013/2014 term. I am thankful to have been a part of the leadership in an organization with so many dedicated colleagues. I was blessed to serve with a wonderful Executive Committee and surrounded by loyal friends, colleagues, and NLA staff.

We have fulfilled our important mission this year through many significant initiatives. In coordination with the Familial Hypercholesterolemia (FH) Foundation, we applied for a new ICD-10 code for FH which will have a significant effect on the underdiagnoses and undertreatment of this deadly disease; we petitioned the National Committee for Quality Assurance to NOT retire low-density lipoprotein cholesterol (LDL-C) screening and LDL-C control (<100 mg/dL) HEDIS quality measurements for 2015 in patients discharged alive for acute myocardial infarction, coronary artery bypass graft or percutaneous coronary interventions in the year prior to the measurement year, or who had a diagnosis of ischemic vascular disease or with diabetes; published the 2013 Statin Safety Update and Health Information Technology papers in the Journal of Clinical Lipidology (JCL); and conducted a successful public awareness campaign with the Foundation of the NLA educating patients and providers on FH through the “Are You the One?” campaign that coincided with National Cholesterol Education Month. During my time as President, the NLA held three successful meetings. The latest of the three, the Spring Clinical Update in Maui, HI was our first international meeting with speakers from around the globe, and we exceeded our goal number of attendees.

Perhaps the most important undertaking within the past year, however, was reviewing the newly released ACC/AHA cholesterol guidelines. Following their release, the NLA convened an expert panel to develop recommendations to assist clinicians in the exercise of clinical judgment regarding the management of dyslipidemias. The NLA issued a draft of the clinical recommendations planned to be released on May 2. The panel will be presenting these draft recommendations titled ‘The National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia’ in a Special Education Session at the Annual Scientific Sessions in Orlando, FL. We welcome your thoughts on these recommendations; please view and comment on the draft here: www.lipid.org/patientcentered. The final document will be published in the fall issue of the JCL in coordination with the Fall Clinical Lipid Update in Indianapolis.

Thanks as always for your continued support of the NLA. Our members are our most valuable asset, and we appreciate your participation at every level. I urge you to continue to be involved with the NLA in any way possible.
From the MWLA President:
Our Outcome Challenges are Universal in Scope

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When the task of writing the quarterly Lipid Spin was announced at our Board meeting, the vast geographical 11 state volunteers immediately responded. The knowledge, talent, skills and passion expressed show the commitment and specialized expertise of the membership. Their enthusiasm for participating in this issue showed their commitment to educating health providers and patients.

Lipidologists and the National Lipid Association are rapidly evolving to keep pace with the overwhelming research and information available to enhance our specialty skills. This age of high technology and methods of communications are changing our practices and standards of care. Health care is a comprehensive team approach as lipid specialists communicate with professionals who treat patients’ complex lipid abnormalities.

Medical costs continue to escalate and lipidologists, with their specialty expertise, help to control costs, reduce patient risks and the number of vascular events. The informed lipidologist practices and utilizes the best scientific evidence for medical interventions and treatments.

As lipidologists, the privileged patient encounter is a relationship to optimize our patients’ health. It is a very trusting relationship as we plan their primary or secondary prevention or tertiary health plans.

A lipidologist’s intervention for a successful outcome continues to be a challenge. It must include daily recommendations, personal attitudes, behavioral activity, medication effects and available resources. Time is always at a premium as we inform and educate patients to optimize their health outcomes.

C. Everett Koop, MD, our former United States surgeon general, once said, “Drugs don’t work in patients who don’t take them.” As specialists, we have the ability to teach and encourage as we impact our patients’ future health.

The Midwest Lipid Association and NLA culture is global. Lipidologists’ challenges are to modify risks in the face of the varied ethnic and broad cultural and medical beliefs in patients we manage. The shared risks are universal – smoking, diabetes mellitus, lipid control, obesity, hypertension, diet, physical activity, alcohol and
The challenge of specialists is to collect accurate health information and conditions. We must recommend treatments and share health care information to be able to work on alternative treatments that will improve cultural beliefs for personal health status.

Our practices are in the rural states of North Dakota and Wisconsin. We value discussions of complex cases with experts from our association. Thank you all for your expertise.

The NLA membership is a vast care-giving team. The health care provided by lipid specialists is an area of expertise in the continual challenge of vascular diseases that remain the No. 1 cause of death. A respectable career as a lipidologist in our health care system has a mission to impact our patients for a positive health outcome.

As members of the NLA it has made our professional growth in this extensive area of lipids a valuable educational asset that has benefited the health of our patients. We hope you all realize the impact you have made in your local communities as a specialist in lipids. We are a small organization, but by each of us committing to the mission of the NLA and the challenge of preventing vascular events, we have an impact on the health of America. We all must keep our passion for excellence in the care of our patients. We are few but we continue as specialists in the world of academia and in the day-to-day challenges of primary care in rural America.

It is with great pleasure that we bring you this issue focusing on Clinical Conundrums in Special Populations. As Dr. Ito mentions in his Presidents Message the NLA has been very busy this year. In an effort to help clinical lipidologists we convened a panel of Clinical Lipidology experts to provide guidance given the plethora of guidelines now available regarding management of dyslipidemia. Our draft document posted on the website on May 2 addresses recent guidelines and how to use them from the perspective of a Clinical Lipidologist. We have taken the position of helping simplify the approach to management and have summarized and provided our perspective in contrast to recent American College of Cardiology (ACC), American Heart Association (AHA) and International Atherosclerosis Society (IAS) guidelines which we hope will be very useful for people taking care of patents with lipid disorders. We have aimed to help practicing health care providers move forward in a time when guidelines differ even after reviewing much of the same evidence. We believe that population inference is important and the guidelines that have recently emerged do a good job of giving readers opinions for best management for average patients presenting with average yet different risk status. We believe that no patient is average and each management decision needs to be informed by best evidence, clinical experience and patient values. Our plan is to provide more guidance for special populations in further panel discussions. Most of the systematic literature reviewed providing basis for the ACC/AHA and IAS approaches data is reviewed for persons over 40 years of age. Younger subjects and women, particularly pregnant women or those at risk for pregnancy, tend to be excluded, even if they have substantially elevated modifiable risk factors and are consequently at high lifetime risk or their offspring is at higher lifetime risk. Evidence is accumulating that long term exposure to CVD risk factors drives atherogenesis and that early treatment can modify disease evolution and risk of future CVD events. This represents an opportunity for ‘investment’ in future cardiovascular health.

We are pleased to provide several approaches to special population in this issue. We are delighted that Neil Stone, MD, the first author on the recently published 2013 ACC/AHA guidelines, has given us a wonderful example of how to individualize the ACC/AHA approach. We are also pleased to see efforts for management for persons who are not specifically addressed by these guidelines. As always we welcome diverse opinions and fully recognize that there are divergent approaches to interpreting best evidence and using it individually. This requires best clinical judgment and no amount of past experience or collection of past experiences can substitute wholly and exclusively for the exercise of good clinical judgment.

With this in mind we hope you enjoy the different approaches taken in the articles in this issue. We also look forward to your input and we do hope you will comment on the draft document posted on the NLA website. Viva la differences.
Clinical Feature:
South Asian Ethnicity – An Underappreciated Cardiovascular Risk

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South Asians are defined as individuals who derive their ethnic origin from the Indian subcontinent. Nearly 3.4 million South Asians currently reside in the United States experiencing a growth of 81% from 2000 to 2010. Interestingly, while South Asians account for only 25% of the world’s population, they account for a disproportionate 60% of the world’s cardiovascular disease burden. Amongst South Asians who live in the western world, rates of coronary heart disease are greater than 10% of the population with mortality rates in the United States nearly two times that of any other major ethnic group. Traditional risk factors, as defined by ATP III Framingham based risk calculators, often fall short of identifying South Asians for their more aggressive, earlier onset, and often more fatal forms of heart disease. While the specific etiologies that define South Asian cardiovascular risk is a subject of continuous investigation, current data suggests that a unique combination of lipid and metabolic abnormalities contribute to this disease burden.

Beyond Traditional Lipid Measurements
The South Asian lipid profile is characterized by elevated LDL and triglycerides with depressed HDL (SHARE Study) when comparing South Asian lipid profiles to those of Caucasians and Chinese living in Canada. In the SABRE Study comparing South Asians to Europeans this is also observed (see table). This profile often fails to raise red flags in most Framingham based cardiovascular risk calculators that emphasize total cholesterol and HDL. The landmark INTERHEART Study looked at 15,152 first time acute myocardial infarction cases across 52 countries compared to a nearly equal number of age matched non-myocardial infarction controls. Of the acute myocardial infarction cases studied, 1,732 cases were of South Asian descent across 5 countries. One key finding was that both the prevalence and value of ApoB100/ApoA-1 ratio was statistically greater in South Asian cases compared to other ethnicities. Furthermore, the ApoB100/ApoA-1 ratio was found to be a much stronger indicator of cardiovascular disease risk than traditional LDL, HDL, and LDL/HDL ratios.

Small lipid particle size creates a more atherogenic LDL particle that is prone to oxidation and a HDL particle that is rendered less protective. KR Kulkarni et
once coronary disease has been intervened upon with either coronary artery bypass surgery or coronary angioplasty in South Asians who possess Lp(a) levels between 20 and 30 mg/dl, there is a two to threefold increase in acute myocardial infarctions and restenosis. \(^{2,17,19}\) Lp(a) is being considered as a screening tool to identify those South Asians at most risk for premature heart disease.

**Metabolic Syndrome**

Patients with metabolic syndrome have a 50-60% greater risk of cardiovascular disease and a two to threefold greater risk of cardiovascular mortality. \(^{2,20,21}\) The risk of cardiovascular mortality is increased in ethnic individuals. \(^{2,20,21}\) The INTERHEART study demonstrated that 20% of South Asian acute myocardial infarction cases and 26.5% of South Asian controls consumed more than one serving of fresh fruits and vegetables daily. \(^{6}\) This illustrates a major nutritional misconception of South Asians whose diet is actually dominated by prolonged cooking of vegetables \(^{6}\) as well as a high consumption of cooked carbohydrates and fats.

**Homocysteine**

Treatment of hyperhomocysteinemia (>15 µM) in the setting of coronary artery disease for the purposes of primary

### Table 1. Compiled lipid data from Study of Health Assessment and Risk in Ethnic groups (SHARE) and Relationship Between Metabolic Risk Factors and Incident Cardiovascular Disease in Europeans, South Asians, and African Caribbeans [Southall and Brent Revisited] (SABRE) Studies \(^{3,5}\) Data from SABRE Study was converted from mmol/L to mg/dl.

<table>
<thead>
<tr>
<th>Factor (mg/dl)</th>
<th>SHARE</th>
<th>SABRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td><strong>211.77</strong></td>
<td>184.6</td>
</tr>
<tr>
<td>LDL</td>
<td><strong>128.7</strong></td>
<td>123.63</td>
</tr>
<tr>
<td>HDL</td>
<td><strong>38.56</strong></td>
<td>46.41</td>
</tr>
<tr>
<td>Triglycerides</td>
<td><strong>174.44</strong></td>
<td>145.96</td>
</tr>
</tbody>
</table>

**Lipoprotein (a) [Lp(a)]**

Lipoprotein (a) has been associated with elevated cardiovascular risk independent of LDL-C, non-HDL-C, and the presence of other cardiovascular risk factors. \(^{14}\) High Lp(a) levels (greater than 40 mg/dl) in the setting of total cholesterol/HDL ratios greater than 5.8 increase the odds of premature coronary artery disease by a factor of 2.95. \(^{15}\) Since South Asians are often characterized by low HDL levels compared to total cholesterol values and are known to have markedly elevated Lp(a) (greater than 30 mg/dl) levels compared to their Caucasian counterparts, it is reasonable to presume that excess Lp(a) levels might play a role in the severe and high premature rates of coronary artery disease amongst this ethnic population. \(^{3,16}\) Evidence suggests that relationship between insulin resistance and obesity, cornerstones of the metabolic syndrome definition, seems to be somewhat different amongst South Asians. The “thin-fat phenotype”, a body structure consistent with high visceral fat to low lean muscle ratios, is often found in the South Asian body habitus. \(^{22,23}\) As a result of this, South Asians have demonstrated evidence of diabetes and insulin resistance at BMI values as low as 23 kg/m². \(^{24}\) For this reason, many have favored the use of waist circumference or waist-to-hip ratio as a more precise measure of South Asian obesity and therefore as a practical measurement to screen for metabolic syndrome. INTERHEART found South Asian men and women with acute myocardial infarctions often had significantly higher waist-to-hip ratios compared to control subjects (27.9% and 39.9% respectively). \(^{6}\) McKeigue et al found Asian Indians in the United Kingdom to have higher waist-to-hip ratios compared to their European counterparts despite comparable BMIs. Furthermore, this same group of South Asians were found to have a fourfold increase in diabetes and a twofold increase in post-glucose insulin levels for every 0.04 unit rise in waist-to-hip ratio. \(^{25,26}\) Such characteristics have led to nearly a third of South Asians studied in trials within the United States and Canada to be diagnosed as diabetic. \(^{3,22,27}\) These factors are overlooked by lay and medical professionals within and outside the South Asian community because vegetarianism, which is thought to be heart healthy, is a common hallmark of the South Asian community’s diet. The INTERHEART study demonstrated only 20% of South Asian acute myocardial infarction cases and 26.5% of South Asian controls consumed more than one serving of fresh fruits and vegetables daily. \(^{5}\) This illustrates a major nutritional misconception of South Asians whose diet is actually dominated by prolonged cooking of vegetables \(^{6}\) as well as a high consumption of cooked carbohydrates and fats.
and secondary prevention has failed to show significant benefit. These studies however, failed to include South Asians and a number of other ethnic groups. Boushey et al reported that for every 1 µM increase in homocysteine in the setting of hyperhomocysteinemia there exists a 12% and 16% greater coronary artery disease risk among men and women respectfully. Furthermore, evidence exists that among South Asians in the United Kingdom, elevated homocysteine levels contributed to twice as many cardiovascular deaths compared to their European counterparts. Studies also concluded that this elevated homocysteine level was largely due to vitamin B12 and folate deficiency suggesting a possible reversible mechanism to curb the cardiovascular disease incidence in this high risk community. Further study regarding benefit of therapy in this population is required.

**Adipokines**

There is strong evidence linking inflammation to cardiovascular disease and this has often been thought to be another component of the South Asian cardiovascular risk profile. The SHARE study demonstrated that South Asians possessed elevated (age- and sex-adjusted) hs-CRP levels compared to those of Chinese and European descent. Raji et al demonstrated that Asian Indians were found to have depressed levels of adiponectins, which were associated with endothelial dysfunction, diminished fibrinolysis capacity, and increased insulin resistance. When looking at the inverse relationship of leptin and insulin sensitivity amongst non-diabetic South Asians, significantly higher levels of leptin with lower insulin sensitivity were noted compared to Caucasian and Chinese participants. Ethnicity was the only statistically significant variable associated. Elevated inflammatory markers mechanistically may be important with regards to the South Asian cardiovascular epidemic. The study of novel biomarkers may assist in the early identification of cardiac risk in South Asians.

"Health care providers need to become much more aware of risk in this minority group."

**Conclusion**

South Asians are a major ethnic community within the United States. They face a higher risk of acute myocardial infarction and prevalence of coronary artery disease at a much younger age. This community demonstrates a more atherogenic lipid profile, a body habitus with higher visceral fat content rendering them more prone to insulin resistance, and a unique level of inflammatory markers that make them more susceptible to thrombosis and coronary plaque buildup. More than one out of ten South Asians are affected by heart disease with a mortality rate that is twice the general population. This community can ill afford the effects of false negative screening measures provided by traditional cardiovascular risk stratification tools. European based guidelines such as the United Kingdom’s NICE lipid modification measures explicitly state that South Asians are more likely to develop cardiovascular disease at a younger age and estimates of cardiovascular risk by Framingham based calculators should be increased by a factor of 1.4. Unfortunately, NHLBI pooled cohort risk estimators do not take South Asian ancestry into account. Health care providers need to become much more aware of risk in this minority group. Earlier and more aggressive use of non-medication and medication interventions should be considered. Advanced lipid testing might be more valid and clinically useful for predicting risk in the South Asian community. Clearly, research investigating both novel testing and treatment in this high risk community is both necessary and lacking. Public education measures should be adopted that inform South Asians of their risk and advise on lifestyle changes, dietary habits, and the utility of preventive care services in a culturally competent manner. Finally, an understanding within the ranks of South Asian community organizations must be attained so appropriate public health campaigns can be initiated and validated as truthful by trusted community leaders. In the end, it is a multidisciplinary approach of public health, education, clinical prevention, and investigation that will curb this cardiovascular epidemic that deeply affects this significant community in the United States and abroad.

Disclosure statement: Dr. Sitafalwalla and Dr. Norris have no disclosures to report. References are listed on page 27.
What will it take to lower your patient’s risk of heart attack and stroke? Can we improve on previous risk prediction tools? Can we address global cardiovascular disease risk better in women and African Americans? Can we initiate atherosclerotic cardiovascular disease (ASCVD) risk reduction with evidence based “proven” therapy? Finally, can we optimize the risk reduction obtained by a focus on adherence to both lifestyle and, in higher risk cases, the proper intensity of appropriate cholesterol lowering drug therapy? These are the challenges that the new AHA/ACC guidelines attempt to address.

The Risk Assessment Working Group designed a new risk calculator that improves on the Framingham Risk equation for “hard CHD” in ATP III in several important ways. It uses pooled data from several long-standing, community-based US cohort studies. These new sex-specific and race-specific equations predict 10-year risk for atherosclerotic cardiovascular disease (ASCVD) and do an excellent job in rank ordering risk (from highest to lowest). Unlike the older Framingham risk scores, women and African Americans especially benefit. Now stroke is added as an outcome and African-American status as an input. For patients younger than age 60, lifetime risk can be estimated. We believe this is a superb aid for counseling patients on ASCVD risk reduction. Although there were accuracy concerns raised by some when the calculator was released, further review suggested that the problem might have been in the comparator groups chosen. These groups consisted of clinical trial candidates or participants with self-reported risk factors. They were not from long-standing community based cohorts such as those used to determine the risk equations. Indeed, it seems likely that the difference between observed and reported events in those predicted to be at higher risk by the calculator may represent statin use! This may be what occurred with participants of the Multi-ethnic Study of Atherosclerosis (MESA). MESA participants are not necessarily a sample representative of the greater US population as the cohort was selected from men and women 45-84 years of age, who were free...
of clinical ASCVD at entry. Furthermore, MESA participants received their coronary calcium scores during the study which likely prompted preventive cardiovascular therapies, such as statins.

Two examples of how the risk calculator works are given in Table 1.

This compares the same risk profile for an African American and non-African American woman. Her lipids are: TC 212, TG 140, HDL-C 47, LDL-C 137, non-HDL-C 165. Non-HDL-C is in the risk equation because we enter total cholesterol and HDL-C.

The African American woman, age 62, with SBP 140, on no medication; without diabetes, not smoking, lipids: ASCVD risk 8.7%. The ACC AHA Guidelines suggest she should be offered the option of statin therapy considering the potential for benefit and adverse effects, drug-drug interactions and preferences. You explain to her that age represents a measure of the exposure to her risk factors. You note that she needs to follow either a DASH or a Mediterranean diet.

She is concerned about stroke (her mother had one in her 50s). We point out here that the guidelines discuss other factors that can be used when a risk decision is uncertain. These include family history of premature ASCVD, LDL-C ≥ 160 mg/dl, hs-CRP ≥ 2.0 mg/L, coronary calcium score ≥ 300 Agatston units; ankle brachial index (ABI) and a lifetime risk estimate.

The guidelines indicate that before a statin prescription is written in primary prevention, a risk discussion occurs. You review potential for statin benefits, adverse effects and drug-drug interactions, control of other risk factors, and her preference.

You expect, however, that she will likely attain an LDL-C < 100 mg/dl based on both improved lifestyle and moderate intensity statin therapy. You specifically recommend a “system” such as a weekly pillbox next to the toothbrush as reminder for example so she won’t forget to take her statin.

You also have a risk discussion with a white woman, age 62, SBP 140 on no treatment, without diabetes and not smoking: Her ASCVD risk is 5.5%. She wants to know if she should take a statin to lower her LDL-C to less than 100 mg/dl. You point out that under the new guidelines, the emphasis is on therapy whose benefits outweigh potential adverse effects. In those at lower global cardiovascular risk, the benefit/risk balance is not as favorable as when risk is higher. She has a family history of longevity but wants to be reassured that she doesn’t need a statin. You determine an hs-CRP which is 1.5. She reports improved lifestyle habits and will self-monitor with a diet diary, a pedometer, and daily weights. She is eager to see her progress and is scheduled to see your nurse for a BP check, weight, and lipid panel in 3 months.

Both of these cases emphasize that the guidelines are not “one size fits all.” For high risk individuals such as those with ASCVD already, or diabetes in the 40-75 age range with LDL-C in the 70-189 mg/dl range, or a primary elevation of LDL-C ≥ 190 mg/dl, the focus is on maximally tolerated statin intensity. For primary prevention, use of the risk calculator is designed to initiate a risk discussion to address the patient’s options. Whether a statin is used depends on numerous factors as described above and includes the patient’s preferences. Finally, other factors mentioned above can be helpful for the clinician-patient discussion.

For young adults, a family history of premature ASCVD or a primary elevation...
of LDL-C ≥ 160 mg/dl should prompt consideration of statin therapy despite the low 10-year ASCVD risk. For older adults, especially those 65-75 concerned that “age” alone is prompting a statin prescription, there is the potential to inform that decision with a coronary artery calcium score, hs-CRP, or ankle-brachial index. Physicians should find the safety section on statin therapy useful. Although non-statin are not drugs of first choice to lower ASCVD risk, the guidelines note they may be considered in higher risk patients (secondary prevention, primary elevation of LDL-C ≥ 190 mg/dl, and diabetes 40-75 years, LDL-C 70-<190 mg/dl) who cannot tolerate maximal intensity of statin therapy or are completely statin intolerant.

These new guidelines focus on global cardiovascular risk assessment to determine those who are candidates for statin therapy. Statins were chosen as initial drugs of choice both to lower cholesterol and reduce ASCVD risk. Statins are both inexpensive (most are generic), and effective as shown in multiple, large-scale secondary and primary prevention clinical trials. Indeed, in primary prevention, both the per-person Cholesterol Treatment Trialists’ Meta-Analysis⁴ and the most recent Cochrane Review⁵ have shown that there is now evidence for reducing total mortality with statin therapy. The guidelines should focus therapy more precisely on those who will benefit the most.

As noted above, the cholesterol guideline mandated that the patient and clinician engage in a risk discussion before prescription of a statin occurs. This clinician-patient discussion was designed to understand the sources of the patient’s predicted risk, review potentially modifiable lifestyle factors that could help to reduce that risk, and provide a balanced perspective on the net gain from a statin prescription. This meant reviewing the potential for benefit as well as the potential for adverse effects or drug-drug interactions of statins. This is best appreciated by using an estimation of absolute risks as determined from randomized clinical trials.

Disclosure statement: Dr. Stone has no disclosures to report. Dr. Goldberg has received research grants from Abbott, Amarin, Merck, GlaxoSmithKline, ISIS, Genzyme, Sanofi, Regeneron, Genentech, Roche, Amgen and has received honorarium from Merck & Co., Inc. and Astra-Zeneca. Dr. Watson has received honorarium from Merck & Co. Inc.

References are listed on page 27.
**EBM Tools for Practice: Metabolic Syndrome Guidelines for Populations Around the World. How Do Screening Tools Differ?**

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**Definition of Metabolic Syndrome**  
Metabolic syndrome is considered a “multiplex” cardiovascular risk factor, in that each component of the cluster of abnormalities is a risk factor in its own right. Metabolic syndrome is recognized clinically by the findings of abdominal obesity, elevated triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, high blood glucose and/or insulin resistance.¹ Metabolic syndrome is characterized by a pro-thrombotic and a pro-inflammatory state. When introduced as Syndrome X by Reaven in 1988 and also called insulin resistance syndrome, surprisingly obesity was omitted.² The term “metabolic syndrome” was formerly adopted by the World Health Organization (WHO) in 1999³ and soon after by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in 2001⁴ and then by other major organizations, such as the International Diabetes Federation (IDF)⁵ American Association of Clinical Endocrinologists (AACE)⁶ and European Group for the study of Insulin Resistance (EGIR)⁷. Table 1 summarizes the clinical tools used to diagnose metabolic syndrome identified by different professional organizations.

**How Do Screening Tools Differ?**  
Although similar, some organizations put special emphasis on certain variables by using different cut-off values. Most organizations have criteria for obesity (mostly abdominal), insulin resistance, dyslipidemia and blood pressure. The proposals put forward by the NCEP expert panel on dietician evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III or ATP III)⁴ and the International Diabetes Federations (IDF)⁵ use virtually the same criteria and cut-off values. The exception is waist circumference, for which the IDF cut-off value is lower. The IDF also has proposed different waist-circumference cut-offs for various regions of the world to address the question of ethnicity. In addition, the IDF also has proposed different waist-circumference cut-offs for various regions of the world to address the question of ethnicity. In addition, the IDF makes waist circumference a mandatory criterion. To be diagnosed with metabolic syndrome, one should have a waist circumference above the proposed IDF waist cut-off plus two other components of metabolic syndrome. In a given population, metabolic syndrome...
prevalence can be expected to be higher when IDF criteria are applied. Moreover, since the AACE did not propose a working definition, its criteria can hardly be tested in population studies unless investigators decide to specify their criteria/cut-offs in advance. Therefore, when comparing the criteria for metabolic syndrome and incident cardiovascular disease (CVD) or diabetes, investigators can choose from the clinical criteria of NCEP ATP III, IDF, WHO or EGIR. The hypertriglyceridemic waist also has been launched as an approach for metabolic syndrome, though the component of blood pressure has not been considered in this approach and, therefore, will not further be discussed within the scope of cardio-metabolic syndrome.8 (Table 2)

Metabolic Syndrome and CVD Risk or Cardiometabolic Syndrome
A few prospective studies have compared metabolic syndrome criteria in assessing CVD risk. Although most criteria have a similar relationship to CVD risk, NCEP ATP III criteria seem to have the strongest ties to CVD. Independent of the clinical criteria studied, metabolic syndrome better predicts type 2 diabetes risk than CVD risk. During the past year there has been debate about whether one should consider metabolic syndrome to be a cluster of different metabolic components leading to additive CVD risk prediction or if it more directly relays to CVD risk as a cardiometabolic syndrome.1

1. The Insulin-Resistance Atherosclerosis Study (IRAS)
One of the few prospective population studies to compare NCEP ATP III, IDF, WHO and hypertriglyceridemic waist criteria is the Insulin-Resistance Atherosclerosis Study (IRAS).9 This study followed 822 subjects ages 40 to 69 without diabetes for 5.2 years. A total of 148 people developed type 2 diabetes. The best predictor of incident diabetes was impaired glucose tolerance. The prevalence of metabolic syndrome was 27.5%, 34.4%, 39.5% and 18.4% with NCEP ATP III, WHO, IDF and hypertriglyceridemic waist criteria, respectively. NCEP ATP III criteria showed the strongest association with incident diabetes, with an odds ratio (OR) of 4.14 (95% CI, 2.79-6.16). The population attributable risk (PAR), which is an estimate of the proportion of CVD in a population attributable to metabolic syndrome, was very similar between NCEP ATP III, WHO and IDF criteria (46.3%, 48.0% and 48.7%, respectively) and lower with hypertriglyceridemic waist criteria (21.7%). The authors of the IRAS concluded that IDF and NCEP ATP III criteria predicted diabetes at least as well as WHO criteria.

2. The San Antonio Heart Study
Lorenzo, et al.10, used data from the San Antonio Heart Study (SAHS) to compare NCEP ATP III, IDF and WHO screening tools in predicting CVD and diabetes incidence. SAHS recruited 2,559 Mexican American and non-Hispanic white individuals and followed them for an average of 7.4 years. Metabolic syndrome prevalence was higher when IDF criteria were used and lower when WHO criteria were used. During the follow-up, 93 men and 63 women developed CVD events and 195 subjects developed diabetes. NCEP ATP III, IDF and WHO clinical criteria yielded an OR for CVD events of 2.00 (95% CI, 1.33-3.01), 1.69 (95% CI, 1.13-2.34) and 1.73 (95% CI, 1.12-2.67), respectively. The authors found that metabolic

<table>
<thead>
<tr>
<th>Clinical Tools to Diagnose the Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCEP ATP III</strong></td>
</tr>
<tr>
<td>• Elevated Waist circumference</td>
</tr>
<tr>
<td>• Reduced HDL -C</td>
</tr>
<tr>
<td>• Elevated Triglycerides</td>
</tr>
<tr>
<td>• Elevated Blood Pressure</td>
</tr>
<tr>
<td>• Elevated fasting Glucose</td>
</tr>
<tr>
<td><strong>IDF</strong></td>
</tr>
<tr>
<td>• Waist Girth</td>
</tr>
<tr>
<td>• HDL Cholesterol</td>
</tr>
<tr>
<td>• Triglycerides</td>
</tr>
<tr>
<td>• Blood Pressure</td>
</tr>
<tr>
<td>• Glucose</td>
</tr>
<tr>
<td><strong>WHO</strong></td>
</tr>
<tr>
<td>• WHR, BMI</td>
</tr>
<tr>
<td>• HDL Cholesterol</td>
</tr>
<tr>
<td>• Triglycerides</td>
</tr>
<tr>
<td>• Blood Pressure</td>
</tr>
<tr>
<td>• Glucose</td>
</tr>
<tr>
<td>• Insulin</td>
</tr>
<tr>
<td>• Microalbuminuria</td>
</tr>
<tr>
<td><strong>EGIR</strong></td>
</tr>
<tr>
<td>• Waist Girth</td>
</tr>
<tr>
<td>• HDL Cholesterol</td>
</tr>
<tr>
<td>• Triglycerides</td>
</tr>
<tr>
<td>• Blood Pressure</td>
</tr>
<tr>
<td>• Glucose</td>
</tr>
<tr>
<td>• Insulin</td>
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<tr>
<td><strong>AACE</strong></td>
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<tr>
<td>• BMI</td>
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<tr>
<td>• HDL Cholesterol</td>
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<tr>
<td>• Triglycerides</td>
</tr>
<tr>
<td>• Blood Pressure</td>
</tr>
<tr>
<td>• Glucose</td>
</tr>
<tr>
<td>• Other Features</td>
</tr>
<tr>
<td>of insulin resistance</td>
</tr>
</tbody>
</table>
Lipid syndrome was better able to predict CVD in men ages 45 and older and in women ages 55 and over. They also suggested that, for both men and women, adding the diagnosis of metabolic syndrome to traditional risk factors included in the Framingham risk score could enhance CVD prediction.

3. The DECODE Study
The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study compared the ability of NCEP ATP III, WHO and IDF criteria to predict CVD deaths. A total of 4,715 men and 5,554 women ages 30 to 89 were followed for a period ranging from 7 to 16 years. Metabolic syndrome prevalence using WHO criteria was 27.0% in men and 19.7% in women. using NCEP ATP III criteria, it was 32.2% in men and 28.5% in women. With IDF criteria, it was 35.9% in men and 34.1% in women. With respect to CVD deaths, the Hazard Ratios (HR) s for WHO clinical criteria were 2.09 (95% CI, 1.59-2.76) in men and 1.60 (95% CI, 1.01-2.51) in women; with NCEP ATP III criteria, the corresponding HRs were 1.72 (95% CI, 1.31-2.26) and 1.09 (95% CI, 0.70-1.69). They were correspondingly 1.51 (95% CI, 1.15-1.99) and 1.53 (95% CI, 0.99-2.36) using IDF criteria.

In the DECODE study, WHO clinical criteria seemed to predict CVD death risk the best, and this association generally was stronger in men than in women.

Does Ethnicity Matter?
In the past, most cardiovascular risk factors have been derived from findings in Caucasian populations. Obesity and diabetes are on the rise in other ethnicities as well. A more tailored definition for metabolic syndrome may be more useful here. There was an attempt in 2005 to determine that the waist circumference cut-off value for the definition of metabolic syndrome as dependent on ethnicity. One key question is whether the same criteria should be applied to someone of a particular ethnic group, regardless of his or her country of residence. IDF waist-circumference recommendations for metabolic syndrome are the same for women everywhere, owing in part to the paucity of good data, but they are somewhat higher for men of European origin (Europids) than for those of Asian origin. Levels for Asian populations are based on WHO recommendations. Fewer data are available for other regions, but Europid male recommendations also are currently applied to men of the Middle East, Eastern Mediterranean region and Sub-Saharan Africa, pending the provision of new data.

Conclusion
The growing epidemic of obesity has led to a cluster of risk factors – abdominal obesity, pre-hypertension, pre-diabetes and dyslipidemia – defined as metabolic syndrome. The syndrome is associated with inflammation and insulin resistance. There have been several definitions of metabolic syndrome in the past. With the universal definition of metabolic syndrome and a high associated risk for CVD and diabetes, greater efforts have been put forth to individualize the definition of metabolic syndrome in relation to ethnicity (especially for the waist circumference component).

Future study is necessary to determine the optimal treatment cut off values of individual risk factors and for the global treatment of metabolic syndrome beyond lifestyle changes to reduce cardiovascular disease.

Disclosure statement: Dr. Godishala and Dr. Duprez have no disclosures to report.

References are listed on page 27.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Waist Circumference</td>
<td>Population-and country-specific definitions</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>≥150 mg/dL (1.7 mmol/L)</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>&lt; 40 mg/dL (1.0 mmol/L) in males</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>&lt; 50 mg/dL (1.3 mmol/L) in females</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>systolic ≥130 and/or diastolic ≥ 85 mm Hg</td>
</tr>
<tr>
<td></td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>

Table 2. Criteria for Clinical Diagnosis of Metabolic Syndrome
Chronic kidney disease (CKD) has been established as an independent risk factor for cardiovascular disease. The data from multiple studies link a decrease in glomerular filtration rate (GFR) and/or proteinuria with increased risk for cardiovascular disease. Dyslipidemia likely plays a significant role in the pathophysiology of cardiovascular disease. In patients with CKD, the typical pattern of dyslipidemia is different from the general population: low-density lipoprotein (LDL) cholesterol level remains normal, high-density lipoprotein (HDL) cholesterol level is decreased and hypertriglyceridemia is common. The composition of LDL is altered, resulting in a predominance of atherogenic, small dense LDL. The presence of proteinuria, especially when significant – such as with the nephrotic syndrome – alters that profile with a rise in serum LDL and VLDL cholesterol levels. When patients have end-stage renal disease (ESRD), the decrease in proteinuria leads to a return to the classical pattern of dyslipidemia in CKD, with evidence that HDL particles are not only decreased in number but also dysfunctional. These data, among others, help explain the current recommended approach to managing dyslipidemia in patients with CKD. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recently have been published and have signaled a shift from the traditional approach to the use of LDL thresholds to determine the need for statin use in patients with CKD. Instead of “treat-to-target,” the KDIGO work group recommends against the use of LDL thresholds to determine the need for statin use in patients with CKD, instead advocating that all adults at least 50 years of age with a GFR below 60 ml/min/1.73 m² and not on dialysis should receive a statin with or without ezetimibe. For adults younger than 50 years and with CKD, a cardiovascular disease (CVD) risk assessment is used instead of LDL cholesterol levels to determine initiation of statin therapy.

While an initial assessment of lipid profile is still accepted practice, follow-up LDL cholesterol levels are no longer advised, based on the fact that LDL cholesterol levels do not correlate well with cardiovascular risk in CKD. The use of statins to treat dyslipidemia and prevent CVD in patients with CKD has been proven beneficial in numerous randomized controlled trials, including...
the Study of Heart and Renal Protection (SHARP), the Collaborative Atorvastatin Diabetes Study (CARDS) and the Cardiac Angiography in Renally Impaired Patients (CARE) study. The safety of statins in CKD traditionally has been of concern, especially when used in high doses. The side effects could be the result of decreased clearance or interaction with other commonly prescribed medications, such as calcium channel blockers. The recent guidelines did acknowledge this concern and suggested the use of specific doses of statins that have been shown to be safe in randomized controlled trials involving patients with CKD. It is worth noting that ezetimibe has been included in the recommendations as an add-on therapy to statins for patients with CKD. In the U.S., this constitutes an off-label indication that was based primarily on the results of the SHARP trial. The implications and feasibility of the use of a statin/ezetimibe combination in patients with CKD, considering the stance of the U.S. Food and Drug Administration (FDA), remain to be seen.

Patients with ESRD and already on dialysis have an even greater risk of CVD. Very little data exist about the optimal therapeutic options for dyslipidemia in these patients. The German Diabetes Dialysis Study (4D), SHARP and the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Hemodialysis: An Assessment of Survival and Cardiovascular Events) trials did not show improvement in outcomes despite reductions in LDL cholesterol levels. This has led the KDIGO group to recommend against initiation of statins and/or ezetimibe in patients on dialysis while at the same time suggesting that, if the patients were already on such medications, they be continued on the same regimen. This approach reflects the lack of high-grade evidence in this field.

Hypertriglyceridemia also should be addressed in patients with CKD. Lifestyle changes should constitute the cornerstone of therapy, with emphasis on decreasing carbohydrate intake and the use of fish oils. Fibrates are recommended only when triglyceride levels exceed 1000 mg/dl. When combined with a statin, fenofibrate is generally considered safer than gemfibrozil. Nevertheless, the combination of a statin with any fibrate should be avoided because of an increased risk of toxicity.

As compared to the traditional “treat-to-target,” the latest recommendations for the management of dyslipidemia in patients with CKD takes a “fire-and-forget” approach, with simpler algorithms. The KDIGO workgroup also identified several areas where evidence is weak or lacking and made them obvious targets for future research.

Disclosure statement: Dr. Krikorian and Dr. Lerma have no disclosures to report.

References are listed on page 28.
Cardiovascular disease (CVD) remains the leading cause of mortality in those > 75 years of age. In the United States, an estimated 84 million people have CVD, with approximately 50% of these Americans being ≥ 60 years old. The prevalence of CVD increases with age, from 15% in men and 9% in women between the ages of 20 and 39 to 79% in men and 85% in women ages 80+. Although the CVD burden is noted to be high in this subset of individuals, most studies and recommendations – including the recent 2013 ACC/AHA cholesterol treatment guidelines – primarily address individuals ages 40 to 75 years and place the elderly (>75 years) as a population needing special consideration. According to the 2013 ACC/AHA guidelines, moderate-intensity statins are recommended for those individuals >75 years of age with clinical atherosclerotic CVD. For primary prevention in this subset of patients, the recent guidelines recommend that physicians take into account comorbidities and side-effect profiles before initiating statin therapy.

A limited number of randomized clinical trials have evaluated the benefit of statin therapy specifically in the elderly population. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial randomized to pravastatin 40mg/day or placebo 5,804 individuals ages 70 to 82 years with a history of vascular disease. After a mean 3-year follow-up, statin therapy significantly reduced the risk of the primary end-point of coronary death, non-fatal myocardial infarction and fatal/non-fatal stroke. Moreover, in the Heart Protection Study (HPS), 20,536 individuals (5,806 were ≥ 70 years) with CVD, occlusive arterial disease or diabetes were randomized to simvastatin 40mg/day or placebo. In those individuals from 75 to 80 years old, CVD events decreased by approximately 25% and all-cause mortality decreased by 14.7%. The JUPITER study (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) was a multicenter, randomized, double-blinded, placebo-controlled trial evaluating the role of statins in primary prevention of CVD. Subjects enrolled had low-density lipoprotein cholesterol (LDL-C) levels < 130mg/dL and a C-reactive protein
(CRP) level of at least 2.0 mg/L and were randomized to treatment with rosuvastatin 20mg or placebo. Of the 17,802 patients enrolled, 5,695 participants were 70 years of age. The absolute risk reduction in the primary endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina or death associated with rosuvastatin was 48% greater in the elderly group when compared with the younger group. Based on the limited clinical trial data and subgroup analysis, statin therapy appears to benefit elderly patients in reducing coronary heart disease (CHD) events in both primary and secondary prevention. However, future clinical trials are needed to better establish the benefits of statin therapy in the elderly, particularly in those special populations over the age of 80 or with multiple co-morbid conditions.

When initiating statin therapy, it is important that health care providers pay careful attention to potential side effects. Elevated transaminases have been reported at incidences of up to 1%. These elevations were found to be dose related, with the majority of liver abnormalities occurring within the first three months of therapy. Statin-related myopathies range from myalgias or myositis to overt rhabdomyolysis with elevated creatine kinase (CK) levels and evidence of renal failure. Furthermore, polypharmacy in the elderly is a common concern and physicians must play close attention to possible drug and food interactions. With the exception of pravastatin, which is metabolized in the liver cytosol, all statins undergo metabolism by the cytochrome P450 isoenzyme systems. Approximately half of all drugs currently available in clinical practice are metabolized in the liver by the same CYP450 system. Concomitant use of large quantities of grape fruit juice and certain drugs such as fibrates, erythromycin, itraconazole, calcium channel blockers and cyclosporine can increase blood levels of some statins and, consequently, the risk for side effects. Total avoidance of all drug interactions is likely impossible, but careful consideration of medication pharmacokinetics and pharmacodynamics should be made with specific attention.

“Statin therapy appears to benefit elderly patients in reducing coronary heart disease (CHD) events in both primary and secondary prevention.”

In the care of hypercholesterolemia in your elderly patients, adherence to a few basic treatment pearls may be helpful:

- Review the patient’s medication list and diet for potential interactions with statins; choose statin therapy that may have the least likelihood for side effects.
- Regardless of the recommended goal dose, initiate statin therapy at a low dose and titrate to the goal dose as tolerated.
- Frequently assess for changes in the patient’s overall health status and goals of care to determine if an indication arises that would warrant stopping statin therapy.

Disclosure statement: Dr. Memon and Dr. Phan have no disclosures to report.

References are listed on page 28.
Treatment of the HIV-infected patient has evolved over the past decade into a prototype of how multidisciplinary team effort becomes an essential element in the practice of evidence-based medicine.

Prior to 1996, HIV-related mortality was >20% because of the disease itself but, since the advent of potent combination highly active antiretroviral therapy (HAART), the annual AIDS-related mortality is <2%.

Life expectancy for a patient diagnosed at the age of 25 has increased for the HIV-positive patient from 20 years to 33 years (compared with 51 years for a non-infected patient). Treatment has become lifelong.

This population of patients is thereby susceptible to all non-HIV-related chronic disease conditions occurring with advancing age. In terms of cardiovascular disease, the compounded risks of the HIV infection, superimposed on traditional cardiovascular risks, and the contribution of HAART creates a challenging task of clinical management.

Studies reflecting international clinical databases and cohorts suggest an overall increased rate of cardiovascular events in the HIV-infected population compared with those not infected. Not surprisingly, the relative coronary heart disease (CHD) risk is especially high in the cohort over 45 years of age.

Incidence of myocardial infarction and silent myocardial ischemia appear higher, even when corrected for other traditional risk factors, including dyslipidemias. Risk is compounded in patients who have increased duration of disease, prolonged exposure to therapy and poor immunologic recovery (cluster of differentiation 4 [CD4+] counts <200) after 2 years of HAART, with these patients having almost twice the rate of adverse cardiovascular events.

One of the significant HIV-associated clinical syndromes, which was first described in 1997 and, therefore, thought to be associated with HAART, is characterized by a change in body habitus due to abnormal fat distribution, known as HIV-associated lipodystrophy (HAL).

The term lipodystrophy embraces the combined changes of peripheral lipoatrophy (face, buttocks and limbs) resulting in excess waist:hip ratio (WHR), localized fat accumulation in the dorsocervical neck, abdomen including visceral adiposity, and metabolic changes of dyslipidemia, insulin resistance and hyperglycemia. In addition to the metabolic derangements and increased cardiovascular risks of this syndrome, the psychological impact of the dysmorphic changes is substantial and can be individually devastating. This stigmatizing syndrome also is associated with risks for reduced adherence to HAART.

Case Study:
Management of Dyslipidemia in a Patient with Advanced HIV-Associated Lipodystrophy

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Official Publication of the National Lipid Association
Case Study:
DB is a 51-year-old African American woman referred to our lipid clinic in June 2012 by her infectious disease physician for assistance in managing her dyslipidemia, complicated by marked HIV-associated lipodystrophy and new onset diabetes.

She had been initially diagnosed with HIV in 1996 following a hospital admission for *Pneumocystis carinii* pneumonia. Most details of her early drug treatment were not available.

Records were available for review after 2007. At the time of referral, she had just been diagnosed with Type 2 diabetes and had clinical evidence of worsening HAL. She was struggling with changes impacting insurance coverage for her medications and was trying to maintain her job but had reduced to part-time work.

Her major concerns included distress over the progressive dysmorphic changes in her body habitus, as well as establishing her cardiovascular risks and controlling her glucose and cholesterol.

Review of her HAART history showed use of the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, didanosine and stavudine (nucleoside reverse transcriptase inhibitor [NRTI]) prior to 2007. She had gradually begun to gain weight from 135 pounds to 145 pounds and was switched from stavudine and didanosine to combination therapy with tenofovir and emtricitabine with efavirenz. From 2010 to 2012, she progressively developed a “buffalo hump,” followed by truncal obesity, facial and limb atrophy and insulin resistance. Her CD4+ count had consistently remained above 600 and her viral load was undetectable.

With clear evidence of HAL, she was switched to raltegravir (integrase inhibitor) and a nucleoside-sparing regimen of lopinavir/ritonavir. As she continued to have progressive weight gain and evidence of hyperglycemia, her regimen was switched to etravirine, while the raltegravir was continued. Another manifestation of the insulin resistance was worsening hyperpigmentation of her distal extremities.

In our lipid clinic in June 2012, her glycated hemoglobin (HbA1c) was recorded at 8.6, her weight was 178 pounds and her triglycerides (TG) were >240. Metformin 500 mg ER and 10 mg atorvastatin were begun. She began an intensive lifestyle-modification program with changes in her nutrition and joined a gym, where she worked out four days a week. Niacin was added for further possible benefit in April 2013, when she was noted to have a mild elevation of lipoprotein(a) [Lp(a)].

Her lab work progressed as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>2mo ago (11/22/13)</th>
<th>7mo ago (07/02/13)</th>
<th>8mo ago (05/29/13)</th>
<th>10mo ago (04/19/13)</th>
<th>1yr ago (12/13/12)</th>
<th>1yr ago (09/05/12)</th>
<th>1yr ago (05/05/12)</th>
</tr>
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<tbody>
<tr>
<td>Cholesterol</td>
<td>0 - 199 mg/dL</td>
<td>114</td>
<td>130</td>
<td>137</td>
<td>169</td>
<td>147</td>
<td>178</td>
<td>178</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0 - 149 mg/dL</td>
<td>89</td>
<td>84</td>
<td>111</td>
<td>173 (H)</td>
<td>181 (H)</td>
<td>274 (H)</td>
<td>274 (H)</td>
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<tr>
<td>HDL</td>
<td>40 - 99 mg/dL</td>
<td>42</td>
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<td>55</td>
<td>51</td>
<td>44</td>
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<tr>
<td>LDL Cholesterol</td>
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<td>54</td>
<td>64</td>
<td>60</td>
<td>83</td>
<td>67</td>
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<td>74</td>
</tr>
<tr>
<td>Chol/HDL Ratio</td>
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<td>2.7</td>
<td>2.7</td>
<td>2.5</td>
<td>3.3</td>
<td>3.3</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Non-HDL Chol (LDL+VLDL)</td>
<td>0 - 129 mg/dL</td>
<td>72</td>
<td>81</td>
<td>82</td>
<td>118</td>
<td>103</td>
<td>129</td>
<td>129</td>
</tr>
<tr>
<td>VLDL</td>
<td>2 - 38 mg/dL</td>
<td>18</td>
<td>17</td>
<td>22</td>
<td>35</td>
<td>36</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

Her weight by December 2013 had decreased to 171 pounds and her A1c was then 7.1.

Her mood has improved but she is still very troubled by her physical appearance. She continues to have substantial issues with truncal obesity and increased abdominal girth. Efforts to have her seen at a nearby university medical school for consultation regarding novel options for HAL treatment have been consistently declined by her insurance. She has recently been referred to our plastic surgery department. She is compliant with medication and lifestyle modification and has appeared to stabilize. She has no clinical evidence of cardiovascular disease but understands the importance of close monitoring and is seen monthly by either her infectious disease specialist or the lipid clinic.

The prevalence of HAL in patients on HAART is thought to be >40% and varies with the drugs used.

**Nucleoside reverse transcriptase inhibitors** (NRTIs), particularly thymidine derivatives such as stavudine, are largely associated with lipodatrophy.

**Protease inhibitors** (PIs) are more typically associated with fat accumulation and hyperglycemia. The syndrome was first noted in patients treated with indinavir. Risks for HAL include the same factors described above for coronary heart disease, plus high viral load and low CD4 nadir prior to treatment.

Other HAART classes, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), fusion inhibitors and integrase inhibitors are least associated with HAL.

Mechanisms by which lipodystrophy occurs are related to abnormal gene expression in the adipocyte, mitochondrial toxicity, genetic polymorphisms and insulin resistance. Drug-induced symptoms do not seem to be class effects but may be associated with specific agents. Change in adipocyte biology is induced by the PIs with reduced expression of sterol regulatory element binding protein (SREBP-
1), which results in downregulation of transcription factors such as peroxisome proliferator-activated receptors (PPARs) for adipogenesis. The drugs particularly associated with this effect include ritonavir and saquinavir.

Deranged function of the adipocyte is thought to be associated with the development of insulin resistance. Inhibition of the glucose transporter GLUT-4, induction of cytokines, reduced secretion of both adiponectin & leptin, and increased lipolysis combine to cause these metabolic changes.

Of particular concern to the lipidologist is the change in lipoprotein metabolism related to HIV infection, and HAL, as well as the increased risk of cardiovascular disease present in these patients. Subtle changes in lipid metabolism with reductions in high-density lipoprotein cholesterol (HDL-C) occur early in the course of the HIV infection. Subsequently, an increase in apolipoprotein B (ApoB) and small dense low-density lipoprotein (LDL) particles occurs. Plasma triglyceride (TG) and very low-density lipoprotein (VLDL) levels commonly rise as the patient develops more symptomatic disease. One postulated mechanism for these changes associates HIV infection with accumulation of lipids within macrophages, which occurs because of an effect on the ATP-binding cassette transporter A1 (ABCA1) with resultant inhibition of cholesterol efflux.

Initiation of HAART, particularly with PIs, continues to affect lipid metabolism. A treatment-related increase in plasma TG, VLDL and ApoB may occur within two weeks of initiating therapy with ritonavir because of increased hepatic TG production. This is because of the excess ApoB in hepatocytes and the hypersecretion of ApoB containing VLDL associated with increased intracellular fatty acids.

Genetic factors play an important role in the development of HAART-associated dyslipidemias. One potential target is apolipoprotein C3 (ApoC-III), which is a major constituent of VLDL particles. Two polymorphisms in this apolipoprotein have been associated with hyperTG in HIV patients on HAART. Accelerated cardiovascular risk is suggested by loss of vascular patency, which occurs with PI-induced loss of endothelial function is measurable as an increase in carotid intimal media thickness (CIMT). It also appears that HDL-C levels are lower for six to 24 months, on average, prior to development of clinical HAL.

Success in caring for these patients must be dominated by collaboration between medical specialists, including infectious disease, cardiology and clinical lipidology. Observation of altered lipid profiles with declining HDL-C prior to phenotypic recognition of lipoatrophy may lead to interventions that prevent the development of HAL.

The challenge of providing best-practice care by the medical team can be described as:

1. Control of the dyslipidemia with attention to possible drug-drug interactions
2. Mitigating overall cardiovascular risk and understanding the unique contributing factors in this setting
3. Treatment of the HIV infection with awareness of the inherent and sometimes competing cardiovascular (CV) risks of HAART drugs without compromising virologic suppression.
4. Addressing the etiology and contribution of HIV-associated lipodystrophy and its unique effect on the overall morbidity and mortality of the affected patient.

Treatment options for HAL are varied and have limited success. Lifestyle intervention with diet and exercise has demonstrated reduction of truncal obesity – but at the risk of increasing lipoatrophy. With the known effect of the mitochondrial toxicity of the HAART drugs, especially the NRTIs, supplements such as thiamine, riboflavin, ubiquinone and acetyl-carnitine have been deployed with variable results.
Pharmacologic interventions such as switching HAART therapy to nucleoside-sparing regimens or use of newer alternative drugs such as integrase inhibitors (e.g. raltegravir) appear to be useful. There are competing complications, however, as in the case of abacavir, an NRTI that is beneficial in terms of lipid management but has been associated with an increased risk of myocardial infarction (MI).

Some clear parameters have emerged, including avoidance of thymidine-based NRTIs such as stavudine and zidovudine. Lipid-lowering interventions including statins and fibrates are valuable, but careful selection of drugs is needed. Pravastatin, atorvastatin and rosuvastatin have been the most successfully utilized, the latter two being most favorable in terms of their potency. Some data also suggest that statin-induced lowering of LDL-C in HIV-infected patients is more difficult to achieve than in the non-infected patient.

Pitavastatin is emerging as a reasonable option in some settings, but when ritonavir is used as a PI booster, this may increase the risk of rhabdomyolysis resulting from an increased concentration of the statin. Simvastatin and lovastatin clearly have an increased area under the curve when used with most PIs and are definitely contraindicated. Statins are known to be associated with hyperglycemia and diabetes risk, so regular glucose monitoring is necessary.

Fibrates, niacin, fish oils and ezetimibe have all been used as alternatives or adjuncts to statins. In particular, fenofibrate appears to have benefit in decreasing ApoC-III.

Control of insulin resistance with metformin and peroxisome proliferator-activated receptor (PPAR) agonists such as thiazolidinediones also may be helpful but, with the latter group of drugs, the current concerns related to increased CV events may constrain their use. Metformin may increase limb atrophy and does not improve visceral adiposity.

Cosmetic surgery with the use of gel fillers (e.g. poly-L-lactic acid) may improve lipoatrophy for some patients for a limited time. Uridine, which counteracts pyrimidine depletion induced by the thymidine analogues, offers some improvement to lipoatrophy.

Recombinant human growth hormone (rGH), with its effect on lipolysis and fat oxidation, has led to a reduction in visceral adiposity, but it can worsen insulin resistance. Tesmorelin, a growth-hormone-releasing hormone, has the multiple benefits of decreasing visceral fat, increasing limb fat, increasing HDL-C and decreasing TG. However, it is costly and requires parenteral administration.

In order to provide optimal treatment for this complex population, more evidence from large trials is needed. However, these data may be difficult to obtain. At present, an informed and collaborative team effort is mandatory to provide these patients with the multidisciplinary support necessary to achieve successful outcomes.

I am indebted to Dr. Sonia Dhingra (Wheaton Franciscan Healthcare All Saints), for generous sharing of her expertise and clinical collaboration.

Disclosure statement: Dr. Willard has received honorarium from Merck & Co. Inc.

References are listed on page 28.

The following algorithm provides guidance in current treatment strategies.

![HIV Associated Lipodystrophy Treatment Strategies](image-url)
Dr. Carl Orringer recently moved to Florida and is currently an Associate Professor of Medicine at the University of Miami Miller School of Medicine. Previously he was an Associate Professor of Medicine at the Case Western Reserve University School of Medicine and the Harrington Chair in Preventive Cardiovascular Medicine at University Hospitals Case Medical Center. Before his move he directed the Preventive Cardiovascular Medicine Program, the Lipid Clinic and the LDL Apheresis Program at University Hospitals Case Medical Center.

According to Dr. Orringer, the best part of what he does is the wide variety of activities in which he is involved, such that no two days are ever the same. It is that mixture of patient care, education, administrative work and research that provides Dr. Orringer with a very high level of professional happiness.

In his everyday work, he sees cardiology patients two days per week and runs the Lipid Clinic one day per week. The other two days are taken up primarily with administrative work and educational activities. He has developed several interactive programs for the third-year students at the Case Western Reserve University School of Medicine focusing on the metabolic syndrome and familial hypercholesteremia and has mentored a select group of cardiology fellows and internal medicine residents to serve as preceptors for these educational sessions. He has also developed a series of educational seminars for cardiology fellows, teaching them basic principles of clinical lipidology, and then provided regular clinical conferences focusing on application of these principles in patient care.

One of Dr. Orringer’s most gratifying educational activities was to serve as Editor-in-Chief of the National Lipid Association Self-Assessment Program. The opportunity to work with his NLA colleagues and with the NLA staff to create this updated and intellectually challenging teaching tool was a privilege that he says he will always treasure.

He attended Western Reserve University (now Case Western Reserve University) during his first two undergraduate years. He then finished his final two years at the University of Miami (Florida). He went to medical school at the University of Miami School of Medicine and did his cardiology.
fellowship at the Peter Bent Brigham Hospital, now Brigham and Women’s Hospital.

He learned about the NLA from his good friend, Michael Davidson, MD. The two had met each other on the “lecture circuit” and Dr. Davidson asked him to attend one of the regional meetings of the Midwest Lipid Association. After that experience, Dr. Orringer says he was “hooked for life.”

Dr. Orringer hopes to inspire young physicians and many of his “not-so-young” colleagues to focus more of their energy on prevention, which he sees as the highest calling in medicine. He has had the blessing to see the evolution of the statin story, from the first days in which these drugs were prescribed because they effectively lowered cholesterol levels to the current focus on prescribing these agents because they reduce atherosclerotic cardiovascular disease risk in both secondary and primary prevention.

Dr. Orringer is a very active person in his spare time. Exercise has always been a big part of his life usually on an elliptical trainer at least four times per week, and an hour of brisk walking with his wife and best friend, Linda, twice a week. What he really loves is the chance to visit and spend time with his seven children and 14 grandchildren, who are spread out across the U.S. from San Francisco to south Florida.

When asked to share something interesting that everyone may not know, Dr. Orringer said he and his wife Linda love ballroom dancing, and have plans to improve their skills in this area over the coming years.

Dr. Orringer is grateful to have served as Secretary, and now Treasurer of the NLA in 2013 to 2014. He looks forward to the opportunity to continue to serve the NLA for many years to come.

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Need Help Filling out the FH Patient Registry?

Your health care provider may have suggested you join the FH Patient Registry. If you have been diagnosed with FH (familial hypercholesterolemia) or suspect you may have it, it is important for you to register at [www.thefhfoundation.org](http://www.thefhfoundation.org). Click on “Cascade FH Registry.” The purpose of this registry is to collect information that can help researchers and then lead to improved care and a longer and better life for people with FH. The FH Foundation and the FH Patient Registry are not affiliated with the Foundation of the National Lipid Association.

To assist you in filling out the online patient registry form, you will need the following information from your health care provider. Take this card to your next appointment and ask your provider to help fill in this information.

**To register go to** [www.thefhfoundation.org](http://www.thefhfoundation.org)

_The Foundation of the National Lipid Association is pleased to provide this simple worksheet to assist you in signing up for the FH Patient Registry. For more information on FH or cholesterol issues, go to [www.learnyourlipids.com](http://www.learnyourlipids.com)._
Integrated Guidance on the Care of Familial Hypercholesterolemia from the International FH Foundation

The International FH Foundation (IFHF) announced new guidance for the care and management of familial hypercholesterolemia (FH) in an effort to bring attention to the dangers and costs of leaving FH patients untreated. A group of leading experts reviewed existing international framework on FH with the view to provide a unique global perspective and integrated approach towards the care and management of the disorder. The final recommendations focus on the standards required for the detection, diagnosis, assessment and management of FH in adults and children. They also identify best practices for (cascade) screening, risk notification and strategies for testing families for FH, including the use of genetic testing. To read the new guidance, go to www.ncbi.nlm.nih.gov/pubmed/24418289.

NLA-SAP Approved by ABIM for MOC

The NLA-SAP has been approved by the American Board of Internal Medicine (ABIM) for self-evaluation points towards ABIM’s Maintenance of Certification (MOC) program! The NLA-SAP will now be listed on the ABIM’s website as an approved medical knowledge program, and will be viewable to all physicians searching for MOC programs on their website. Having the program listed on their website will help the NLA reach a new audience of physicians interested in lipid management, but unfamiliar with our organization and our quality educational programs.

As part of ABIM’s MOC program, physicians must earn 100 points every five years, and 20 of these points must come from participating in a medical knowledge program. The 5-volume NLA-SAP was approved for 174 MOC points. To order your copy of the NLA-SAP visit www.lipid.org/nlasap.

Fellows Self-Assessment Program

Invite your fellows-in-training to participate in the Fellows SAP. This program, based upon the NLA’s 500 question Self-Assessment Program, is a complimentary 100-question online interactive educational tool that objectively validates and enhances your fellow’s knowledge of clinical lipidology and challenges their problem-solving skills in the diagnosis and management of patients with dyslipidemia. This online program provides real-time feedback after each question, and includes detailed critiques of each item along with bibliographic references. The Fellows SAP is a non-CME activity, but is offered complimentary to all fellow members of the NLA. Fellows can join the NLA for free and access the Fellows SAP by visiting www.lipid.org/education/fellows. All fellows must submit a letter from their program director validating their fellowship status when submitting a membership application.

Fellows in Training Travel Grants Available for Lipid Academy

All Fellows in Training are invited to attend the Lipid Academy Course in conjunction with the NLA 2014 Fall Clinical Lipid Update. Lipid Academy registration fees will be waived, registration for the Fall Clinical Lipid Update is complimentary (must attend the full Lipid Academy Course for complimentary registration), and a travel scholarship of $500 will be provided at the meeting to help cover the cost of trainee travel and accommodations.* A discounted rate of $395 for the Masters in Lipidology Course is also available for Fellows in Training, however, travel grants are not applicable to this course. Please download a registration form for the Fall Clinical Lipid Update at www.lipid.org/fallclu (registration information available soon). Please contact sgoode@lipid.org for more information.

*Limited number of spots, restrictions apply

Renew Your Membership Today to Avoid Interruption of NLA Benefits!

If you have not renewed your membership in the NLA to date, then your membership is about to expire! But there is still time to renew without losing any of the great benefits that membership has to offer. To avoid interruption of NLA services, renew today quickly and easily online. Go to www.lipid.org/about/dues.

Pediatric Dyslipidemia Questionnaire

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

As we reported in our most recent annual report, Foundation of the NLA donors in 2013 can say that they have helped us achieve our goal as shown by the impact that several of our initiatives had last year on a national level. To continue on this path of success, we need your help! There are various ways you can support the Foundation. You should have received an envelope with support options in the most recent issue of the Lipid Spin. If you haven’t had a chance to review it yet, we’d like to let you know what your donation does for us.

Outreach
Through your donations we are able to disseminate resources and materials to communities where NLA members work and live, at community health fairs and other organizational events.

Awareness
With your help we are able to spread public awareness of cholesterol disorders. We can distribute printed patient education materials and initiate public awareness campaigns that better inform patients and health care providers on the diagnosis and treatment of cholesterol disorders.

Education
Because of you, the Foundation can fund grants to support promising research and educational program activities related to the field of lipidology.

The Foundation hosted three successful fundraising events in 2013 and we have been continuing this in 2014.

During the 2014 Spring Clinical Lipid Update in Maui, HI over 100 attendees supported the Foundation of the NLA at a Hawaiian Luau, a traditional party filled with Hawaiian foods, music and dance. It was the perfect time for a traditional Hawaiian luau looking out over the Pacific Ocean.

Join the Foundation of the NLA for a fun evening of dinner, dancing and games on Saturday, May 3 during the 2014 Annual Scientific Sessions. Enjoy the perfect backdrop of the lush tropical landscaping and free-flowing lagoon pool with 12 picturesque waterfalls. It will be a wonderful setting for a fantastic buffet meal. Dance under the stars to music of the 50s, 60s, and 70s or grab some friends and colleagues for a friendly game of Giant Jenga or Connect Four that will be available for your enjoyment.

Saturday, May 3 | 7:30 – 10:00 p.m.
Cocktails 7:30 p.m. – Dinner 8:00 p.m. – Games 9:00 p.m.
$150 per person

If you would like to attend only the games portion of the event after 9:00 p.m., the cost is $75 per person; a cash bar will be available. The location may change depending on the weather. You may register online at lipid.org/sessions.

Discuss this article at www.lipid.org/lipidspin
Clinical Feature

8. Olsson AG, Pedersen H, Apolipoprotein B/A1 ratio is a better discriminator of risk of coronary heart disease than is LDL/HDL cholesterol ratio in the IDEAL study. Atherosclerosis. 2006; 7 (Suppl 16).
References continued from page 27.


Specialty Corner


Practical Pearls


Cholesterol and Supplements

Fish Oil
The Omega-3 fatty acids found in fish oil can lower triglycerides when taken in moderate to high doses. There may be several types of fatty aids found in fish oil, but the fatty acids shown to lower triglycerides are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Add the amounts of EPA and DHA from your bottle together. To lower triglycerides you will need at least 2,000 mg to 4,000 mg of EPA or EPA/DHA combined on a daily basis. If your triglycerides are very high (> 500 mg/dL), you may want to discuss prescription omega-3 fatty acids with your health care provider.

Red Yeast Rice (RYR)
Red Yeast Rice (RYR) is a natural product of a fungus (monascus purpureus) that is grown on rice. Studies show active compounds in RYR are monacolins, which are effective in lowering total and LDL cholesterol (“bad” cholesterol). In fact, Monacolin K is the active ingredient in lovastatin, a prescription HMG CoA reductase inhibitor (statin). The FDA has made it illegal to sell a RYR product that contains more than trace amounts of the active ingredient, since patients should be monitored for adverse reactions while taking a statin medication or may not be candidates for them. Hence, many of the products sold in the US would not significantly lower LDL cholesterol levels. Some available RYR products would not meet the U.S. Food and Drug Administration’s standards and may contain a dangerous toxin called citrinin. It is best to consult with your health care provider if you are considering taking RYR. RYR should not be taken if pregnant, breastfeeding or in combination with certain other medications.

Vitamin D
Vitamin D profoundly affects cells throughout the body. A symptom of Vitamin D deficiency is aches and pains in the muscles, joints and bones. A provider may check your vitamin D level if you have been intolerant of statins or before beginning statins. If your vitamin D level is low, your provider may recommend taking a vitamin D supplement to normalize this level. You should take vitamin D with a meal.

Plant Sterols/stanols (also called Phytosterols)
Plant sterols and stanols can lower cholesterol levels by reducing the amount of cholesterol absorbed from food. The Food and Drug Administration states, “foods containing at least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease,” but no studies have demonstrated this reduction of heart disease. Recently, The European Atherosclerosis Society recommended they may be used for people who have high levels but do not qualify for therapy, cannot take therapy, or did not achieve goal on therapy.

Coenzyme Q10 (CoQ10)
CoQ10 is a necessary antioxidant and a key enzyme in the generation of energy in the body. Normal CoQ10 levels decrease with age and with the use of statins. Decreased CoQ10 levels may contribute to muscle pain while taking statins, but results of studies have not definitely shown that taking CoQ10 levels decreases this side effect. If you experience muscle pain on statins, you may discuss trying a CoQ10 supplement of 100 to 200 mg daily with your provider.

Soluble Fiber
This type of fiber dissolves in water to form a gel-like substance that helps to prevent cholesterol absorption from the food you eat. Soluble fiber is present in many plant foods including broccoli, apples, oatmeal, carrots, plums, prunes, pears, citrus fruits, beans, and nuts. Psyllium, the plant that is used in most fiber supplements, including Metamucil, Fiber One, and Citrucel, contains soluble fiber, which is recognized by the FDA to help lower cholesterol. Remember to drink adequate amounts of water when taking a fiber supplement. Ten to 25 grams of soluble fiber per day is generally recommended to lower LDL cholesterol.


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

This in conjunction with eating a Mediterranean diet, achieving and maintaining ideal weight, daily physical activity, and avoiding tobacco products will assist in optimizing your cholesterol levels and your overall health.
SAVE THE DATE

Clinical Lipid Update
National Lipid Association
JW Marriott Hotel • Indianapolis, IN
August 22–24, 2014

JW Marriott Hotel, Indianapolis, IN
Room Rate: $169/night ++
NLA Room Reservation Cutoff Date: July 22, 2014

Featured Sessions:
- Special Session on the Importance of Triglycerides in Total Lipid Control and Benchmarks Required to Facilitate Successful Treatment
- Special Session on the National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia

For more information visit lipid.org/fallclu