Gender Differences in the Identification and Treatment of Cardiovascular Risk

Also in this issue:

- Gender Differences in the Diagnosis and Treatment of the Metabolic Syndrome
- Turner Syndrome: An Overlooked Gender-Specific Cardiovascular Risk Factor

This issue sponsored by the Northeast Lipid Association
NATIONAL LIPID ASSOCIATION
SCIENTIFIC SESSIONS

Palmer House Hotel
Chicago, IL

Scientific Sessions
June 11–14, 2015

Professional Development Courses
June 10–11, 2015

lipid.org/sessions

Featured Speakers
• Philip J. Barter, MD, PhD
• Robert H. Eckel, MD
• W. Timothy Garvey, MD
• Donald M. Lloyd-Jones, MD
• Paul M. Ridker, MD
• Neil J. Stone, MD
• George L. Bakris, MD
• Keith C. Ferdinand, MD

Cutting-Edge Topics
Each day of the conference, thought leaders will present cases and discuss the latest research, guidelines, controversies and clinical strategies on topics including:
• Recent Guidelines and Treatment Recommendations
• Novel Targets and Emerging Therapies
• Treatment Strategies for High Risk Populations
• Risk Assessment, Statin Safety, and Patient Adherence
• Management Strategies for Obesity, Hypertension and Diabetes
• Special Interest Workshops on Pediatric Dyslipidemia, Women’s Issues and Complex Cases

Professional Development
Prior to the sessions, attend courses to develop your professional skills, prepare for certification in Clinical Lipidology, and integrate evidence into your clinical decisions:
• Lipid Academy
• Masters in Lipidology
In This Issue: Spring 2015 (Volume 13, Issue 2)

2 From the NLA President
Planning for the Future
—Terry A. Jacobson, MD, FACP, FAHA, FNLA

4 From the NELA President
Let the Recommendations Roll
—Joyce L. Ross, MSN, CRNP, FPCNA, FNLA

6 Letter from the LipidSpin Editors
Mentor/Mentee Program Helps Foster Young Practitioners
—Robert A. Wild, MD, MPH, PhD, FNLA

7 Clinical Feature
Gender Differences in the Diagnosis and Treatment of the Metabolic Syndrome
—Dean G. Karalis, MD, FACC, FNLA
—Denise Auberson, MD
—Syed Yaseen Naqvi, MD

11 Guest Editorial
Underdiagnosed, Undertreated, and Understudied: An Epidemic of Cardiovascular Risk in Women
—Sharayne Mark, MD
—Emil M. deGoma, MD, FAHA, FACC, FNLA

14 EBM Tools for Practice
Gender Differences in Clinical Trials
—Spencer Kroll, MD, PhD, FNLA

16 Lipid Luminations
The Impact of Hormonal Imbalance on Cardiovascular Health in Men: The Good, the Bad, and the Unknown
—Monique S. Tanna, MD
—Roda Plakogiannis, PharmD, BCPS, CLS, FNLA

19 Foundation of the National Lipid Association Annual Report

23 Specialty Corner
Gender Differences and Risk Factors in Coronary Heart Disease
—Saleem Naina, PharmD, BCPS, CGP

26 Practical Pearls
Should Lipid Recommendations for Children be Gender Specific?
—Samuel S. Gidding, MD

28 Case Study
Turner Syndrome: An Overlooked Gender-Specific Cardiovascular Risk Factor
—Karen E. Aspry, MD, MS, ABCL, FACC

32 Chapter Update
Philadelphia Lipid and Atherosclerosis Club and More
—Daniel Soffer, MD, FNLA

33 Member Spotlight
Merle Myerson, MD, EdD, FACC, FNLA

35 Education, News and Notes

37 Events Calendar

38 References

41 Provider Tear Sheet

Look for the NLA Community logo to discuss articles online at www.lipid.org

*Indicates ABCL Diplomate status
After a successful 2014, the National Lipid Association is poised for an even better 2015. We are consistently seeking ways to improve our educational programs and professional development opportunities. We want to continue to be the voice for Clinical Lipidology.

One of the ways we do this is by conducting a biennial Strategic Planning Meeting where the NLA Leadership meets to discuss the NLA’s vision for the future and steps required to successfully get there. This year’s Strategic Planning Meeting was held in Orlando, Fla., Feb. 7–8, and proved to be a tremendous success.

During the meeting, important initiatives and ideas in Education, Practice Management, Lipid Certification, Publications, Position Statements, Advocacy, and Membership Services were discussed and new plans set forth for the future of the organization.

The recommendations discussed during the planning meeting will be brought before the NLA Board for consideration. I think all will be encouraged and excited by our plans for progress.

In addition to our strategic planning recommendations, the annual meeting will be an excellent opportunity to enhance your scope of practice with cutting-edge topics that include:

- Recent Guidelines and Treatment Recommendations
- Novel Targets and Emerging Therapies
- Treatment Strategies for High Risk Populations
- Risk Assessment, Statin Safety, and Patient Adherence
- Management Strategies and Controversies in Hypertension, Diabetes, and Obesity
- Special Interest Workshops on Pediatric Dyslipidemia, Women’s Issues, and Complex Cases

For more information on the Annual Scientific Sessions and to register, visit lipid.org/sessions.

Please also keep in mind that the Fall Clinical Lipid Update, which is hosted by the Northeast and Southeast chapters, will take place Sept. 18–20, 2015, at the Omni William Penn Hotel in Pittsburgh. Check lipid.org/fallclu for ongoing updates.

Another important project to keep in mind is the release of Part 1 and Part 2 of the National Lipid Association’s Recommendations for Patient-Centered Management of Dyslipidemia. The full and expanded version of Part 1 is scheduled to appear in the March/April issue of the Journal of Clinical Lipidology, and Part 2 is scheduled to be released around the time of the annual meeting.

In addition, look out for two new NLA publications in 2015. The new CLM-SAP on Guidelines in Clinical Lipidology: Concepts and Controversies edited by Carl

From the NLA President: Planning For the Future

TERRY A. JACOBSON, MD, FACP, FAHA, FNLA
President, National Lipid Association
Professor of Medicine, Emory University
Atlanta, GA
Director, Lipid Clinic and Cardiovascular Risk Reduction Program
Diplomate, American Board of Clinical Lipidology

Discuss this article at www.lipid.org/lipidspin

After a successful 2014, the National Lipid Association is poised for an even better 2015. We are consistently seeking ways to improve our educational programs and professional development opportunities. We want to continue to be the voice for Clinical Lipidology.

One of the ways we do this is by conducting a biennial Strategic Planning Meeting where the NLA Leadership meets to discuss the NLA’s vision for the future and steps required to successfully get there. This year’s Strategic Planning Meeting was held in Orlando, Fla., Feb. 7–8, and proved to be a tremendous success.

During the meeting, important initiatives and ideas in Education, Practice Management, Lipid Certification, Publications, Position Statements, Advocacy, and Membership Services were discussed and new plans set forth for the future of the organization.

The recommendations discussed during the planning meeting will be brought before the NLA Board for consideration. I think all will be encouraged and excited by our plans for progress.

In addition to our strategic planning recommendations, the annual meeting will be an excellent opportunity to enhance your scope of practice with cutting-edge topics that include:

- Recent Guidelines and Treatment Recommendations
- Novel Targets and Emerging Therapies
- Treatment Strategies for High Risk Populations
- Risk Assessment, Statin Safety, and Patient Adherence
- Management Strategies and Controversies in Hypertension, Diabetes, and Obesity
- Special Interest Workshops on Pediatric Dyslipidemia, Women’s Issues, and Complex Cases

For more information on the Annual Scientific Sessions and to register, visit lipid.org/sessions.

Please also keep in mind that the Fall Clinical Lipid Update, which is hosted by the Northeast and Southeast chapters, will take place Sept. 18–20, 2015, at the Omni William Penn Hotel in Pittsburgh. Check lipid.org/fallclu for ongoing updates.

Another important project to keep in mind is the release of Part 1 and Part 2 of the National Lipid Association’s Recommendations for Patient-Centered Management of Dyslipidemia. The full and expanded version of Part 1 is scheduled to appear in the March/April issue of the Journal of Clinical Lipidology, and Part 2 is scheduled to be released around the time of the annual meeting.

In addition, look out for two new NLA publications in 2015. The new CLM-SAP on Guidelines in Clinical Lipidology: Concepts and Controversies edited by Carl
E. Orringer, MD, FACC, FNLA, and the 2015 NLA Annual Summary of Clinical Lipidology edited by Harold E. Bays, MD, FTOS, FNLA. The NLA Summary of Clinical Lipidology will be updated each year and will include any new developments in the science or practice of Clinical Lipidology.

Lastly, you may have seen several emails announcing the NLA’s new Membership Recruitment Competition. If your chapter recruits the most new members by May 15, 2015, every member of that chapter who is also attending the annual meeting will have all-day access to a private lounge with free wi-fi, soft drinks, and snacks. If you want your chapter to win, make sure you reach out to your colleagues who are not NLA members yet and tell them why they should join the NLA.

To request membership and marketing materials, email Membership Manager Britney Caldwell at bcaldwell@lipid.org. Visit lipid.org/competition2015 for more information and to see the chapter currently in the lead. This is your chance to put peer-to-peer recruiting to the test and be a positive voice for the National Lipid Association and help us grow like never before!

I hope to see you all at our upcoming annual and regional meetings and appreciate your continued support of the NLA and the field of Clinical Lipidology.

---

**Complex Lipid Management Self-Assessment Program**

Guidelines in Clinical Lipidology: Concepts and Controversies

Objectively validate and enhance your knowledge of the available clinical practice guidelines and recommendations related to lipid management

- Review similarities and differences among these important guidelines in order to reduce gaps in implementation of evidence-based therapies
- Complete the web-based program at your own pace – whenever and wherever you choose
- Real-time feedback after each question – includes access to mobile applications designed for Apple and Android devices*

For more information visit lipid.org/education/clmsap

*NLA members only.

---

CME credit provided by the National Lipid Association

This activity has been approved for AMA PRA CATEGORY 1 CREDIT™

This activity is eligible for CDR credit.

This activity is supported by educational grants from Amarin and AstraZeneca.

CE credit provided by Advancing Knowledge in Healthcare, Inc.

Jointly provided by AKH, Inc., Advancing Knowledge in Healthcare and the National Lipid Association.

This activity is eligible for ACPE and ANCC credits.

Full accreditation information available at www.lipid.org.

For questions about this educational activity contact the NLA at 904-998-0854.
I am greatly honored and humbled to hold the office of President of the Northeast Lipid Association (NELA). I appreciate the endorsement of this multidisciplinary organization, one in which a nurse practitioner has the opportunity to rise to the level of president. I have been a board member since the inception of this NLA chapter and have had the opportunity to see it grow not only in number but also in professionalism.

It is in this spirit of collegiality that NELA moves forward this year. The Board of Directors has identified three areas of concentration that will continue to foster opportunities for professional education, leadership, and growth.

Once again NELA has been engaged in community outreach projects and we look forward to the continuation of events such as the New York Yankees FanFest this past September during which we were able to offer cholesterol screening and individual risk assessment information for participants.

A second focus is recognizing and supporting smaller regional programs within our region with chapter endorsements. We are able to promote these meetings to the entire chapter, bringing interested professionals to these informal gatherings. As we serve a large geographic area, we are hopeful that several regions will be inclined to promote gatherings in their area, bringing pertinent and up-to-date information to our members, especially those who may not have the opportunity to attend formal NLA functions.

Our third area of focus is membership. Membership not only connotes paying dues, but becoming an active contributor to the group. We are greatly interested in mentorship and advocacy between our members as a way to bring along those newer to the field of dyslipidemia. I am pleased to report that several of the articles that are presented in this issue of the LipidSpin represent collaboration with seasoned lipid specialists, along with residents, students, and others interested in this field of study.

Along this same line of thought is committee involvement both at the chapter and national level. We have a goal that any member who wishes to be on a committee can be accommodated as a means to develop a feeling of partnership within the chapter. We believe these initiatives will assist in the ongoing success of NELA.

We enjoyed an excellent Fall 2014 CLU in Indianapolis in conjunction with MWLA. This was an outstanding opportunity to introduce discussion on the ACC/AHA Guidelines and the NLA Recommendations for Patient-Centered Management of Dyslipidemia. This agenda encouraged a discussion about the complementary

From the NELA President:
Let the Recommendations Roll

JOYCE L. ROSS, MSN, CRNP, FPCNA, FNLA
President, Northeast Lipid Association
Secretary, National Lipid Association
Past President, Preventive Cardiovascular Nurses Association
Consultative Education Specialist, Cardiovascular Risk Intervention
University of Pennsylvania Health System-Retired
Philadelphia, PA
Diplomate, Accreditation Council for Clinical Lipidology

Discuss this article at www.lipid.org/lipidspin
nature of these documents but also heralded a “call to action” to not be content with treatment of LDL cholesterol alone. We were able to reinforce our beliefs that goals are still significant and that all apolipoprotein B containing cholesterol particles are atherogenic and worthy of consideration for treatment.

This concept was once again reinforced with the findings of the IMPROVE-IT trial, which were revealed at the recent AHA meeting. The study’s confirmed that lower LDL-C is important and that “targets” even as low as the 50s are superior to those provided with high intensity statin alone. The study further confirmed the safety of ezetimibe therapy. A recent American Journal of Cardiology article on the extensive follow up of the SEAS trial revealed no increased cancer risk from ezetimibe, an issue that was questioned in the original study, and was confirmed in IMPROVE-IT.

The results of IMPROVE-IT further support the NLA Recommendations that targeting LDL below 70 in very high-risk patients is important, and that ezetimibe is a safe and effective drug to assist achievement of that goal. This study additionally reinforced the NLA contention that non-statin drugs that target LDL-C as well as non-HDL-C are useful in clinical practice to achieve goals in selected high-risk patients. These recent findings beg the question that perhaps the year-old ACC/AHA Guidelines are obsolete and reinforces the role of the NLA Recommendations in assisting those treating dyslipidemic patients.

NELA hopes to foster similar interest with the focus of this edition of LipidSpin in which we initiate a discussion of “Gender Differences in the Identification and Treatment of Cardiovascular Risk.” Contributions include topics from genetics to treatment of young women with Familial Hypercholesterolemia who require statin therapy during the childbearing years. We fully appreciate that all patients are individuals and are deserving of individual assessment and management. This discussion is in ideal timing for Part II of the NLA Recommendations for Patient-Centered Management of Dyslipidemia, which will focus on “Special Populations” and is in preparation by the NLA at this time. Along with our guest editor, Dr. Emil deGoma, it is with great pleasure that we present this edition of the LipidSpin.”
It is with great pleasure that I update all with the wonderful progress being made by the career development committee. The committee chair, Binh An P. Phan, MD, FNLA, and members come from all regions of the country and from all disciplines. The vitality of our organization is enhanced because of these efforts.

The committee charge is to foster a mentoring program between established experts and young practitioners in the field of Clinical Lipidology. Specifically they have been charged with establishing a means by which organizational leadership and involvement within the National Lipid Association (NLA) is promoted to young practitioners and fellows-in-training. The committee encourages fellows-in-training to become involved in this committee, the NLA, and its scientific sessions and educational programs. Educational meetings and courses are targeted specifically for early career practitioners and fellows-in-training. “Boot camps,” day meetings, and weekend meetings have been developed to help young lipidologists get involved in writing reviews/topical papers, case studies, etc. in collaboration with a mentor. In addition, the committee has been working to develop a path for young members to develop a relationship with more established clinical trialists who are NLA members.

Check out lipid.org/education/fellows/mentors, where we are organizing mentors/mentees in pairing. The LipidSpin is planning to highlight articles formally written by mentor/mentee pairs. Opportunities for fellows in training are outlined in the membership letter. Notifications have been sent to all CVD program directors regarding free membership in the NLA and other opportunities including our educational offerings for fellows in training.

We are planning a strategic meeting for pairing at the Denver CLU and at our annual meeting in Chicago. Early career development committee members are invited to participate in all of our committees and are invited to participate as a nonvoting member at our board meetings. In addition, the early career and mentors will be gathering together during the annual meeting in Chicago.

I encourage everyone to reach out and help others along their career path. Introduce them to people you know who can help them along. Our organization is interdisciplinary and that is a wonderful strength. It also offers many opportunities for scholastic excellence designed to enhance practice. Do your part for the next generation!

From my vantage point, it is one of the most rewarding things we can do.
The metabolic syndrome is a clustering of interrelated risk factors for cardiovascular (CV) disease and type 2 diabetes. Although various definitions for the metabolic syndrome exist, several national and international health organizations — including the American Heart Association (AHA); the National Heart, Lung and Blood Institute (NHLBI); and the International Diabetes Federation (IDF) — have proposed a harmonized definition for the metabolic syndrome.1 By this definition, the metabolic syndrome is diagnosed when three of the following five risk factors are present: (1) abdominal obesity that is gender-, population- and country-specific, (2) elevated blood sugar, (3) high blood pressure, (4) low levels of high-density lipoprotein (HDL) cholesterol, and (5) elevated triglycerides. In addition to waist circumference, the level of HDL cholesterol used to define the metabolic syndrome differs between men and women. Low HDL cholesterol is defined as < 40 mg/dL for men and < 50 mg/dL for women. (Table 1)

Underlying these metabolic risk factors is adipose tissue dysfunction and insulin resistance. In the metabolic syndrome, increased free fatty acids delivered to the liver also increases hepatic secretion and triglyceride enrichment of very-low-density lipoprotein (VLDL) cholesterol. Incomplete lipolysis of VLDL particles leads to an accumulation of triglyceride-rich remnant lipoproteins, and triglyceride enrichment of HDL cholesterol via cholesteryl ester transfer protein (CETP) results in smaller HDL particles and low levels of HDL cholesterol.2 Although low-density lipoprotein (LDL) cholesterol is not specifically part of the metabolic syndrome, people with the metabolic syndrome have a high concentration of small, dense LDL cholesterol particles. The atherogenic dyslipidemia associated with the metabolic syndrome is an important risk factor for CV disease. The presence of the metabolic syndrome is associated with a two-fold increased risk of CV disease and a five-fold increased risk of type 2 diabetes.3 In this article we examine gender differences in the metabolic syndrome, focusing on the associated atherogenic dyslipidemia.

Gender Differences in the Prevalence of Metabolic Syndrome

The most current estimates from the National Health and Nutrition Examination Survey (NHANES) are that 23.7 percent...
of men and 21.8 percent of women in the U.S. have the metabolic syndrome. This translates into more than 37 million men and more than 36 million women in the U.S. who have the metabolic syndrome. In another analysis from NHANES, the prevalence of the metabolic syndrome was shown to increase with age for both sexes but was greater in older women compared to older men. (Figure 1) About 20 percent of men and 16 percent of women under the age of 40, and 41 percent of men and 37 percent of women between the ages of 40 to 59 met the criteria for the metabolic syndrome. In people over the age of 60, 54 percent of women met the criteria for the metabolic syndrome compared to 52 percent of men. There also are differences between men and women in the individual risk factors that constitute the metabolic syndrome. Men have a higher age-adjusted prevalence of hypertriglyceridemia, hypertension, and hyperglycemia than women, while women have a higher age-adjusted prevalence of abdominal obesity and low HDL cholesterol compared to men. For women, the prevalence of abdominal obesity, hypertriglyceridemia, hypertension, and hyperglycemia increases with age. In contrast, in men, only the prevalence of hypertension and hyperglycemia increases with age. Among younger women, the most prevalent metabolic syndrome combination is the clustering of high triglycerides, low HDL cholesterol, and increased waist circumference. In older women, the presence of all five risk factors is the most prevalent metabolic syndrome combination. Although the overall age-adjusted prevalence of the metabolic syndrome has fallen for both men and women in the past decade, it has increased in younger and middle-aged women. The increasing prevalence of the metabolic syndrome in younger women is primarily the result of an increase in abdominal obesity in this group. The rates of the metabolic syndrome are highest among non-Hispanic black and Mexican American women (Figure 2) and women in the lowest economic strata.

The difference between men and women in the prevalence of the metabolic syndrome and its individual components may be explained in part by differences in central fat distribution, hormonal factors, and the onset of menopause. Both increasing waist circumference and age are associated with an increase in visceral adipose tissue (VAT) and VAT is more strongly correlated with metabolic syndrome and cardiovascular risk than is subcutaneous adipose tissue. Younger women have a lower prevalence of the metabolic syndrome compared to younger men, and this may be because younger women have less VAT than men, even after correcting for total body fat. Compared to younger men, younger women need to accumulate significantly more total body fat before increases in visceral fat are observed, however, the increasing trend of obesity in younger women may well erase any gender benefit that younger women enjoy. For men, age-related increases in VAT are greater than for women, however, after menopause, VAT accumulation...
in women increases rapidly, to a rate similar to that of men. Furthermore, estrogen decline in menopause stimulates adipocyte hypertrophy and leads to adipocyte dysfunction, which may lead to more visceral fat accumulation. It is the increase in abdominal obesity and the postmenopausal state that leads to the increased prevalence of metabolic syndrome in older women.

Gender Differences in the Risk of CV Disease and Diabetes

Metabolic syndrome is associated with an up to two-fold increase in CV disease, CV mortality, stroke, and all-cause mortality. For both men and women, the presence of three or more components of metabolic syndrome is a stronger predictor of CV and all-cause mortality than when fewer components are present. Compared to CV risk, the metabolic syndrome has been shown to be an even stronger predictor for diabetes. Across many populations, including Europeans, Asians, Hispanics, and those of Middle Eastern descent, the presence of the metabolic syndrome is associated with a five-fold increase in the risk of diabetes.

Several meta-analyses have shown that the CV risk conferred by the metabolic syndrome is higher in women than in men. In one meta-analysis that included 172,573 people, the CV risk associated with the metabolic syndrome was a third higher in women than in men. There are several possible reasons for the higher CV risk in women with the metabolic syndrome. After menopause, central adiposity is more pronounced in women than in men and the lipid profile is different in post-menopausal women compared to men. After menopause, HDL cholesterol decreases, LDL cholesterol increases, and LDL particle size shifts to smaller and denser particles. Among people with the metabolic syndrome, HDL cholesterol has been shown to be a stronger predictor of CV events in women compared to men. Furthermore, there is evidence that triglycerides are more highly associated with CV disease in women than in men. Other studies have shown no gender differences in CV risk in metabolic syndrome. In a prospective population-based study of 1,260 older people in Finland who were followed for nine years, fatal and non-fatal coronary, cerebrovascular, and all vascular events occurred more commonly in people with the metabolic syndrome compared to those without the metabolic syndrome. However, in this study, the vascular risk was lower in women than in men. The different findings among studies that gender confers on CV risk may be related to differences in the definition used to diagnose the metabolic syndrome, heterogeneity in patient populations, and the inclusion of studies with a small sample size in some of the meta-analyses. Although these studies may differ in whether the metabolic syndrome confers a higher CV risk in women than in men, the consistent finding among these studies is that the metabolic syndrome in women is a strong predictor of increased CV risk.

Gender Differences in the Treatment of the Metabolic Syndrome

The primary goal of treating the metabolic syndrome is to reduce the risk of CV disease. The first-line treatment of the metabolic syndrome is lifestyle modification directed at weight loss and increased physical activity. A reduced-calorie diet of between 1,200 and 1,500 kcal/d for women and between 1,500 and 1,800 kcal/d for men is recommended to achieve a weight loss of approximately 5 to 10 percent of initial body weight. Both men and women lose weight on a low-calorie diet, however, studies suggest that men, on average, lose more weight than women, despite diets with similar caloric restrictions. In a study of 133 younger men and women with risk factors for the metabolic syndrome, men had a significantly lower waist circumference than did women after following a Mediterranean-style diet for 12 weeks. In addition, changes in triglyceride levels and in the ratio of total cholesterol to HDL cholesterol were significantly more pronounced in men than in women. In an observational study of a weight-management program sponsored by the National Health Service in the United
Kingdom, men, on average, lost almost 4 pounds more than women over a 12-week period, almost 7 pounds more than women in six months, and more than 11 pounds more than women by the end of one year.22 These findings are consistent with previous research that indicates men lose more weight than women when engaged in weight-loss intervention. There are several possible explanations for these findings. Men may have a higher starting weight than women, women may already have better baseline dietary habits than men, or other psychosocial factors may be at play. However, irrespective of these gender differences, lifestyle modifications alone often are insufficient to address the CV risk factors associated with metabolic syndrome, leaving both men and women at increased CV risk.

When lifestyle changes alone are unsuccessful, pharmacologic therapy to target the dyslipidemia associated with the metabolic syndrome is recommended. Statins are the drug of choice and are effective in lowering not only LDL cholesterol, but also triglyceride-rich remnant lipoproteins; they also have favorable effects on the size and concentration of LDL cholesterol particles.23 Post-hoc analyses from several clinical outcome studies have shown that statin therapy reduces major CV events in patients with the metabolic syndrome.24,25 Studies show that women derive the same CV-event-reduction benefit from statins as men.26 Despite the benefits women derive from statin therapy, high-risk women tend to be less aggressively treated with statin therapy compared to high-risk men.27

Although the new ACC/AHA cholesterol-lowering guidelines28 do not specifically address the metabolic syndrome nor set cholesterol goals for treatment, most people who have the metabolic syndrome will have a high CV risk score or other indications that would warrant statin therapy. The National Lipid Association (NLA)29 and several international societies30,31 also recommend lipid-lowering therapy for people with the metabolic syndrome and, in contrast, to the ACC/AHA cholesterol guidelines, have set both LDL and non-HDL cholesterol goals for these patients. In patients with the metabolic syndrome, non-HDL cholesterol may be a better predictor of CV risk than LDL cholesterol. Among people with a discordantly high non-HDL compared to LDL cholesterol, CV risk may be underestimated when only LDL cholesterol is considered.32 To this point, the recent NLA cholesterol guidelines have placed non-HDL ahead of LDL cholesterol as a therapeutic target.29

Many patients with the metabolic syndrome will be considered high-risk and their LDL and non-HDL cholesterol goals may be difficult to achieve with statin therapy alone. Subgroup analyses from other clinical trials suggest that fibrates, niacin, and omega-3 fatty acids may further reduce CV risk in statin-treated patients with high triglycerides and low HDL cholesterol33,35 and the recent IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed the added benefit of additional LDL cholesterol lowering when ezetimibe was added to statin therapy.36 Several studies have found that high-risk women are less likely to achieve optimal LDL and non-HDL cholesterol goals compared to men. In a study of 9,950 coronary artery disease patients in the U.S., of whom 34 percent were women, women were less likely to achieve an LDL cholesterol goal of < 70 mg/dL and a non-HDL cholesterol goal of < 100 mg/dL compared to men. In the Dyslipidemia International Survey-China (DYSIS-China), women with the metabolic syndrome were less likely to achieve their non-HDL cholesterol goals compared to men.37 In both of these studies, combination lipid-lowering therapy was infrequently used.

Conclusions
The metabolic syndrome is common, occurring in more than one-half of postmenopausal women. Because of the increase in obesity, the prevalence of the metabolic syndrome is on the rise, especially in younger women. Women with the metabolic syndrome are at increased CV risk, and the metabolic syndrome may confer a higher CV risk in women than in men. To reduce the CV risk associated with the metabolic syndrome, lifestyle interventions need to target the dyslipidemia and other risk factors of the metabolic syndrome. When lifestyle changes alone fail to achieve a patient’s target lipid goals, pharmacologic therapy often is needed. Statins should be the foundation of lipid-lowering therapy, however, many people with the metabolic syndrome will likely benefit from combination lipid-lowering therapy to target both LDL and non-HDL cholesterol. Clinicians need to be aware of the gender differences that exist in the prevalence and treatment of the metabolic syndrome. However, irrespective of gender, early recognition and treatment of the metabolic syndrome is essential to prevent CV events.

Disclosure statement: Dr. Karalis received consulting fees from Aegerion. Dr. Auberson has no disclosures to report. Dr. Naqvi has no disclosures to report.

References are listed on page 38.
Cardiovascular disease is the leading killer of women, accounting for more than 200,000 deaths in the U.S. each year. Cardiovascular disease is not simply a disease of older women. Heart attacks afflict one in 90 women ages 45 to 54 years old, exceeding the one in 240 diagnosed with breast cancer. Despite these sobering statistics, the burden of cardiovascular disease in women remains vastly underappreciated. In a survey of 2,300 women in the U.S., approximately half correctly identified cardiovascular disease as their leading cause of death; 1 in 2 incorrectly reported cancer as their greatest health risk, and only 1 in 6 reported cardiovascular disease as their leading health risk. Below we briefly summarize the underdiagnosis and undertreatment, specifically, of atherosclerotic cardiovascular disease risk in women and lend our perspective on potential strategies to bridge the gap.

Ischemic Heart Disease
The diagnosis of ischemic heart disease in women is more elusive than in men. While the predominant symptom in men with acute coronary syndrome is chest pain or pressure, women report chest discomfort less than half of the time. The most common presentation of acute myocardial infarction in women is sudden cardiac death; followed by back, jaw, and neck pain; dyspnea; indigestion; nausea; and emesis, the latter of which generally are labeled as “atypical,” leading practitioners astray to alternate diagnoses such as gastrointestinal reflux, esophageal spasm, or anxiety. Moreover, the afflicted woman may overlook her symptoms and delay seeking medical attention because she is unaware. Retrospective analysis of the Immediate Myocardial Metabolic Enhancement during the Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial found that women diagnosed with probable acute coronary syndrome took a longer time to call 911 from symptom onset — 73 minutes compared to 45 minutes in men (p<0.01). It is hypothesized that differences in presentation may be related to gender differences in the pathogenesis of ischemic heart disease.
Striking differences contrast the pathophysiology underlying ischemic heart disease in women and men. Whereas obstructive epicardial stenosis explains the overwhelming majority of coronary disease in men, approximately 25 to 50 percent of women — or from three to five times that of men — who undergo coronary angiography for the evaluation of ischemia have normal or minimal epicardial disease. The constellation of angina, objective evidence of ischemia on non-invasive stress testing, and the absence of angiographic epicardial coronary obstruction is referred to as cardiac syndrome X. Importantly, despite the absence of angiographic disease, angina in women is associated with a significantly worsened outcome. In the Women’s Ischemia Syndrome Evaluation (WISE) study, the five-year annualized event rates for adverse cardiovascular outcomes were 7.9 percent in symptomatic women without angiographic disease and 2.4 percent in asymptomatic controls (p <0.002). Vasomotor dysfunction appears to identify a particularly high-risk subgroup of women. A WISE sub-study revealed that women with minimal coronary artery disease (defined as 20 to 49 percent stenosis) who had an abnormal intracoronary vasodilator response to acetylcholine had a significantly higher risk of cardiovascular events compared to women with a normal response (hazard ratio 2.8, 95 percent CI 1.26-6.44). The pathogenesis of cardiac syndrome X remains poorly characterized. In addition to vasomotor dysfunction, other leading hypotheses include abnormal nociception and inflammation. Evidence-based strategies to treat angina and cardiovascular risk associated with cardiac syndrome X also are lacking.

Assessment of Cardiovascular Risk
Underestimation of cardiovascular risk in women is a significant concern because it leads to missed opportunities in aggressive preventive care. In this regard, limitations of the 10-year Framingham risk score (FRS) for risk prediction in women are well recognized. Systematic variation in risk factor levels revealed that women ages 55 and younger do not exceed a risk of 10 percent, regardless of risk factor burden. Among women ages 65 and older, only the combination of smoking with marked abnormalities in high-density lipoprotein cholesterol (HDL-C), total cholesterol, and systolic blood pressure produces a 10-year predicted risk >10 percent. In fact, according to the National Health and Nutrition Examination Survey, the prevalence of high-risk FRS (>20 percent) among women ages 50 to 69 is 0.3 to 0.4 percent, in stark contrast to the actual observed incidence of coronary artery disease. Although questions linger regarding appropriate calibration, the 2013 Pooled Cohort risk equations better address the underestimation of cardiovascular risk in women, at least in part by the incorporation of stroke.

In clinical practice, “global” cardiovascular risk assessment of any individual patient incorporates myriad risk factors that are not captured by currently available clinical risk scores. Several additional risk factors that are particularly important to consider in the risk calculus for women are early menopause and features of metabolic syndrome. Most data indicate that early menopause predicts coronary heart disease and possibly stroke. In the Nurses’ Health Study, the relative risks across categories of age at natural menopause (<40, 40-44, 45-49, 50-54, and > or = 55 years) were 1.53, 1.42, 1.10, 1.00, and 0.95 after adjusting for traditional risk factors. In the Multi-Ethnic Study of Atherosclerosis (MESA), women with early menopause (either natural menopause or surgical removal of ovaries at an age <46 years) exhibited more than a two-fold higher risk of coronary heart disease and stroke compared to women without early menopause after adjusting for other risk factors. In addition, features of metabolic syndrome — namely insulin resistance, dyslipidemia, hypertension, and abdominal obesity — confer greater cardiovascular risk in women. A sub-study of the WISE cohort showed that, compared with women with normal metabolic status, women with metabolic syndrome had a significantly lower four-year survival rate (94.3 percent versus 97.8 percent, P=0.03) and event-free survival from
major adverse cardiovascular events (death, nonfatal myocardial infarction, stroke, or congestive heart failure; 87.8 percent versus 93.5 percent, P=0.003). Subclinical atherosclerosis imaging in selected women may be useful to refine cardiovascular risk and guide the intensity of preventive therapy above and beyond clinical risk factors or blood tests. Both coronary artery calcium scanning (CACS) and assessment of carotid intima-media thickness and plaque (CIMT) have consistently shown a positive association with coronary heart disease (CHD) risk. A meta-analysis evaluating 24,260 women demonstrated progressively increased risk of myocardial infarction with higher coronary artery calcium scores (CACS 0-10 reference, CACS 11-100 relative risk 3.0, CACS 101-399 RR 5.7, CACS 400-999 RR 9.7, CACS >1000 RR 21.5). Among low-risk women (10-year CHD risk <10 percent), an analysis of MESA further demonstrated that CACS was highly associated with CHD events, yielding an adjusted relative risk of 8.3 and an absolute annual risk of 1.8 percent among women with a CAC above 300. The Atherosclerosis Risk in Communities (ARIC) study evaluated 12,841 people free of clinical CHD at baseline over a median of 5.2 years. Among the 7,289 women, a CIMT of 1 mm or greater was associated with a relative risk for CHD events of 5.1 compared with a CIMT below 1 mm, adjusted for age and race. CACS and CIMT improve reclassification and discrimination for CHD above and beyond traditional risk factors, effecting statistically significant increases in the area under the curve (AUC), a rigorous measure of discrimination that fails to improve even with the incorporation of several accepted traditional risk factors. CACS and CIMT may be useful in refining cardiovascular risk in selected women by guiding the intensity of preventive therapies when standard clinical risk assessment yields equivocal results. Notably, randomized trials comparing clinical outcomes and cost-effectiveness of various risk assessment strategies, including those incorporating subclinical atherosclerosis imaging modalities, are lacking.

“Perhaps the greatest impact we can have in day-to-day patient care is to view each and every encounter as an opportunity to increase awareness.”

**Narrowing the Gaps**

In 2012, Dr. Nanette Wenger outlined major recommendations to improve coronary heart disease outcomes in women (Table 1). Proposed strategies to help implement these recommendations in clinical practice have included: 1) building clinical-decision support embedded in electronic medical records to facilitate the identification and treatment of women at risk, 2) leveraging social media to engage a wider audience, emulating the success of breast cancer campaigns, and 3) identifying local champions — women with atherosclerotic cardiovascular disease — to foster peer-to-peer education. Perhaps the greatest impact we can have in day-to-day patient care is to view each and every encounter as an opportunity to increase awareness. This approach is most obvious for the female patients for whom we care directly, but, for our male patients, do we consider the women in their families? How often do we take a moment to share information about the risk of heart disease in women with the spouses and female relatives who accompany our male patients to their clinic appointments? A brief message highlighting cardiovascular disease risk in women, systematically reinforced by healthcare providers at each clinic visit, may be a simple and practical way to improve awareness, detection, and treatment.

**Disclosure statement:** Dr. Mark has no disclosures to report. Dr. deGoma received research honoraria from Aegerion, Pfizer, Regeneron, Sanofi, and Amgen.

References are listed on page 38.

---

**Treatment of Cardiovascular Risk**

Even after women have been diagnosed as being at high risk, with all the pitfalls and perils described above, women — far more frequently than men — fail to receive evidence-based therapies and fail to meet guideline-based targets for primary and secondary prevention. In a large, retrospective chart review led by Dr. Dean Karalis examining 9,950 patients with coronary artery disease, women were more likely not to be treated with a statin (16.9 percent versus 11.6 percent, p <0.001) and more likely to be on no lipid-lowering therapy at all (12.8 percent versus 7.8 percent, p <0.001) compared with men. Moreover, compared with men, women on statins were less likely to achieve Adult Treatment Panel III (ATP III) target low-density lipoprotein cholesterol (LDL-C) (30.6 percent versus 38.4 percent, p <0.001) and non-HDL-C (37.1 percent versus 48.2 percent, p <0.001).
The disparity in treatment effects between men and women has long been established. In some cases, these differences are quite large. While researchers once relied on the assumption that treatment effects in women would be similar to those in men, the historical lack of inclusion of women in clinical trials has highlighted treatment differences as clinical trial information is applied across gender. Today, the proportion of treatments to which men and women respond differently remains unknown.

Controversy over inclusion of women in clinical trials has been motivated, in part, by theoretical concerns about the effect of gender differences on treatment and, in part, by fears of exposing fetuses to investigational drugs. Other reasons have been put forward as to why these disparities traditionally have existed. The exclusion of women from clinical trials means that women’s healthcare is compromised by a lack of sex-specific information about drug dosing and unique indications.

Cardiovascular clinical trials and research notoriously have perpetuated these differences. Three-fourths of cardiovascular clinical trials do not report sex-specific results, making it difficult for researchers and clinicians to draw conclusions about their effects on women. (Figure 1)

The historic rationale for studying only men in cardiovascular trials also stems from an apparent misimpression that there is a lower incidence of cardiovascular disease among middle-aged women compared to middle-aged men and a desire to minimize the heterogeneity of the trial population. The differential incidence pattern of disease between men and women should be accounted for when including women in clinical trials. Among the first major trials to exclusively study women was the Women’s Health Initiative, which identified the dangers of combined hormone replacement in postmenopausal women in terms of cardiovascular and cerebrovascular disease.

Beginning with the National Institutes of Health (NIH) Revitalization Act of

![Figure 1.](https://example.com/figure1.png)
1993, there has been a sustained effort to recognize underrepresentation of women and ethnic diversity in clinical trials. This effort stems from the inability to adequately answer two questions: 1) Do results of clinical trials apply consistently across all clinically meaningful subclasses of patients enrolled in the studies? 2) Can the results of studies be extrapolated to patients who did not participate in the original research? NIH-funded trials now must have sample sizes adequate to support a “valid analysis” of gender and racial subgroup effects. Prior to 1993, most primary-prevention cardiovascular trials only studied men.

Gender-based differences in cardiovascular disease exist in terms of incidence, prevalence, presentation, diagnosis, and treatment. Women in the early stages of coronary artery disease (CAD) often present with symptoms such as fatigue; abdominal discomfort; and back, jaw, or neck pain. These symptoms are all considered “atypical” because diagnostic standards mostly were established via research on men. Diagnostic tests, such as exercise electrocardiography and radionuclide myocardial perfusion imaging, do not detect CAD with the same sensitivity in women as in men. The testing and treatment of pregnant women is another challenging problem, because of a reluctance to expose developing fetuses to investigational drugs. The implication is that pregnant women are unable to weigh the potential benefits against the risks of treatment. Pregnant women traditionally have not participated in early stage clinical trials, creating significant safety concerns for treatment. Although the 1993 guidelines have increased the number of women in clinical trials, criticism is ongoing because of continued under-representation of women in some study groups. More women than men are now enrolled in NIH-sponsored Phase III trials. (Figure 2) However, this is mainly attributable to large, single-sex studies for breast and cervical cancer, the Women’s Health Study and The Women’s Health Initiative. This causes a skewed perception of female participation in clinical trials.

Identifying andremedying differences in clinical trials is only part of recognizing previous sex-difference underrepresentation. Researchers also have identified differential responses to treatments based on test animal gender and even sex chromosome status in individual cell cultures. The NIH is now developing guidelines and complex data-mining techniques to study these differences even in preclinical research.

How can further improvements be implemented? First, scientific journals should require authors to clearly label single-sex studies and to address sex-based differences in their research designs and analyses. Second, regulatory bodies and funding agencies should insist on the appropriate representation of both sexes in human and animal trials. Third, it is vital that knowledge of sex differences makes the leap from lab to clinic and becomes an essential consideration in physicians’ interactions with patients. Finally, health organizations should encourage more women to join clinical research trials.

Disclosure statement: Dr. Kroll received speaker honorarium from LipoScience.

References are listed on page 39.
Cardiovascular disease affects one in three adult males and accounts for 25 percent of their mortality, making it the leading cause of death for men in the U.S.\(^1,2\) Clinical androgen deficiency, characterized by low testosterone levels with manifest symptoms, affects a large number of middle-aged and older men and can significantly impact not only quality of life but also several cardiovascular risk factors and mortality. The Massachusetts Male Aging Study estimated the prevalence of androgen deficiency in the 40- to 69-year-old U.S. population to be 12.3 percent (2.4 million people), with an expected incidence of 481,000 cases per year in this age group.\(^3\)

Testosterone levels peak in the second and third decade of life,\(^4\) followed by an age-related decline of 1 to 2 percent per year.\(^5\) Bioavailable testosterone is further reduced because of an age-related increase in sex hormone-binding globulin.\(^4\) The prevalence of testosterone deficiency therefore increases with age, affecting 20 percent of men over the age of 60, 30 percent over age 70, and 50 percent over age 80.\(^6\)

Common conditions such as obesity and obstructive sleep apnea can also suppress the hypothalamic-pituitary-testis axis, leading to testosterone deficiency.\(^7\)

Low testosterone levels are associated with an increased risk of metabolic syndrome and its individual components, including central adiposity,\(^8\) an adverse lipid profile, insulin resistance and subsequent type 2 diabetes mellitus.\(^9\) Testosterone deficiency is also associated with atherosclerosis and several cardiovascular risk factors, including increased carotid intimal media thickness,\(^10,11\) peripheral arterial disease,\(^12\) and elevated high-sensitivity C-reactive protein,\(^13\) as well as increased all-cause and cardiovascular mortality.\(^14,15,19\)

**Testosterone Deficiency and Lipid Metabolism**

Testosterone down-regulates lipoprotein lipase activity, resulting in decreased triglyceride levels,\(^20\) and testosterone deficiency has been associated with
elevated atherogenic lipoproteins, elevated triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C). The impact of testosterone on HDL-C and low-density lipoprotein cholesterol (LDL-C) metabolism has not been clearly defined given conflicting data. While the effects of testosterone therapy on LDL-C are debated, studies have consistently shown a reduction in total cholesterol with testosterone supplementation, and some studies have also shown triglyceride reduction.

Treatment of Testosterone Deficiency

The pressing question — a current topic of debate — is whether testosterone supplementation should be administered in males with low testosterone levels and cardiovascular risk factors. Small, randomized controlled trials have demonstrated favorable effects of testosterone therapy on components of metabolic syndrome, including improved dyslipidemia, decreased insulin resistance, improved glycemic control, and decreased inflammatory markers including C-reactive protein. Testosterone therapy has also been shown to decrease exercise-induced myocardial ischemia, as evidenced by a delay in time to one millimeter ST-segment depression on treadmill exercise testing in men with stable angina. Notably, despite the benefits of testosterone supplementation seen in these studies and others showing improved mortality, a few recent studies have led to growing concern regarding a potential increase in cardiovascular events with testosterone therapy. However, these studies had several limitations in design, participant selection, and adherence to guideline-recommended diagnosis and treatment of clinical androgen deficiency, confounding their interpretation.

Despite the unchanged prevalence of male hypogonadism, there has been a recent dramatic increase in patients asking about testosterone therapy, possibly as a result of increased marketing of “low T” syndrome and a concomitant rise in inappropriate therapy and inadequate monitoring can lead to testosterone levels that are too high or too low, both of which are likely harmful. Testosterone therapy must, therefore, be prescribed only after appropriate diagnosis of clinical androgen deficiency and with adequate safety monitoring as recommended by the Endocrine Society Clinical Practice Guideline.

Conclusion

Testosterone deficiency adversely impacts many cardiovascular risk factors, including lipoprotein metabolism. There is evidence that testosterone deficiency may lead to progression of atherosclerosis and ultimately cardiovascular disease, and that appropriate supplementation mitigates many of these risks. Larger randomized controlled trials with long-term follow-up are needed to elucidate the role of testosterone supplementation in cardiovascular risk reduction and further evaluate its risks and benefits.

Disclosure statement: Dr. Tanna has no disclosures to report. Dr. Plakogiannis received speaker honoraria from Sanofi, Pfizer, and LjU CE.

References are listed on page 39.

“Testosterone deficiency adversely impacts many cardiovascular risk factors, including lipoprotein metabolism.”
Get Certified in Lipid Management

Improve Patient Care
Enhance Your Professional Stature and Credibility
Demonstrate Your Commitment to Continued Professional Development in Dyslipidemia

Testing Windows

Spring 2015 Test Window
March 30 – May 16, 2015 (application deadline: March 27, 2015)

Summer 2015 Test Window
June 29 – August 15, 2015 (application deadline: June 26, 2015)

Fall 2015 Test Window
October 5 – November 21, 2015 (application deadline: October 2, 2015)

Applications must be postmarked by the application deadline.

The only advanced certification program of its kind available to physicians who wish to validate their rigorous training and expertise in lipidology.

The American Board of Clinical Lipidology was established to assess the level of knowledge required to be certified as a Clinical Lipidologist, to encourage professional growth in the practice of lipidology, and to enhance physician practice behavior to improve the quality of patient care.

The Accreditation Council for Clinical Lipidology offers two levels to recognition:

Basic Competency in Clinical Lipidology Exam:
For individuals with general involvement in lipidology who want to sharpen their skills and knowledge in lipid management.

Clinical Lipid Specialist Certification Program:
Provides an opportunity for health care professionals who provide specialized care to patients with dyslipidemia and related cardiometabolic conditions to become certified as clinical lipid specialists.

Physicians

www.lipidboard.org

Pharmacists, Nurses, Physicians, Physician Assistants, Dietitians, Exercise Specialists, Industry and Research Professionals

www.lipidspecialist.org
The Foundation supports patient and clinician educational, research, and community outreach activities that enhance and support the initiatives of the National Lipid Association in its efforts to reduce cardiovascular events and deaths related to abnormalities of cholesterol metabolism.
The Foundation of the National Lipid Association achieves its mission through raising funds to support the initiatives of the National Lipid Association. The Foundation continually seeks funding to support programs that raise awareness about dyslipidemia for healthcare providers and patients through research, education, and community outreach grants. Foundation donors in 2014 can say that they have helped us work toward this goal as shown by the impact that several of our initiatives had last year on a national level. I am pleased to give you an update on several successful initiatives by the Foundation of the National Lipid Association in the past calendar year.

**Triglycerides Public Awareness Campaign**
In keeping with the Foundation’s mission to educate clinicians (as well as the lay public), the Foundation of the National Lipid Association supported and sponsored a public awareness campaign about high triglycerides that launched Sept. 1, 2014, to coincide with National Cholesterol Education Month. The Foundation continues to lay important groundwork for the future regarding dyslipidemia and ultimately helping to decrease early deaths related to cardiovascular disease. The cornerstone of this initiative was a large-scale PR campaign developed to raise awareness about the role triglycerides play in consumers’ health and as a key part of their entire lipid profile. You can view related materials and information at learnyourlips.com.

**Hunninghake Abstract Award**
In honor of Donald Hunninghake, MD, a pioneer in lipid research, the Foundation of the NLA received funding in 2014 to begin offering The Foundation of the National Lipid Association Hunninghake Familial Hypercholesterolemia Abstract Award for the best submitted abstract at the NLA Annual Scientific Sessions, specifically in the area of familial hypercholesterolemia (FH) research. The Foundation has had a significant focus geared toward patient awareness and education concerning FH, and this award has been created in order to continue that focus and to further encourage clinicians in their research and study of such disorders. Each year the winner will be determined by the Foundation of the NLA Board of Directors once the abstract committee has approved the abstracts in this category. The award will be presented to the winner at the Honors and Awards Ceremony at the NLA Scientific Sessions.

**FNLA Meeting Events**
The Foundation hosted three successful events to coincide with the NLAs Annual and Clinical Lipid Update meetings: A luau in Maui; a night of dinner, dancing, and games in Orlando; and a wine tasting and social gathering in Indianapolis. These Foundation events continue to be successful at each of the NLAs meetings and are a great opportunity for people to have fun and enjoy time with peers while supporting a great cause.

**New York Yankees FanFest**
As part of the community outreach component of the Triglyceride Awareness Campaign, the Foundation was able to purchase a Cholestech LDX Machine and related materials (banner, case, etc.) in order to participate in patient community events and offer cholesterol screenings with the help of FNLA and NLA volunteers. The first successful event utilizing the machine took place at the Yankees FanFest held in New York City in September 2014, with the help of several NELA Board Members. The volunteers were busy providing screenings for the entire duration of the event and were able to help more than 60 individuals by providing each of them with their cholesterol numbers and guidance on how to better manage their numbers. With the acquisition of the machine, the Foundation can now help educate more patients at screening events in the future.

**NLA Young Investigator Award**
The Foundation is happy to report that it has received a commitment from LipoScience Inc. (recently acquired by LabCorp) to continue the sponsorship of the NLA Young Investigator Award for an additional three years. This will allow the Foundation, along with the NLA, to continue to recognize cardiology, endocrine, and lipidology fellows and other trainees presenting abstracts at the NLA Scientific Sessions with an award for their outstanding work and commitment to the field.

As always, thank you for your support of the Foundation, and I look forward to building on this success in the coming year!

Anne C. Goldberg, MD, FNLA
President
Foundation of the National Lipid Association
What is Your Number? Campaign

In conjunction with Cholesterol Awareness Month in September 2014, the Foundation launched an awareness campaign titled “What is Your Number?” to encourage patient education and drive discussion around lipid management and the resulting consequences of high cholesterol and triglycerides. Through the month of September patients were encouraged to ask questions to better interpret and manage their triglyceride level during visits with healthcare providers. The Foundation partnered with a local Jacksonville, Fla., public relations firm, St. John & Partners, to carry out the following activities:

- Media outreach conducted by St. John & Partners to include blogs, print, television, and broadcast interviews of Foundation and NLA leadership;
- ReachMD radio shows including topics such as “The Role of non-HDL Cholesterol in Risk Assessment and Treatment” and “Triglycerides and Pregnancy”;
- Development of patient tools including a patient tear sheet and a pop-up easel display with a tear pad containing a tool for managing triglyceride levels and how to engage in conversation with healthcare providers;
- Participation at the Yankees FanFest that took place Sept. 20, 2014, in New York City, attracting more than 8,000 people from the local area. A cholesterol screening took place at the booth with the Foundation’s newly-acquired Cholestech LDX Machine and related materials and
- Posting of a patient resource page on the Foundation’s patient site, learnyourlipids.com, offering information on triglycerides, exercise, weight loss, etc.

100 Questions & Answers About Managing Your Cholesterol

The Foundation continues to offer this valuable patient resource, produced in partnership with the NLA. The book features frequently asked questions with answers that are provided in lay language. To order a copy for your office, visit amazon.com. The book is also available on Kindle and Nook e-readers!

LearnYourLipids.com

As a patient resource, the Foundation maintains learnyourlipids.com. During the 2014 Triglyceride Awareness Campaign launched in September during Cholesterol Education Month, the site was updated with new materials focusing on hypertriglyceridemia and continues to be updated with additional information on a monthly basis.
Thank you to our Sustaining Donors in 2014:

J. Chris Bradberry, PharmD, FNLA
Eliot A. Brinton, MD, FNLA
W. Virgil Brown, MD, FNLA
Thomas D. Dayspring, MD, FNLA
Brian S. Edwards, MD, FNLA
Anne C. Goldberg, MD, FNLA

Thank you to our Contributing Donors in 2014:

Enrique J. Griego, MD
John R. Guyton, MD, FNLA
Linda C. Hemphill, MD, FNLA
James M. Mckenney, PharmD, FNLA
Carl E. Orringer, MD, FNLA
Gregory J. Phillips, MD
Raul D. Santos, MD, PhD
Cesare R. Sirtori, MD, PhD
Paul D. Thompson, MD
James A. Underberg, MD, MS, FNLA &
Terry Underberg

The Foundation recognizes two contribution levels: Sustaining and Contributing. Sustaining donors make a gift of $1,000 or more throughout the course of the year. All other private donations are considered Contributing donors. Every donation is greatly appreciated and helps make the Foundation projects and outreach possible.

Scan for Lipids

2014 was the fourth year the Foundation benefited from the NLA’s “Scan for Lipids” program at its scientific meetings. Participating exhibitors agreed to donate $1 for every attendee name badge scanned.

Thank you to our “Scan for Lipids” Donors in 2014:

Acasti Pharma Inc.
Aegerion Pharmaceuticals Inc.
Amarin Pharma Inc.
Amgen Inc.
Atherotech Diagnostics Lab
Boston Heart Diagnostics
CardioDx Inc.
Carlson Laboratories
Cleveland HeartLab Inc.
diaDexus Inc.
Genzyme Corporation, a Sanofi company
Kaneka Pharma America LLC
Kowa Pharmaceuticals America LLC
Lilly
Lipoprotein(a) Foundation
LipoScience Inc.
Medtelligence LLC
Novartis
Sanofi US
Step One Foods
Synageva BioPharma

Khattar Aizooky, MD
Vincent S. Akridge, BS
Esmeraldo C. Arada, RN
Angela T. Bachelor, ARNP
Connie Baforo in honor of Mary Button
Michael F. Bartell, MD
Harold E. Bays, MD, FNLA
Thomas D. Dayspring, MD, FNLA
Brian S. Edwards, MD, FNLA
Anne C. Goldberg, MD, FNLA
Enrique J. Griego, MD
John R. Guyton, MD, FNLA
Linda C. Hemphill, MD, FNLA
James M. Mckenney, PharmD, FNLA
Carl E. Orringer, MD, FNLA
Gregory J. Phillips, MD
Raul D. Santos, MD, PhD
Cesare R. Sirtori, MD, PhD
Paul D. Thompson, MD
James A. Underberg, MD, MS, FNLA &
Terry Underberg

Fundraising

J. Chris Bradberry, PharmD, FNLA
Eliot A. Brinton, MD, FNLA
W. Virgil Brown, MD, FNLA
Thomas D. Dayspring, MD, FNLA
Brian S. Edwards, MD, FNLA
Anne C. Goldberg, MD, FNLA

The Foundation recognizes two contribution levels: Sustaining and Contributing. Sustaining donors make a gift of $1,000 or more throughout the course of the year. All other private donations are considered Contributing donors. Every donation is greatly appreciated and helps make the Foundation projects and outreach possible.

Scan for Lipids

2014 was the fourth year the Foundation benefited from the NLA’s “Scan for Lipids” program at its scientific meetings. Participating exhibitors agreed to donate $1 for every attendee name badge scanned.

Thank you to our “Scan for Lipids” Donors in 2014:

Acasti Pharma Inc.
Aegerion Pharmaceuticals Inc.
Amarin Pharma Inc.
Amgen Inc.
Atherotech Diagnostics Lab
Boston Heart Diagnostics
CardioDx Inc.
Carlson Laboratories
Cleveland HeartLab Inc.
diaDexus Inc.
Genzyme Corporation, a Sanofi company
Kaneka Pharma America LLC
Kowa Pharmaceuticals America LLC
Lilly
Lipoprotein(a) Foundation
LipoScience Inc.
Medtelligence LLC
Novartis
Sanofi US
Step One Foods
Synageva BioPharma

Khattar Aizooky, MD
Vincent S. Akridge, BS
Esmeraldo C. Arada, RN
Angela T. Bachelor, ARNP
Connie Bafaro in honor of Mary Button
Michael F. Bartell, MD
Harold E. Bays, MD, FNLA
Carl R. Berg, PA-C
James E. Berry, MD
Kim K. Birtcher, PharmD, FNLA
Vera A. Bittner, MD, MSPH, FNLA
Veita J. Bland, MD
B Alan Bottenberg, DO, FNLA
Lynne T. Braun, PhD, CNP, FNLA
Basil A. Brikho, MD
Scott A. Brodarick, MD
Joan Broder in honor of Joy Avidan
Finley W. Brown, Jr., MD
Alan S. Brown, MD, FNLA
David M. Capuzzi, MD, PhD, FNLA
Barbara L. Ciesliga, MD
Nicole A. Ciffone, MS, NP
Jerome D. Cohen, MD, FNLA
Randi E. Cohen, MD
Judith A. Collins, MSN
John R. Crouse, MD, FNLA
Dennis R. Cryer, MD
William S. Dacus, MD
Seshadri Das, MD
Quintin H. Dickerson, Jr., MD
Michael S. Doyle, MD, MPH
Robert H. Eckel, MD, FNLA
Robert M. Evans, MD
James M. Falko, MD, FNLA
Edwin E. Ferguson, MD, FNLA
Herbert A. Fischer, MD, PhD
Tobin J. Fisher, MD
Philip H. Frost, MD
Susan K. Fujii, PharmD, FNLA
Richard J. Galloway, MD
James H. Gault, MD
Robert K. Gleeson, MD, FNLA
Herbert M. Green, MD
Robert S. Greenfield, MD, FNLA
Nathan C. Griffin, MD
Ian Hamilton-Craig, PhD
Yehuda Handelsman, MD, FNLA
Era Gunar K. Hathototawa, MD
Richard J. Havel, MD
Wm. James Howard, MD, FNLA
Lisa C. Hudgins, MD
Michael L. Humphrey, DO
Laurea M. Irwin, PharmD
Michael L. Isaacson, MD
Marc K. Israel, PharmD
Jason B. Jerabek, DO
Peter H. Jones, MD, FNLA
Joseph K. Kaholokula, PhD
Wahida Karmally, MD, DrPH, CDE, FNLA
Carol Kirkpatrick, PhD, MPH, RDN
Raymond W. Kordonowy, MD
Gerald M. Kovar, MD
Maris H. Krasnow
Tuan Nizam Lot
Henry K. Lui, MD
Timothy J. Lyons, MD, FNLA
Alejandro Martin-Morales, MD
Yuji Matsuzawa, MD, PhD
Jan L. McAlister, NP, DNP, FNLA
Jim Metropoulos, MD
Thomas G. Miglis in honor of Joy Avidan

Scan for Lipids

2014 was the fourth year the Foundation benefited from the NLA’s “Scan for Lipids” program at its scientific meetings. Participating exhibitors agreed to donate $1 for every attendee name badge scanned.

Thank you to our “Scan for Lipids” Donors in 2014:

Acasti Pharma Inc.
Aegerion Pharmaceuticals Inc.
Amarin Pharma Inc.
Amgen Inc.
Atherotech Diagnostics Lab
Boston Heart Diagnostics
CardioDx Inc.
Carlson Laboratories
Cleveland HeartLab Inc.
diaDexus Inc.
Genzyme Corporation, a Sanofi company
Kaneka Pharma America LLC
Kowa Pharmaceuticals America LLC
Lilly
Lipoprotein(a) Foundation
LipoScience Inc.
Medtelligence LLC
Novartis
Sanofi US
Step One Foods
Synageva BioPharma
Coronary heart disease (CHD) is the leading cause of death of men and women in the world but in younger age groups, the CHD-related death rate is strikingly higher in men compared to women. Emerging evidence suggests that a disparity exists in regards to cardiovascular risks and outcomes among the sexes. The lifetime risk of developing CHD by age 40 is 50 percent for men and 33 percent for women. In general, both CHD incidence and mortality in women lag by almost a decade behind that of men. However, this trend changes after the age of 75 and is mostly attributed to menopausal changes in women.

Because CHD has been thought of as a disease that plagues men, women often are not fully aware of their own risks of heart disease. Furthermore, there is a misperception that women are protected against CHD because it tends to emerge from seven to 10 years later compared to their male counterparts. Clinicians also often underestimate in women the same risk factors that they target with prevention and medications for men. This leads to differences in traditional diagnostic and therapeutic methods that are not necessarily optimized for women. Women, thus, arguably have had a poorer prognosis than men after myocardial infarction (MI). Mortality after a coronary bypass graft also has been shown to be higher in women as compared to men and may be attributed to comorbid conditions such as older age, smaller vessel size and the presence of hypertensive heart disease. However, over the past decade, there have been substantial efforts made to improve understanding of the sex and gender differences in cardiovascular disease. Studies have evolved to detect these differences, assess risk factors, and define goals for women as well as for men.

Hormonal Status
Unique to women is the influence of estrogen hormones on heart disease. Endogenous estrogen has been shown to delay the onset of atherosclerosis in women by influencing the process through a variety of mechanisms. Estrogen plays a role in regulating several metabolic factors, including lipoproteins and inflammatory markers. After menopause, atherosclerotic plaque composition develops into more vulnerable lesions with an increase in associated inflammatory factors.

Thus, incidence of CHD is lowest in premenopausal women as compared to men and to postmenopausal women of similar age. In the Women’s Ischemia Syndrome Evaluation (WISE) study, younger women with low blood estrogen were linked to a significantly greater prevalence — up to a seven-fold increase — in coronary artery disease.

Conversely, because men die from heart disease at an earlier age than women do, it is instinctive to think that lower testosterone levels would be beneficial for cardiovascular protection. However, a number of studies have suggested a link between low testosterone levels in men and the development of heart disease.
and its associated mortality. Several mechanisms may explain this association, although the precise nature of the link remains unclear. Men whose levels are too low may experience obesity, diabetes mellitus, and other health problems that make them susceptible to heart disease. Men with higher testosterone levels have more muscle mass and may be at lower risk for cardiovascular disease. One study that evaluated low testosterone levels in male veterans over 40 years suggested a 40-percent increased risk in mortality over the following 20 years compared with men with normal testosterone, independent of age, adiposity, and lifestyle.

“Coronary heart disease (CHD) is the leading cause of death of men and women in the world but in younger age groups, the CHD-related death rate is strikingly higher in men compared to women.”

Hypertension
Systolic blood pressure affects women more considerably than men in terms of cardiovascular outcomes. This may be related to a decrease in estrogen levels following menopause, as well as an up-regulation of the renin-angiotensin system, increase in plasma renin activity, salt sensitivity, and sympathetic activity. Isolated systolic hypertension (ISH), defined as systolic blood pressure > 160 mmHg and diastolic blood pressure < 90 mmHg, also is associated with an increased risk of CV disease, stroke and all-cause mortality in both men and women. However, the prevalence of ISH seems to be increasing more sharply in women than in men > 55 years of age. Women with a history of pre-eclampsia — defined as blood pressure > 140/90 mmHg and proteinuria (0.3 g/24 hrs) after 20 weeks of gestation — have twice the CHD risk as compared to normotensive women during pregnancy. Despite these risks, blood pressure reduction has been shown to benefit both men and women as evidenced in the Systolic Hypertension in the Elderly Program (SHEP). Antihypertensive treatment reduced the incidence of stroke and non-fatal MI by 36 and 27 percent, respectively.

Diabetes
Diabetes has long been recognized as a major risk factor for CHD and has been incorporated in numerous guidelines, including the current ACC/AHA guidelines and NLA Recommendations. Not surprisingly, CHD accounts for 75 percent of the deaths in adult diabetics. Diabetes is more prevalent among women.
> 20 years of age than among men. Furthermore, women with diabetes have a three- to seven-fold increased risk of CHD as compared to a two- to three-fold increase in men with diabetes.\(^4\) Mortality from MI also is significantly higher in diabetic women than it is in non-diabetic women and diabetic or non-diabetic men.\(^4\) Because of the high mortality rate in these patients, aggressive treatment is strongly recommended. A high level of evidence supports the use of a moderate-intensity statin in diabetics ages 40 to 75 years, regardless of gender.\(^10\)

In summary, CHD continues to be the leading cause of death among men and women. Despite varying hormonal composition between men and women, risk factors remain consistent between the sexes. On closer review, however, several factors — including lipids, diabetes, tobacco use, and high blood pressure — have been shown to play a larger role in women’s risk. This has led to an increase in research and a focus on more aggressive preventive strategies and treatment strategies in women with the goal of reducing the incidence of heart disease. There has been a near doubling of the rate of awareness of heart disease as the leading cause of death in women between 1997 and 2009 and a 50 percent decrease in the number of deaths resulting from CHD.\(^3\) At this time, secondary prevention of CHD in women with hormone replacement therapy is not recommended, because its use has not been shown to be favorable in this endeavor.\(^14\) Similarly, with men, clinical studies have yet to establish a role for testosterone replacement in reducing heart disease. Other agents — such as statins, ACE-inhibitors, and insulin — have been proven to be beneficial in risk reduction and should be considered as first-line options along with smoking cessation, if applicable.

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

References are listed on page 40.
It is well known that women are not protected from cardiovascular events but experience event rates at older ages equivalent to men after a 10-year lag time. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study showed similar findings regarding atherosclerosis, with 25- to 34-year-old women having much less atherosclerosis than similarly aged men and only slightly more atherosclerosis than 15- to 24-year-old adolescents/men.1 This naturally raises the question: Should girls start statins at an older age than boys given equivalent risk?

To answer this question, one must consider two issues: Are there risk scenarios that obliterate the gender protection for women and does the need to interrupt medication during pregnancy and lactation influence treatment decisions — that is, could the “legacy effect” of more intensive treatment regimens in clinical trials be reasonable to apply in this setting?

There are, in fact, three scenarios in which risk overwhelms gender protection. The most important of these is childhood-onset diabetes mellitus, with which men and women experience cardiovascular events at similar rates.2 In PDAY, atherosclerosis related to dysglycemia also is gender independent and more severe at young ages.1 Smoking is the second great leveler of gender-specific risk. A female smoker has the same risk as a male non-smoker when other risk factors are equivalent.3 Height of low-density lipoprotein (LDL) cholesterol level is the third. Again based on PDAY estimates, an elevation of LDL cholesterol of about 60 mg/dl will undo gender protection; thus, girls with familial hypercholesterolemia (FH) and severe elevations of LDL cholesterol should be treated at a young age.

A further consideration with regard to FH will be the need to interrupt treatment during pregnancy. Thus, for several prolonged periods, women may be exposed not only to the impact of interrupted treatment but to physiologic increases in lipid levels during pregnancy and lactation. Legacy effects observed in large clinical trials show a sustained benefit from receiving more intense statin therapy for the duration of the trial.4, 5 This observation suggests that statin therapy at any point in life when risk is present is likely beneficial.

Which girls might get statin treatment in childhood or adolescence?6 There essentially are two groups: those with FH and those with elevated LDL cholesterol in combination with another major risk factor. For FH, the discussion above suggests that the “legacy effect” provides a rationale for treating boys and girls without a gender preference, despite known differences in the onset of cardiovascular disease in men and women with this disorder. Earlier initiation of treatment compensates for the need to interrupt treatment later in life, thus providing better treatment of atherosclerosis across the lifespan. Similarly, in the setting of
diabetes, the absence of a gender gap in outcomes mandates against gender bias in lipid treatment recommendations.

For those with other risk factors (principally hypertension, tobacco use, and obesity) and LDL cholesterol that is elevated (above 130 mg/dl) but below 190 mg/dl, the PDAY study again provides some guidance. All the risk factors contribute to early atherosclerosis development independent of LDL cholesterol. Thus, in a hypertensive girl or smoker with an LDL cholesterol above 160 mg/dl, initiating a statin is reasonable. Between 130 mg/dl and 160 mg/dl, patient discussion should be undertaken. Since the impact on atherosclerosis when a patient has obesity without other risk is much greater in boys than in girls in PDAY, I tend to be conservative in starting obese girls on statins.

To summarize, as a general rule, I tend to start statins at the same age and for the same indications in boys and girls. This is because either overall risk is sufficiently high that medication is warranted or the need to interrupt treatment later in life balances gender protection for atherosclerosis development. However, in the setting of multiple risk factors and borderline indications, there is no substitute for patient discussion, behavioral risk modification, and careful follow-up before initiating treatment.

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

References are listed on page 40.
Case Study:
Turner Syndrome: An Overlooked Gender-Specific Cardiovascular Risk Factor

KAREN E. ASPRY, MD, MS, ABCL, FACC
Director, Lipid and Prevention Program
Lifespan Cardiovascular Institute
Assistant Clinical Professor of Medicine
Brown University, Alpert Medical School
Providence, RI
Diplomate, American Board of Clinical Lipidology

Introduction
Symptomatic coronary atherosclerosis is rare in women under age 40, even when conventional risk factors are present. This “athero-protection” has been attributed to the female “hormonal advantage” during premenopausal years. However, it has been speculated that other, non-hormonal X-linked factors and/or absence of Y-linked factors also contribute to gender differences in atherosclerotic risk. Whatever its causes, the case presented below confirms that athero-protection can be lost very early in young women with Turner Syndrome (TS), a complex and poorly understood disorder marked by loss of all or part of one female X chromosome. This may be especially true when hypoestrogenemia, a cardinal feature of the syndrome, is untreated for long periods and co-exists with dyslipidemia, vascular inflammation, a strong family history of coronary disease and, very likely, other unknown traits that influence vascular risk.

Case Presentation
M.T. was a 29-year-old woman referred to our practice for exertional dyspnea, upper back pain, and an echocardiogram suspicious for occult ischemic cardiomyopathy. Past medical history was significant for TS diagnosed after pubertal delay. Although the patient was treated with standard hormone therapy, including growth hormone from ages 13 to 15 and exogenous estrogen to induce feminization beginning at age 14, she self-discontinued the latter at age 19. At the time of her referral, she had been off female hormones for about a decade. Past medical history also was notable for osteoporosis, combined hyperlipidemia, obesity, and newly diagnosed hypertension recently treated with atenolol 25mg daily. There was no personal history of diabetes or smoking. Family history was notable for premature coronary artery events in both parents and paternal grandparents during middle age.

On exam, her blood pressure was 140/90 mmHg, heart rate 68 bpm, respirations normal, weight 181 pounds, height 60 inches, and BMI 35. Physical examination showed findings characteristic of TS, including mild neck webbing, a broad chest wall, and abdominal obesity. A cardiac exam showed a split S2 without murmurs, and trace pedal edema.

The electrocardiogram showed a right bundle branch block and Q waves inferolaterally. The echocardiogram showed a reduced left ventricular ejection fraction (LVEF) in the 35 to 40 percent range and hypokinesis of portions of the anterior and inferior walls. Laboratory data earlier that month showed a total cholesterol of 234 mg/dl, high density lipoprotein-cholesterol (HDL-C), 51 mg/dl; non-HDL-C, 183 mg/dl; low density lipoprotein cholesterol (LDL-C), 150mg/dl; triglycerides (TG), 163 mg/dl; high-sensitivity C-reactive protein (CRP), 3.8 mg/L; fasting blood glucose, 81mg/dl; and
thyroid-stimulating hormone, 4.1 uIU/ml.

A myocardial perfusion scan showed mixed scar and ischemia in the anterior and anterolateral territories and a reduced LVEF in the 40-percent range. Coronary angiography (Figure 1) showed a 95 percent stenosis in the mid-left anterior descending coronary artery (LAD), for which a drug-eluting stent was placed. Upon hospital discharge, atenolol was continued and the patient was prescribed dual anti-platelet therapy with aspirin and clopidogrel, and atorvastatin 40 milligrams daily. At follow-up, trans-dermal estrogen and a progestin had been restarted by the patient’s gynecologist. Repeat lipid testing on atorvastatin and hormone therapy showed a total cholesterol of 127 mg/dl, HDL of 56 mg/dl, non-HDL-C of 71 mg/dl, TG of 51 mg/dl, and LDL-C of 62 mg/dl. An LDL particle number was 837 nmol/L, small LDL-P was < 90 nmol/L, and lipoprotein(a) was 12 mg/dl.

Discussion: Basics of Turner Syndrome
TS occurs in an estimated one in 2,000 to 2,500 live female births and is marked by the loss of all or part of one female sex chromosome, leading to a 45,XO karyotype. Genetic “mosaicism” — the presence of a normal 46,XX karyotype in some cell lines and 45,XO in others (Figure 2) — is believed to exist in a large percentage of affected individuals, leading to wide variations in phenotype. Fragments of the Y chromosome may exist in up to 5 percent of TS patients, causing virilization and additional phenotypic variability. Short stature, neck webbing, pubertal delay, and progressive ovarian failure and infertility are the classic physical findings, the latter the result of ovarian follicle loss that begins in utero and continues after birth. However, the wide variation in phenotype leads to diagnostic delays in a large percentage of girls and women, and some remain completely undiagnosed. The latter fact is sobering, since women with TS have a markedly increased risk of cardiovascular morbidity and mortality, much of which might be prevented by early screening and intervention.

Vascular Pathology in Turner Syndrome
Aortic and arterial pathology, including aneurysms and dissections, and other left-sided cardiovascular anomalies exist in up to 50 percent of TS patients and contribute significantly to the three-fold increase in mortality and reduced life expectancy. Early coronary atherosclerosis and acute myocardial infarctions are additional features of TS that add to the higher death rate, with a reported standardized mortality ratio of approximately 3.5, though some have debated the association. Manifest coronary disease may occur as early as the fourth decade, as seen in our patient, who presented at the cusp of this time period. Studies show increases in carotid intima-media thickness (CIMT) beginning as early as the second decade in TS patients, suggesting that subclinical atherosclerosis probably begins in childhood. Not surprisingly, TS is associated with an increased burden of most major atherosclerotic risk factors, driven at least in part by deficiencies of growth hormone and estrogen, the latter from lack of ovarian function. The fact that mean levels of atherogenic lipoproteins — including LDL-C, TG, LDL particle number, and small LDL particle number — are significantly increased in TS patients compared to genetically normal 46,XX females with premature ovarian failure, (Table 1) suggests that factors other than estrogen deficiency probably play a role in creating the dyslipidemia observed in TS. Significant increases in hypertension, visceral adiposity, and impaired glucose tolerance — the latter independent of body fat mass — also are observed in TS compared to controls. Increased levels of several pro-thrombotic factors are additional features of the phenotype, which may contribute to observable dyslipidemia.

### NMR Lipid Profiles In Women with TS (45,XO) vs. POF (46,XX)

<table>
<thead>
<tr>
<th>Metric</th>
<th>POF (n=51)</th>
<th>TS (n=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>32.1 ± 5.8</td>
<td>34.2 ± 10.6</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>26.4 ± 4.6</td>
<td>27.2 ± 7.2</td>
<td>0.4</td>
</tr>
<tr>
<td>LDL particles, nmol/L</td>
<td>954 ± 350</td>
<td>1,285 ± 345</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Small LDL-particles, nmol/L</td>
<td>298.8 ± 331</td>
<td>603.2 ± 299.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VLDL particles, nmol/L</td>
<td>47.0 ± 40</td>
<td>62.1 ± 45</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL particles, nmol/L</td>
<td>30.5 ± 4.3</td>
<td>34.8 ± 5.4</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Table 1. Data are means ± standard deviation or range. TS = Turner Syndrome. POF = premature ovarian failure. BMI = body mass index. LDL = low density lipoprotein. VLDL = very low density lipoprotein. HDL = high density lipoprotein. Table from Van P, Bakalov V and Bondy C. Jour Clin Endocrinol Metab. 2006;91:2867-70.
increases in acute atherothrombotic events. Our patient had presumed long-standing hypo-estrogenemia before resuming estrogen-progestin therapy, along with dyslipidemia, hypertension, a family history of early coronary disease, and features of the metabolic syndrome, the combination of which likely fueled her early coronary disease.

**Genetic Mechanisms in Turner Syndrome**

The genotypes responsible for early vascular disease, and all other clinical traits in TS patients, remain poorly defined. The genetics of the disorder are believed to be more complex than previously recognized and at least two hypothetical models have been proposed (Figure 3). Whichever is accurate, it is clear that TS probably involves altered transcription of numerous X-linked and autosomal regulatory and structural genes. This, in turn, leads to fundamental alterations in tissue genesis and maintenance, and to dysfunction of vascular, endocrinologic, hematologic, immunologic, and other organ systems, beginning *in utero*. (Figure 4). Indeed, at least one histological fetal autopsy study has shown onset in 45,XO fetuses of an aortic and arterial structural vasculopathy, marked by disruption of smooth muscle cell (SMC) derived collagen, elastin, and other extracellular matrix proteins. These structural abnormalities of the tunica media probably account for the high incidence of aortic dilatation and dissection in TS. Theoretically, these same abnormalities could later inhibit SMC-mediated stabilization of atheroma created prematurely by the hormonal milieu, leading to early clinical events. Abnormalities of T-cell function, increases in inflammatory cytokines, and defective coagulation and fibrinolysis, all observed in TS, may also contribute to early atherosclerotic events.

**Screening and Treatment of Turner Syndrome**

The Turner Syndrome Consensus Study Group updated its guideline for the care of girls and women with TS in 2007. Recommendations include imaging tests, including echocardiography and magnetic resonance imaging (MRI), to screen for structural cardiac and aortic abnormalities, along with routine testing to evaluate for dyslipidemia, hypertension, and diabetes beginning on transition of young TS patients to adult care and regularly thereafter. Recommendations regarding the timing of estrogen treatment are evolving. Previously, experts recommended that exogenous estrogen, administered to induce and maintain feminization, be withheld until after maximum skeletal growth was achieved. However, it is now recognized that any negative effects of estrogen on growth plate closure can be overcome by early growth hormone administration. Therefore earlier estrogen treatment is now recommended in girls with TS. Experts caution that clinicians should not extrapolate negative outcomes from estrogen replacement in post-menopausal women to TS patients suffering from estrogen deficiency early in life, since any pro-thrombotic effects of estrogen are likely outweighed by favorable effects on endothelial, smooth muscle, inflammatory, and cardiac muscle cells, and on hepatic lipoprotein and glucose metabolism. Nonetheless,
no hard endpoint studies of the effects of exogenous estrogen in TS patients exist. Moreover, because the favorable vascular effects of estrogen may be less after prolonged estrogen deficiency, it is difficult to perform a risk/benefit analysis for estrogen therapy in our young patient who probably had longstanding hypoestrogenemia by age 29 and now has established coronary disease.

There are no specific recommendations regarding the thresholds for, or timing and targets of, diet or drug treatment of dyslipidemia in TS patients. Since only a small percentage of women with TS are able to conceive, there may be a role for earlier pharmacologic treatment of lipoprotein disorders to reduce future atherosclerotic vascular risk, because concerns over child bearing and pregnancy are removed (although more women with TS are benefiting from advanced techniques to improve fertility and conception rates). Since multidisciplinary care of TS patients by primary care physicians, endocrinologists, cardiologists, and psychologists has now been recommended by some, strong consideration should be given to including lipid specialists in the care model. Finally, as some have proposed, it is time to recognize TS as a distinct gender-specific vascular risk factor, the presence of which calls for serial imaging to evaluate for aortic pathology, and aggressive diet, lifestyle, and pharmacologic interventions to reduce the risk of early morbidity and mortality from atherosclerotic vascular events.

Disclosure statement: Dr. Aspy received consulting fees from the National Lipid Association.

References are listed on page 40.
Chapter Update: Philadelphia Lipid and Atherosclerosis Club and More

DANIEL SOFFER, MD, FNLA
Clinical Associate Professor of Medicine, University of Pennsylvania
Internal Medicine and Preventive Cardiology
University of Pennsylvania Health System
Philadelphia, PA
*Diplomate, American Board of Clinical Lipidology*

With so many topics in the medical and lay news specifically for us, it’s a great time to be a clinical lipidologist! People are talking about the expanded and nuanced role of statins, IMPROVE-IT hit the press, and you can read about PCSK9 inhibitors in the *New York Times* and *The Wall Street Journal*. Genetic studies regarding lipid and lipoprotein physiology have made their way into journals, and everybody seems to have an opinion about our national guidelines for cholesterol treatment. Even the *New Yorker* included cholesterol cartoons.

With these and other issues on the minds of our colleagues, this is a great time to introduce other colleagues to the NLA. National meetings, such as the American Heart Association Scientific Sessions this past November, made headlines and started conversations. Our regional meetings continue to expand on those conversations and help the community understand the complexity of what we do and the NLA’s positions on crucial issues in lipid management. While nuance can be conveyed in a large lecture hall, it is the more intimate discussions that are critical to helping us understand the details. These meetings and conversations are what drew me to the NLA, the NELA chapter, and the Philadelphia Lipid and Atherosclerosis Club (PLAC).

The Northeast region continues to be a hotbed of academic activities. Philadelphia Lipid and Atherosclerosis Club (PLAC) has been meeting for more than 15 years. We get together two to three times per year. Although there is an invitation list, it’s very flexible — anyone with an interest in lipids and atherosclerosis is invited. We typically have a national speaker and we always have quality discussions, debates, and camaraderie.

It is the camaraderie that makes the PLAC meetings so valuable. While conversations occur at the big meetings too, it is these small gatherings where national thought leaders, local division chiefs, clinicians, scientists, pharmacists, and trainees can really get together and share their experience and get involved. These intimate conversations are one of the most important recruitment tools that the NLA can use because it is an opportunity for attendees from different circles to share common ground and a meal in an era where more and more of our time is spent pouring over a monitor instead of meeting face to face!

The PLAC Steering Committee is made up of clinicians from Pennsylvania, New Jersey, and Delaware, and attendees come from all three states. We’ve hosted Michael Davidson, MD; Christie Ballantyne, MD; Paul Thompson, MD; and Avedis Khachadurian, MD, to name just a few.

The last presentation was our own Douglas Jacoby, on atherosclerosis imaging. Every year I meet more local physicians with an interest in this field. Meetings like PLAC or the regional/national NLA meetings play such an important role in learning and igniting enthusiasm for lipidology. Join us in Philadelphia and let’s toast to our common interests and our love of learning from each other.
Merle Myerson, MD, is a woman of many talents and a wearer of many hats. Her dedication to her work is more of a passion than a career, and according to her, it is her “vocation and avocation.” As founder and director of the Mount Sinai Roosevelt and St. Luke’s Cardiovascular Disease Prevention Program & Lipid Clinic, Pre-Exercise Heart Screening Program, and Cardiology Section in the Institute for Advanced Medicine HIV Clinic, as well as an attending cardiologist, Dr. Myerson spends much of her time seeing patients but also has a passion for education teaching and research. Dr. Myerson went into medicine because of her interest in public health and public service, but she also was very interested in exercise and sports — she holds a doctorate in Applied (Exercise) Physiology. She was and still is fascinated by how the human body works and can be pushed to the limit. Dr. Myerson almost went into orthopedics, but luckily for the lipid field and the NLA, she chose another path. During her first year in medical school she became interested in learning more about CVD prevention and that summer she was able to learn under the guidance of Dr. Thomas A. Pearson, a preventive cardiologist who also ran a lipid clinic at Mary Imogene Bassett Hospital in Cooperstown, N.Y. After working under Dr. Pearson, there was no doubt in her mind what career path she would take. During her cardiology fellowship at Columbia College of Physicians and Surgeons, she had the opportunity to learn from Dr. Henry Ginsberg and work in basic lipid research in his lab. She became a member of the NLA in 2005 and quickly found ways to become involved. She feels that the NLA is a wonderful organization in many ways, especially the multidisciplinary aspect. “We are all ‘one,’” she says. “In other words, it’s not the doctors over here and the nurses over there.” In recent years, she developed the New York Clinical Lipid Forum where healthcare providers and researchers gather to learn about lipids, and the last one was endorsed by the Northeast chapter of the NLA. The April 2015 Forum will focus on cardiovascular disease in patients living with HIV.

Dr. Myerson has made great strides in the clinical care and research of cardiovascular risk in HIV/AIDS patients. In 2008, the American Heart Association (AHA) published proceedings of a conference they had on an initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS. With her prevention and lipid hat on, Dr. Myerson read this and immediately saw a need that needed to be filled. This was a relatively unknown area at the time, as patients infected with HIV were just beginning to live to ages where CVD was prevalent and providers for these patients were not familiar with CVD issues. Dr. Myerson approached the leaders of her hospital’s very large HIV clinic and she soon began cardiology and lipid clinic.
sessions in the HIV outpatient clinics. She now has sessions at three sites and sees over 800 patients a year.

Dr. Myerson continues with her research on exercise and collaborates with the Exercise Physiology Laboratory at Columbia University, Teachers College where she earned her doctorate and is now an adjunct professor. She is currently investigating the influence of both aerobic and resistance exercise on the functional properties of the HDL particle.

Most of her day is spent in direct patient care with research, teaching, and administrative duties taking the remainder of her time and extending to nights and weekends. In addition to enjoying patient care, Dr. Myerson feels that this allows her to be “in the trenches” and have insight into what clinical questions are important for research. Dr. Myerson thinks of herself as very fortunate because she’s able to spend her days doing something that she truly enjoys and is able to create new things. She also enjoys staying active by doing any and all outdoor activities such as running, cycling, cross country skiing, snowshoeing, and horseback riding. She values time spent with her family and friends including her canine buddies — three golden retrievers named Rudy, Ella, and Grace.

Dr. Merle Myerson (right) with then-graduate student Dr. Deborah Varela. Dr. Varela had just presented a poster of her work with Dr. Myerson at the 2012 NLA Scientific Sessions in Scottsdale, Ariz., and they decided to celebrate by climbing to the top!

Read the Journal of Clinical Lipidology on your iPad!

- Free to NLA members and Journal subscribers
- Allows you to download each issue onto your iPad
- Immediate access to full-text content
- Download The JACL app, log in using your JCL username and password
- More info at lipid.org/jclapp
Register Now for the NLA’s Annual Scientific Sessions in Chicago

Register now for the NLA’s Annual Scientific Sessions in Chicago. The 2015 annual meeting will take place June 11–14, 2015, at the Palmer House Hotel. Hear a number of speakers and presentations including the “Role of Exercise and Diet in AHA/ACC Guidelines for Lifestyle Management” by Robert H. Eckel, MD, FNLA, and the “Impact of Hypertension Thresholds and Goals on Special Populations” by Keith C. Ferdinand, MD, FNLA. For reservations, call 877-865-5321 and ask for the National Lipid Association’s room rate. A special room rate starting at $229 per night plus tax has been arranged. This group rate will be available until May 19, 2015, or until the room block is filled. Please make your reservation early as we do anticipate the room block will sell out. For more information, visit lipid.org/sessions.

Membership Competition

Does your chapter have what it takes to be a VIP? Join your fellow colleagues in the Member Recruitment Competition for 2015 to see which chapter has what it takes to win a VIP Lounge at the 2015 Annual Scientific Sessions in Chicago. If your chapter recruits the most new members by May 15, 2015 every member of that chapter who is attending the annual meeting will have all-day access to a private lounge with free wi-fi, soft drinks and snacks — not to mention bragging rights! Your chapter needs your help! If you want your chapter to win, make sure to reach out to your colleagues who are not NLA members yet and tell them why they should join the NLA. To request membership and marketing materials, please email Membership Manager, Britney Caldwell at bcaldwell@lipid.org. These materials are great to hand out or display at lectures, etc. Please visit lipid.org/competition2015 for more information and current winning chapter.


The new CLM-SAP 17 is a complimentary, online self-assessment program that will objectively validate and enhance your knowledge of the available clinical practice guidelines and recommendations related to lipid management in order to reduce atherosclerotic cardiovascular risk. As guidelines and recommendations are routinely updated and released, and as different approaches are advocated, clinicians should become familiar with all available guidelines and recommendations in order to implement an informed, evidence-based approach to patient care.

This program will review similarities and differences among these important guidelines in order to reduce gaps in implementation of evidence-based therapies.

Get real time feedback after each question, including a detailed critique and bibliographic references for further reading and receive a PDF copy of the program upon claiming CME/CE credit. Complete via computer or from tablet app for iPad and Android devices. Visit lipid.org/education/clmsap for more information and to view all available CLM-SAPS.

Diabetes Alliance Educational Forum

Attend the Cardio Metabolic Risk and Diabetes Conference April 3 in Jacksonville, Fla. This meeting will provide physicians, other clinicians, and allied health personnel an excellent opportunity to learn some of the latest information about diabetes and cardio-metabolic risk. To download the brochure, visit lipid.org/sites/default/files/Brochure_Diabetes_Alliance.pdf, or for more information, visit floridadiabetesallianceedforum.org.

PCNA Patient Education Materials

The PCNA recognizes the need for excellent patient education of heart failure. That is why they have developed high-quality patient materials to aid healthcare providers in caring for heart failure patients. The materials are free to download. View them by visiting pcna.net/clinical-tools/education-for-your-patients/heart-failure.
ISA 2015 Meeting in Amsterdam

The 17th International Symposium on Atherosclerosis (ISA) is scheduled for May 23-26, in Amsterdam, Netherlands. The scientific program is designed in a novel format, organized in four major themes: Dyslipidemia, Pathogenesis, Prevention, and Epidemiology of atherosclerosis. Register by May 1, 2015, to avoid late registration. For more information, visit isa-2015.com.

Masters in Lipidology Course Available Online

The Masters in Lipidology Course, traditionally offered as an ancillary course prior to NLA meetings, is now available as an online course. This comprehensive program provides physicians, physician assistants, pharmacists, nurse practitioners, nurses, dietitians, and other healthcare professionals with an interest in lipid management, with complete lectures synchronized with slides from the live course. The Masters in Lipidology online course provides an intensive curriculum covering lipoprotein metabolism, genetics, vascular biology, atherosclerosis, biomarkers, imaging, Cardiometabolic disorders, lifestyle interventions, and pharmacologic therapies. The curriculum is designed for healthcare professionals who desire to practice at an advanced level within the field.

Available via computer, laptop, or iPad/tablet, the program provides participants with the flexibility to complete modules from virtually anywhere. Participants receive access to online resources and tools to enhance learning and practice. For more information, visit lipid.org/masteronline.

FNLA Partners With Regeneron, Sanofi in Cholesterol Awareness Campaign

Regeneron Pharmaceuticals and Sanofi US in collaboration with the FNLA, Mended Hearts, and PCNA, launched Cholesterol Counts, an awareness program that will measure how much Americans know about cholesterol, their numbers, and the risks associated with high LDL-C. FNLA Vice-President Ralph M. Vicari, MD, and Lori Alexander, MSHS, RD, were named by the FNLA as representatives. Throughout the campaign, American adults are asked to take a brief poll at CholesterolCounts.com to answer key questions about their health. The initial data results of the poll are available on CholesterolCounts.com and provide a snapshot of cholesterol awareness levels across the country. Of the respondents, 44 percent report that they are not sure if LDL Cholesterol is referred to as “bad” cholesterol; this shows that there is still a big gap in knowledge across the United States; the FNLA and NLA need to continue to further raise awareness of cholesterol. On the CholesterolCounts homepage, visitors can compare the results on an interactive map. Ask your patients to take the poll on CholesterolCounts.com to get counted. The results will be updated with new data bi-monthly. At the end of 2015, a progress report portraying the awareness of cholesterol in the U.S will be created.

SEL A Chapter Endorses 19th Annual Conference on Hypertension, Diabetes, and Lipids

The Southeast Lipid Association (SELA) has endorsed the 19th Annual Conference on Hypertension, Diabetes, and Lipids. This three-day intensive conference will be held on June 26-28, 2015 at the Charleston Marriott in downtown Charleston, S.C. For more information on this conference, visit cmemeeting.org/charleston-summer-2015-cme.

FNLA Partners With Regeneron, Sanofi in Cholesterol Awareness Campaign

Regeneron Pharmaceuticals and Sanofi US in collaboration with the FNLA, Mended Hearts, and PCNA, launched Cholesterol Counts, an awareness program that will measure how much Americans know about cholesterol, their numbers, and the risks associated with high LDL-C. FNLA Vice-President Ralph M. Vicari, MD, and Lori Alexander, MSHS, RD, were named by the FNLA as representatives. Throughout the campaign, American adults are asked to take a brief poll at CholesterolCounts.com to answer key questions about their health. The initial data results of the poll are available on CholesterolCounts.com and provide a snapshot of cholesterol awareness levels across the country. Of the respondents, 44 percent report that they are not sure if LDL Cholesterol is referred to as “bad” cholesterol; this shows that there is still a big gap in knowledge across the United States; the FNLA and NLA need to continue to further raise awareness of cholesterol. On the CholesterolCounts homepage, visitors can compare the results on an interactive map. Ask your patients to take the poll on CholesterolCounts.com to get counted. The results will be updated with new data bi-monthly. At the end of 2015, a progress report portraying the awareness of cholesterol in the U.S will be created.

NEL A Chapter Endorses 2nd New York Clinical Lipid Forum

The Northeast Lipid Association (NELA) has endorsed the 2nd New York Clinical Lipid Forum Tuesday, Nov. 26. at Roosevelt Hospital in New York. According to the course brochure, the goals of the New York Clinical Lipid Forum are to provide clinicians, researchers, medical and healthcare trainees, and others who work in the field of lipidology, prevention, and cardiovascular disease with: updates on topics in the management of patients with dyslipidemia, and much more. More information will be coming soon.

ISFA 2015 – 10th International Society for Apheresis Congress

The International Society for Apheresis (ISFA) invites all NLA Members to attend the 10th International Society for Apheresis Congress May 13–16, 2015, in Cancun, Mexico. The Congress will focus on topics in apheresis in the following fields Cardiology & Lipids, Nephrology, Gastroenterology, and more. For more information or to register for the meeting, visit isfacongress.com.
2015 National Lipid Association
Scientific Sessions
Hosted by the Midwest Lipid Association
June 11–14, 2015
Palmer House Hotel
Chicago, IL
lipid.org/sessions

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

Lipid Academy
June 10–11, 2015
Chicago, IL
September 17–18, 2015
Pittsburgh, PA

Masters in Lipidology
June 10–11, 2015
Chicago, IL
September 17–18, 2015
Pittsburgh, PA

JOBS
Lipidologist Needed to Take Over Practice in Tallahassee, Fla.

There is an excellent opportunity for an internist, family physician, cardiologist, or endocrinologist to take over a referral practice of lipidology. The applicant must be a diplomate of the American Board of Clinical Lipidology. The Tallahassee Memorial Lipid Center has been in operation for more than five years and has approximately 100 referring physicians, for a total of more than 500 annual referrals. J. Orson Smith, MD, FACC, is the current director, working with Nancy Smith, RD, CDE, CLS. They were joined in December 2014 by Elizabeth Ford, ARNP-BC. The Lipid Center is in the same building as the Tallahassee Memorial Diabetes Center and the Tallahassee Memorial Bariatric Center. Current plans are to eventually move into a larger building, which will allow for the addition of three endocrinologists. Dr. Smith wishes to retire in 2015 but will remain on as a consultant to the new director for a period of time. The work environment is pleasant, academic, and rewarding. The salary, which is based on RVUs, is negotiable and the present conversion factor is quite good.

Telephone: (850) 431-5474
Fax: (850) 431-4711
Address: 1981 Capital Circle NE, Tallahassee, FL 32308
Website: TMH.org/LIPIDCenter
Email: orson.smith@tmh.org
References


Guest Editorial


Specialty Corner


Practical Pearls


Case Study


Contraceptive Hormone in Women with Familial Hypercholesterolemia (FH): More Questions than Answers

There are no published data on the use of OCPs in FH women.

In the general population estrogen increases hepatic synthesis of apo B-100 leading to increased VLDL secretion but also increases expression of the LDL receptor leading to reduced LDL. This latter effect appears to be mediated, at least in part, through downregulation of PCSK9. Estrogen inhibits hepatic lipase and increases Apo A-I synthesis leading to increased HDL. Estrogen decreases Lp(a) by unknown mechanism. Progestins generally have opposite effects, except for the effect on Lp(a), though the mechanisms are unknown. More androgenic progestins have greater LDL raising effect.

In OCPs in the general population, the estrogen and progestogen components balance but the interplay of an LDL receptor defect with the above physiology is unknown.

In addition, the estrogenic component is thrombogenic. This does not appear to be a problem in non smoking women in the general population but FH women are at higher risk of atherothrombotic disease. Is “low dose” estrogen low enough in an FH population?

Nonetheless, women with FH need to understand the importance of- and should receive repetitive reinforcement regarding- not getting pregnant while on statin.

CASE:

Young woman with FH, LDL consistently at approximately 150mg/dL on lipid lowering therapy. Fitted with Mirena IUD (levonorgestrel), LDL increased to 244mg/dL. Confirmed on repeat. Other secondary causes ruled out. IUD removed. LDL fell to 170mg/dL.

BEST ADVICE:

Have well documented baseline lipid values, prior to starting OCP. If levels show significant increase that cannot be managed with up titration of lipid lowering medications, consider switching OCP. Discuss with the patient her preferences.

Resources, Tools, and More Information on the
NLA Recommendations
on Patient-Centered Management of Dyslipidemia

- Slide deck comparing the 2013 ACC/AHA Guidelines and NLA’s Recommendations
- Free CME Activity on Guidelines in Clinical Lipidology: Concepts and Controversies

Find it here: lipid.org/recommendations

Access the latest information, videos, podcasts, and much more on the NLA Resource Center: nlaresourcecenter.lipidjournal.com