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THE Lipid Spin

Clinical Feature:

The LDL to HDL Ratio — Weighing the Evidence

—Maria Luz Fernandez, PhD

Also...
Case Studies from the files of Thomas Dayspring, MD

In this issue

NATIONAL LIPID ASSOCIATION

in this issue...

From the ***President***

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Improving Communication within the Membership

The NLA is working to make communications to its members less of a one-way street and provide opportunities for more dialogue. We also hope to facilitate more communication among members as well. This initiative, Lipid 2.0, is taking shape and many new services will become available. We will be announcing more details as the project nears completion through the end of this year. A test site will be available in the near term so we can collect member input.

Making the NLA Responsive to Member's Needs

Right now, on our home page at www.lipid.org, we have two Professional Development demographic surveys available. We urge all members to complete the questionnaires, as this information will help us tailor our educational programs and meetings to most closely fit member needs.

Communicating with the Public

This past September was Cholesterol Awareness Month, and the NLA press release was selected by news outlets across the country. We directed readers toward our patient information website, www.learnyourlipids.com. Remember that we have this site available to answer patient questions about cholesterol, and we hope to do much more in the year ahead with regard to patient education, public service announcements, and building the NLA into an organization with a voice at the national level.

Lipid Insights Virtual Journal Club

This program is taking off in a big way. The goal is for each chapter to host an online web presentation on a breaking topic in lipidology. Our most recent example was held by the PLA on the topic of Glucose Lowering and Diabetes Mellitus.

The online webcast was chaired by Eliot Brinton, MD, and the faculty were Paul Rosenblitt, MD, PhD, Jeffery Probstfield, MD, and Irl Hirsch, MD. This hour-long program was the equivalent of attending a session of a scientific forum, and drew nearly 40 participants. Our next Lipid Insights will be on the results of the JUPITER Trial, and be hosted by SWLA. Watch for an e-mail blast announcing this program, and information will also be available at www.lipid.org.

Dues and Don'ts

While we do what we can to keep dues low, they don't cover the expense of offering the *Journal of Clinical Lipidology*. Beginning in 2009, we will be raising dues by the cost of our Journal—$50—and thus dues will be $100. I believe that this cost is still very reasonable given all the services the NLA provides, and we want to continue to offer even more. We hope that you will understand and support this adjustment.

Rural Georgia Provider Education Program

The Georgia Division of Public Health has asked the NLA to help them with education for rural providers. We will be holding a series of a special version of our Lipid Management Training Course, at no cost, for all healthcare professionals in Georgia who want to improve their understanding of dyslipidemia management. This is an excellent example of how the NLA is partnering with other health organizations and represents how we are addressing our strategic initiative of forming strong liaisons with groups that share our mission. There are more details about this in the news section of this edition of the *Lipid Spin*.

We now have 4 new NLA Self Assessment Program books available.

New NLA Self Assessment Program (SAP)

We now have 4 new NLA SAP books and these are available online and in the *Journal of Clinical Lipidology*. These offer an assessment component, including clinical problem-solving questions and an answer sheet. After you return the answer sheet to the NLA, it is scored and a confidential personalized score report is returned to you. This will help you ascertain your strengths and weaknesses and offer up to 40 hours of CME/CE credit you can apply toward taking the ABCL or ACCL exam. Details are available at www.lipid.org/sap/.

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The LDL to HDL Cholesterol Ratio, a More Reliable Clinical Tool Than LDL Cholesterol to Evaluate Coronary Heart Disease Risk

Controversy exists regarding what is the best method for identifying those who are at increased risk for coronary heart disease. Some experts have proposed C-reactive protein (CRP), a marker for inflammation, as a screening tool for prediction of cardiovascular disease. Several epidemiological studies have shown positive associations between CRP levels and the incidence of cardiovascular disease,[1] although recent studies have questioned the validity of this connection. The current National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines recommend specific target levels of LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) for determining cardiovascular disease (CVD) risk and for evaluating the effectiveness of lipid-lowering therapies.[2] However, there is a growing consensus that plasma concentrations of apolipoprotein (apo) B and the ratio of apo B/apo A-I are more accurate predictors of CVD risk[3] and, in some cases, this ratio in childhood has been able to predict risk in adults. A recent study examining predictive factors of coronary heart disease mortality in a multi-ethnic population concluded that the apo B/Apo A-I ratio significantly predicted CVD risk independent of dyslipidemias, smoking, hypertension, obesity, diabetes or C-reactive protein.[4] Further, this study concluded that the concentration of apo B alone was sufficient to predict risk and better than any of the routine clinical profiles.

Because each of the apo B containing lipoproteins contains only one molecule of apoB per particle, plasma concentrations of apo B are a direct measurement of the number of potentially atherogenic particles, including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and the various LDL subclasses. Thus, higher concentrations of apo B in plasma may reflect higher concentrations of the small dense LDL particles associated with increased risk for CVD. Similarly, the concentration of apo A-I reflects the number of antiatherogenic HDL particles and not just the concentration of cholesterol carried by this lipoprotein. In other words, the number of atherogenic versus non-atherogenic lipoproteins transported in blood provides a more comprehensive evaluation of CVD risk.

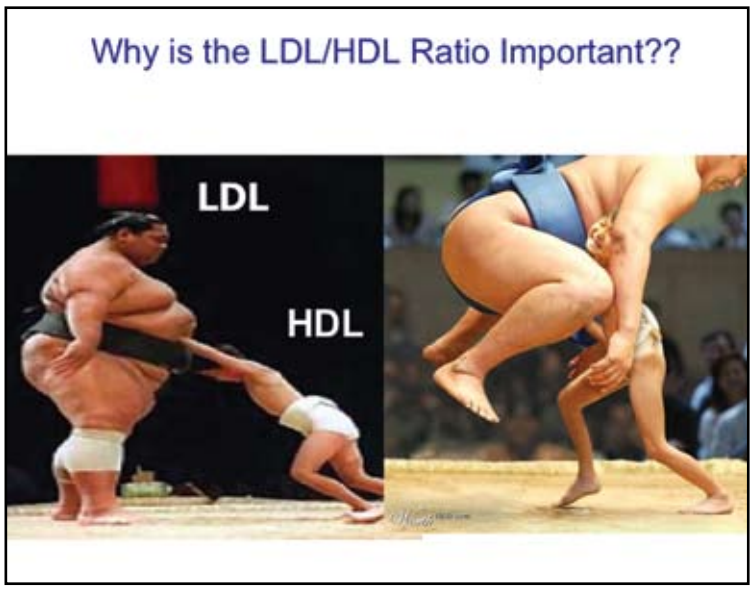
The question is whether it is realistic to expect patients and health professionals to switch from utilizing the standard lipid profile that includes total cholesterol, HDL-C and LDL-C to the utilization of apolipoproteins. From a practical standpoint, questions have been raised as to how readily a change in standards for assessing cardiovascular disease risk would be accepted by patients as well as physicians. The measurement of LDL-C and HDL-C is part of the standard blood lipid profile, while determination of circulating apolipoproteins is not. Additional testing must be ordered by the physician and the additional cost carried by the patient. Major insurance carriers consider testing for apo B to be experimental and not a routine measurement and, therefore, will not reimburse the expense. Insurance companies are unlikely to cover costs of apo B and apo A-I testing as long as these tests are not part of the NCEP guidelines. However, the guidelines are unlikely to focus on apolipoproteins until testing and reimbursement are readily available and affordable for patients.

Measurement of Plasma Apolipoprotein B Concentrations provides information about the total number of atherogenic particles

Aside from the added expense, the implementation of apolipoprotein testing presents some general public education problems. While the term "blood cholesterol" is recognized by the average individual, the terminology of apo B and apo A-I is not. Education of the general public in the function and importance of apolipoproteins is predicted to be a time consuming, difficult task. Replacing

the well-established measurement of plasma cholesterol by the lesser-known plasma apolipoproteins may result in further confusion. Moreover, substituting LDL-C by apo B would oppose the central principle of NCEP guidelines, which supports the use of new knowledge to build upon existing guidelines and not the replacement of these guidelines with new concepts.

This is the reason why a more tenable option, proven to be an accurate predictor of cardiovascular risk, is the LDL-C/HDL-C ratio. This measurement can be obtained from a standard lipid profile and is more reliable than LDL-C or HDL-C alone. Changes in ratios have been shown to be better indicators of successful CVD risk reduction than changes in absolute levels of lipids or lipoproteins. Moreover, while not perfect, measurements of apo B and apo A-I do estimate the levels of LDL-C and HDL-C, respectively.



Several large epidemiological and clinical studies have found the LDL-C/HDL-C ratio to be an excellent predictor of CHD risk and an excellent monitor for the effectiveness of lipid-lowering therapies. In the INTERHEART Study, a case control study involving 52 countries, lipoproteins and cholesterol were compared as indices for acute myocardial infarction.[5] Interestingly, the population attributable risk (PAR) was the highest (54%) for the apo B/apo A-I ratio, however the PAR was 37% for the LDL-C/HDL-C ratio, still a reliable risk index. In the Helsinki Study, a 5-year clinical trial of more than 4,000 middle-aged men with elevated lipids, the LDL-C/HDL-C ratio was found to be the best single predictor of cardiovascular events.[6] By using the LDL-C/HDL-C ratio in combination with fasting plasma triglyceride concentrations, a subgroup that was able to achieve over 70% reduction in CVD risk with gemfibrozil (a lipid-lowering agent) was identified. These findings suggest that relatively simple laboratory measurements can be used to identify groups of people who could potentially benefit from drug interventions.

The ratio of LDL-C/HDL-C was reported to be the most powerful measure of cardiovascular disease risk in elderly people in The PROSPER trial, a retrospective analysis of 6,000 patients using statin therapy.[7] Authors concluded from this study that statin therapy could be targeted to those individuals with an LDL-C/HDL-C ratio >3.3. A continuous and graded relationship between the LDL-C/HDL-C ratio and CVD mortality was reported in The PROCAM Study, which included almost 11,000 men 36 to 65 years of age who were studied for 4 to 14 years.[8] Coronary deaths spiked when the LDL-C/HDL-C ratio was in the range of 3.7 to 4.3. In the Physicians' Health Study, which involved almost 15,000 men 40 to 84 years, a 1-unit increase in the LDL-C/HDL-C ratio was associated with a 53% increase in risk of MI.[9] In addition, comparison of individual LDL-C/HDL-C ratios in subjects from the Framingham Study clearly indicates that the ratios are significantly more robust predictors of CVD than the individual levels of LDL-C or HDL-C.[10]

The effects of dietary cholesterol on blood lipids can be used as an example to illustrate why LDL-C/HDL-C is a better predictor of CVD than LDL-C alone. Numerous studies have shown that the LDL-C/HDL-C ratio is not affected by dietary cholesterol.[11] However, the ATP III guidelines limit the intake of dietary cholesterol and the LDL-C/HDL-C is not considered in these guidelines. On average, the LDL-C/HDL-C ratio is predicted to increase 0.01 units per 100 milligrams/day increase in dietary cholesterol, an amount unlikely to impact CVD risk. In fact, the inclusion of as many as 3 eggs per day (about 640 milligrams of cholesterol) raises both LDL-C and HDL-C in those individuals classified as hyper-responders while a non-significant increase in cholesterol carried by these lipoproteins was observed in hypo-responders resulting in all cases in no effect on the LDL-C/HDL-C ratio.11 Moreover, studies show that when LDL-C increases as a result of eating eggs, the LDL particles are generally large and less atherogenic.[12] A significant decrease in the small

LDL particles, associated with increased risk for CVD has also been observed.[13]

Though apo B levels and apo B/apo A1 ratios appear to be the most accurate predictors of CVD, the question remains whether the potential improvement in risk prediction over that provided by currently available lipid measurements justifies the additional costs. Another issue is whether the difference is enough to warrant major changes in the framework of existing cholesterol guidelines for assessing risk. Existing guidelines (ATP III) for detecting cardiovascular disease risk and treating patients focus on plasma LDL-C concentrations as the primary clinical target and these guidelines are followed by most physicians in patient care. While the current literature supports the use of apoB/apo A-I ratio as the most accurate predictor of CVD risk, it may not be the most practical. In contrast, numerous reports show LDL-C/HDL-C to be a more accurate predictor of risk than LDL-C alone and this is the best approach currently available.

The existing focus on LDL-C as the primary culprit in atherogenesis may divert attention from the more efficient evaluating tool, the LDL-C/HDL-C ratio.

An LDL-C/HDL-C ratio point for initiating lipid-lowering therapy should be determined. The current NCEP guidelines recommend levels of LDL and HDL that represent a ratio of about 2.5.2 Current research suggests risk of death from cardiovascular disease begins to increase significantly around a ratio of 3.3–3.7.7 These numbers should be considered routinely when evaluating CVD in a patient. The existing focus on LDL-C as the primary culprit in atherogenesis may divert attention from the more efficient evaluating tool, the LDL-C/HDL-C ratio. Further, this ratio reflects the two-way traffic of cholesterol entering and leaving the arterial intima in a way that the individual levels of LDL-C and HDL-C do not.

References

1. Lardus O. Knetsch AM. Blleumink GS. Deckers KW, Hofman A. Stricker BJ. Witteman JC. C-reactive protein and risk of heart failure, The Rotterdam Study. *Am Heart J*. 2006;152:514-520.

2. Adult Treatment Panel III. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection evaluation, and treatment of high blood cholesterol in adults. *J Am Med Assoc*. 2001;285:2486-2497

3. Marcovina S, Packard CJ. Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. *J Intern Med*. 2006;259:437-446.

4. Sierra-Johnason J, Risher RM, Romero-Corral A et al. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein A-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population. *E. Heart J*. (Epub ahead of press).

5. McQueen MJ, Hawken S, Wang X et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART Study): a case control study. *Lancet*. 2008:372:224-233.

6. Manninen V, Tenkanen L, Koskinen P, Huttunen JK et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. Jan 1992;85:37-45.

7. Packard CJ, Ford I, Robertson M et al. Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation*. 2005;112:3058-3065.

8. Cullen P, Schulte H, Assmann G. The Munster Heart Study (PROCAM) Total Mortality in Middle-Aged Men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. *Circulation*. 1997;96:2128-2136.

9. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol apolipoproteins and the risk of myocardial infarction. *N Engl J Med*. 1991;325:373-381.

10. Kannel WB. Risk stratification of dyslipidemia: Insights from the Framingham Study. *Curr Med Chem–Cardiovascular & Hematological Agents*. 2005;3:187-193.

11. Fernandez ML. Dietary cholesterol provided by eggs and plasma lipoproteins in healthy populations. *Curr Opin Clin Nutr Metab Care*. 2006; 9:8-12.

12. Herron KL, Lofgren IE, Sharman M, Volek JS, Fernandez ML. High intake of cholesterol results in less atherogenic low-density lipoprotein particles in men and women independent of response classification. *Metabolism*. 2004;53;823-830.

13. Greene CM, Waters D, Clark RM, Contois JH, Fernandez ML. Plasma LDL and HDL characteristics and carotenoid content are positively influenced by egg consumption in an elderly population. *Nutr Met*. 2006;3:6

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A pair of cases presenting more than meets the eye.

CASE 1:

I was contacted about the following case: A 41-year-old white male with a past history of gout and hypertension, currently taking allopurinol, lisinopril and aspirin. He admits to 1–2 beers per day and claims his mother is in her 70s and has high cholesterol without CAD and his father has hypertension. The original lipid profile was:

TC = 540 mg/dL
HDL-C = 57 mg/dL
TG = 3105 mg/dL (thus LDL-C cannot be calculated)
Glucose 114 mg/dL with HgbA1c = 6.2
The ALT = 87 IU (elevated)
Renal function is normal.

The patient was started on full dose fenofibrate, and took it without any problems for 2 months, but returned before his follow-up appointment was due with severe abdominal pain and was diagnosed with pancreatitis, confirmed by lab testing. Repeat fasting lab at this time revealed:

TC = 856 mg/dL
TG = 2406
HDL-C = 42
LDL-C not reported
Glucose 142 mg/dL
ALT = 15 u

After recovery, prescription strength N-3 fatty acid ethyl esters (four 1000 mg tabs daily) was prescribed to reduce his TG. The referring provider thought the patient might also need to be on a statin and/or niacin. He inquired why did the cholesterol go up and what is the primary lipid goal for this patient: triglycerides (TG) or cholesterol?

DISCUSSION:

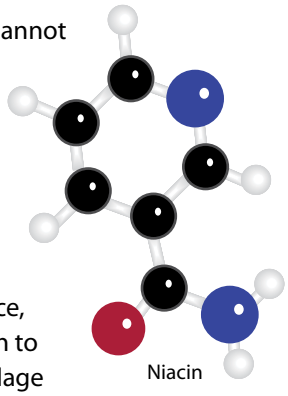
Patients like this have Familial Combined Hyperlipidemia (FCHL) with significant insulin resistance (in this case a T2DM) on top of possible excess alcohol use. One must rule out hypothyroidism and nephrotic syndrome as other secondary causes of the dyslipidemia. The TGs were certainly in the range capable of causing pancreatitis. Fatty acids (and 3 are present in each TG molecule) are soaps. If present in high doses they simply disrupt pancreatic cell membranes releasing amylase and lipase and their destructive abilities. Patients with very high risk hypertriglyceridemia (>500 mg/dL) often have both an over production of as well as delayed lipolysis (lipid hydrolysis) of TG-rich lipoproteins (chylomicrons and VLDLs). The elevated hepatic aminases likely signal liver dysfunction related to steatohepatitis, which is associated with serious cardiovascular (CV) risk.[1]

A case like this leads to a discussion of basic and advanced lipid and lipoprotein physiology and pathology. After the intestinal enterocytes absorb both sterols and fatty acids (FA), they are reassembled into TG in a multistep process catalyzed by multiple enzymes, one of the more important of which is diacylglycerol transferase (DGAT). The TG are then incorporated into apoB48 containing chylomicrons (a truncated apoB with 48% of the molecular weight of apoB100) which, after leaving the lymphatic system, traffic to vascular beds rich in lipoprotein lipase (LPL), specifically muscles and adipocytes. During synthesis, secretion or after release large chylomicron particles rapidly acquire numerous other apolipoproteins such as apoA-I, apoA-II, A-IV, A-V, apoC-I, C-II, C-III, and E, many of which interact in precise ways with each other and with LPL to regulate particle lipolysis.[2] LPL is a powerful triglyceridase which binds with apoC-II present on large TG-rich particles and hydrolyzes the triacylglycerol (proper term for triglycerides) into FA and monoacylglycerol (monoglycerides). As core TG are hydrolyzed, chylomicra become smaller in size and are called remnant particles (an apoB particle carrying less TG along with its original cholesterol load). Ultimately the smaller, now cholesterol-rich, TG-poor chylomicron remnant is cleared by the liver as particle apoE binds to LDL receptors and LDL receptor-related proteins. The released FA are taken up by cells or rapidly bind to albumin for further trafficking. As the large chylomicron particle reduces in size surface numerous apolipoproteins and phospholipids (PL) are also released. The latter picked up by phospholipid transfer protein and the PL become available to tissues or maturing (enlarging) HDL particles. The released apolipoproteins also attach to other lipoproteins, especially HDL particles. Similar to enterocytes, the liver

also assembles excess FA into TG and packages them into apoB100-containing VLDL particles (the more TG available, the larger both the VLDL particle size and number (large VLDL-P) becomes. The VLDLs acquire and carry many of the same surface apolipoproteins (except for apoA-I) and have the same lipolytic fate as do the chylomicra, as both deliver energy (TG) to muscles or adipocytes.

Under normal physiologic circumstances, TG-rich lipoproteins have normal quantities of several apolipoproteins on their surface, including apoA-V, apoE, apoC-II all of which enhance lipolysis and apoC-I, apoC-III and apoA-II which delay lipolysis. If one has the proper physiologic content of these apolipoproteins, lipolysis will occur at a proper physiologic rate. ApoA-V "parks" the TG-rich lipoprotein by binding to proteoglycans in the vicinity of endothelial cells that have LPL on their surface. VLDL receptors are also expressed in muscles and adipocytes and serve as a receptor for apoE to attach to. Once "parked," the apoC-II on the particle surface can attach to LPL and TG hydrolysis begins. Normal chylomicron half-life is 45–60 minutes and that of VLDL 4–6 hours. Why do chylomicra undergo more rapid lipolysis than VLDLs? They are incredibly large lipoproteins (much larger than VLDLs) and their surface carries more apolipoproteins and thus they are more likely to attach to the available LPL binding sites. Of course, once the chylomicrons become smaller remnant particles, they (with their sterols) are internalized by the liver LDL receptors (LDLr) and LDL receptor-related protein (LRP), which bind to apoE on both chylomicra or VLDLs or the apoB100 on VLDLs. Note that LDLr cannot bind to apoB48. Of course, under various pathologic conditions including insulin resistance and genetic disorders, there are factors at play that markedly delay lipolysis of TG-rich lipoproteins, leading to both fasting and postprandial (PP) TG abnormalities. Increasing the residence time of TG-rich lipoproteins increases blood viscosity, impairs endothelial function, impairs coagulation and activates apolipoprotein D, better known as cholesteryl ester transfer protein (CETP), which facilitates an exchange of neutral lipids (TG and cholesteryl esters or CE) between TG-rich particles and LDLs and HDLs; in such patients one often sees that as TG rise, LDL-C and HDL-C drop, but VLDL-C and non-HDL-C increase. If one is quantifying particles (our best measures of lipid and lipoprotein mediated risk) there will be increases in apoB due to increases in large VLDL-P and LDL-P.

ApoC-II deficiency, fortunately rare, results in massive hypertriglyceridemia as the particles cannot attach to LPL and no lipolysis of TG occurs (Fredrickson's Type I Hyperlipidemia). Excess apoC-I prevents VLDLs and remnants from attaching to VLDL receptors and can also inhibit CETP. Excess ApoC-III, common in insulin-resistant patients, displaces apoE from the particle surface, making the particle less likely to attach to the VLDL receptor. It may also camouflage or displace apoC-II and apoA-V. Abnormal apoE (as seen in Fredrickson's Type III hyperlipidemia) also interferes with VLDL as well as IDL binding to LDL receptors. Excess apoA-II may also camouflage or displace other apolipoproteins and delay lipolysis. The characteristic of delayed lipolysis is PP lipemia hypertriglyceridemia, a well known CV risk factor. Potential causes of hypertriglyceridemia and especially PP hypertriglyceridemia are abnormalities of apoC-II deficiency), apoA-V (deficiency), apoA-II (excess), apoE (defective) and apoC-III (excess). ApoA-IV is also involved with intestinal synthesis of chylomicrons and HDL particle catabolism, but its role in TG disorders is not fully understood. Of course a deficiency of lipoprotein lipase will result in defective TG-lipolysis and cause both fasting and PP hypertriglyceridemia.[3]

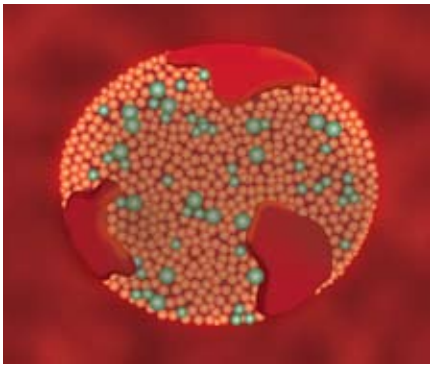

Niacin

What are the consequences of the elevated TG levels? TG-rich lipoproteins associated with delayed lipolysis obviously have increased half-life or residence time. This increases blood viscosity and worsens endothelial function. HDL and LDL are cholesterol-rich particles that typically carry little TG. HDLs contain multiple apolipoproteins, one of which is apolipoprotein D (over-expressed when TG are high). CETP facilitates a swap of TG for CE between TG-rich particles and LDL and HDL. The latter become CE-deficient and TG-enriched. As the CE-poor LDL and HDL undergo further lipolysis by hepatic lipase (a triglyceridase and phospholipase), they become smaller HDL and LDL particles. Very small HDL are apt to be excreted by the kidney (contributing to low HDL-P and HDL-C) and if LDLs are small it takes a lot more of them to traffic whatever cholesterol exists and a lot longer to be cleared, thus driving up LDL-P and apoB (a major coronary risk factor).[4] Multiple studies using NMR have demonstrated the strong association of insulin resistance and CV risk with excess large VLDL-P, small LDL-P (leading to high total LDL-P), reduced large HDL-P as well as total HDL-P.[5]

The severe hypertriglyceridemia in the case at hand is likely the result of bad genes combined with poor lifestyle

(too much glucose, maltose and saturated fat intake), leading to excess hepatic FA stores, and the alcohol use, which decreases the beta-oxidation (burning or catabolism) of fatty acids. If the liver cannot burn excess FA, triglyceride synthesis will be excessive and they will be lipidate with apoB and cholesterol in VLDLs. It is my experience that most men who state they imbibe 2 beers a day actually take more and they all have a nickname—"Joe Six-pack."

The likely explanation of the rising total cholesterol in this FCHL patient is increased lipogenesis: anything that puts FA in the liver, commonly seen in IR patients, will increase lipogenesis. Many of the nuclear transcription factors and genes that stimulate TG production also effect sterols (synthesis of lipoproteins and their lipid content). Also, the sudden loss of appetite and food intake and associated weight loss can stimulate cholesterol production. When one rapidly loses weight, adipocytes lose their lipids, including their substantial cholesterol (present in their cell walls). This will ultimately level out. Anorexics often have paradoxical hypercholesterolemia because of this phenomenon.[6]



Chylomicron lipoprotein

How about treatment for this man using NCEP recommendations? The first mission is to normalize the TG to < 500 mg/dL to remove the pancreatitis risk; excellent glycemic control is required to control TG in diabetics, therefore insulin, pioglitazone, metformin and other therapies would all be of use.

Once that is achieved, then, non-HDL-C (the poor man's apoB-surrogate) becomes the goal of therapy. There cannot be success if this man even touches another drop of alcohol. Lifestyle is also crucial: The DASH or South Beach type diets with daily exercise are very beneficial in these patients. Aggressive BP control is certainly warranted as is the aspirin.

I would continue the prescription strength N-3 FA at 4–6 grams daily; this drug inhibits FA synthesis, increases beta-oxidation of FA, may inhibit DGAT, increases LPL expression as well as affecting other nuclear transcription factors involved with lipogenesis and lipolysis. Fenofibrate has multiple actions that improve TG and atherogenic lipoproteins, including decreasing lipogenesis, increasing beta-oxidation of FA, inhibiting DGAT, increasing LPL, increasing apoA-V, and decreasing apoC-III. Interestingly, this man has pancreatitis that is presumed to be due to the massive hypertriglyceridemia, but pancreatitis is also a known side effect of fibrates. One would have to consider the benefit of TG control vs. the possibility that the fenofibrate is related to the pancreatitis. Because of unstable diabetes one would reserve niacin use, but if required, extended release niacin does not severely aggravate glycemic control in the majority of patients and at high doses (2000 mg) is an effective TG-lowering drug through actions on decreasing lipogenesis, increasing beta-oxidation of FA, and inhibiting DGAT.[7]

Ultimately, a high dose of a powerful statin will be needed to upregulate LDLr to help clear the apoB particle excess. Statins through an indirect effect on PPAR-alpha, also can increase LPL and reduce apoC-III. As noted above, persons with marked TG elevation have significant residence time of these particles, which because of their apoB or apoE, are subject to statin-upregulated LDLr. Statins or statin/ezetimibe or statins/bile acid sequestrants are the best combos to cause increased expression of LDLr. In trials looking at patients with high TG, atorvastatin 80 mg and rosuvastatin 40 mg are the most efficacious statins at reducing TG. Of course, all statins can reduce TG to variable degrees. I'd choose rosuvastatin because it has fewer drug-drug interactions, may have a more beneficial effect on HDL-C (if that is important) and because of atorvastatin's potential to aggravate hyperglycemia.[8] I realize the formulary is likely to mandate the choice of statin. If non-HDL-C or LDL-P (apoB) is not controlled with the above medications, ezetimibe may also be required as it will further upregulate LDLr, and further decrease TG. Ezetimibe is FDA approved to combine with fenofibrate.

CASE 2:

I was contacted by a pharmaceutical representative about his brother, who is a 30-year-old male who works out with weights frequently, eats normally and does not smoke or drink. He is 5' 10" tall with a weight of 170 lbs. His lipid profile is as follows:

LDL-C = 127 mg/dL
HDL-C = 36 mg/dL
TG = 108 mg/dL
VLDL-C = 21 mg/dL
hs-CRP is elevated

The brother's doctor believes that this is a rosuvastatin patient because he wants to get his LDL-C below 100 mg/dL. Several other clinicians, including cardiologists, were asked about this profile and most said they did not see any risk worth treating with anything more than lifestyle changes. The rep is also concerned about the need for raising HDL-C.

DISCUSSION:

The crucial factor that determines how to treat and how aggressively to treat is to accurately define the patient's risk. His only major risk factor is the low HDL-C (one of the criteria for metabolic syndrome) and his elevated CRP. Framingham Risk Scoring, which should be performed if 2 risk factors are present, rates the patient as low risk for an event over the next 10 years and the patient would not qualify for drug therapy and, therefore, should be instructed in lifestyle measures. If indeed the brother is low risk his NCEP ATP-III, LDL-C goal would be 130 mg/dL and non-HDL-C 160 mg/dL. However, if the clinician happens to determine with additional testing that the patient is high risk, then using medication to reduce LDL-C to < 100 mg/dL is indicated. NCEP ATP-III states that in patients with low HDL-C, the goal of therapy is not necessarily to increase HDL-C per se, but rather to first reduce LDL-C to goal and then normalize non-HDL-C, if the TG are still high (≥ 200 mg/dL). Always keep in mind that sterols enter the arteries as passengers inside of apoB-containing lipoproteins and particle number is what forces them into the vessel. Thus, we must determine whether this patient has too many atherogenic apoB particles in his plasma and his lipid concentrations are at best predictors of this lipoprotein-related risk. It is now accepted that it is the number of atherogenic particles that determines risk, not their cholesterol content.[9] Can we estimate particle numbers without advanced particle quantification testing? The lipid surrogates of apoB or LDL-P (the vast majority of apoB particles are LDLs) are TC, LDL-C and especially non-HDL-C.

Let's do a little math:

TC = LDL-C + HDL-C + VLDL-C
VLDL-C = TG/5
VLDL-C = 108/5 = 21 mg/dL
TC = 127 + 36 + 21 = 184 mg/dL
Non HDL-C = 184 - 36 = 148 mg/dL
TC/HDL-C = 184/46 = 5.11 (should be < 4.0)
TG/HDL-C = 108/36 = 3.0*

**If > 3.5 would be highly indicative of small LDL size and most drug naive patients with small LDLs have high LDL-P.*

For discussion purposes, if we consider this man to be high risk, his LDL-C goal would be < 100 mg/dL and if TG are high, his non-HDL-C should be < 130 mg/dL. Of course we now know from a study using Framingham data that non-HDL-C is a better predictor of risk than is LDL-C no matter what the TG level is.[10] Let's look very closely at the lipid profile: the LDL-C at 127, the non-HDL-C at 149 and the TC/HDL-C ratio > 5 (all of which are variable surrogates of apoB) would suggest there is risk and perhaps a mild apoB elevation. If elevated, the best apoB-lowering strategy is lifestyle and drugs, which may decrease apoB synthesis and upregulate LDL receptors (LDLr) to clear apoB particles. With respect to drugs, statins are the best monotherapy to upregulate LDLr. If such therapy does not get the patient to goal, then one would consider adding an adjunctive medication to normalize the non-HDL-C, and in someone with low HDL-C (suggesting insulin resistance) fibrates or niacin or off-label use of N-3 fatty acids would be the proper choice. However, ezetimibe or sequestrants like colesevelam can also help a statin achieve non-HDL-C or apoB goal.

It is now accepted that it is the number of atherogenic particles that determines risk, not their cholesterol content.

By focusing on raising the low HDL-C, the rep is also making the same mistake that many providers make: when they see low HDL-C they think mission number one is to raise it. However, there is no specific HDL-C goal of therapy in NCEP. The elevated CRP is consistent with subclinical systemic inflammation that often accompanies (as does low HDL-C) insulin resistance. The patient may well have dysfunctional, proatherogenic HDL particles.[11] Altering the amount of cholesterol inside his HDL particles does not ensure you are necessarily improving HDL functionality.

I am uncomfortable with the baseline and current lab values. Until proven otherwise, I assume that almost all drug naive men with HDL-C between 25 and 40 or women between 25 and 50 are indeed high risk because they likely have an elevated apoB, specifically LDL-P. I suspect this patient is what is termed "metabolically" (not phenotypically) obese. I have little use for low Framingham Risk scores in such patients. I advised the rep to do lipoprotein quantification. It was my opinion, based

on the above data, that this man would have elevated LDL-P and likely needs aggressive therapy. However, if I am wrong such treatment would be improper. I'd also like to know: what is his glucose, 2-hour postprandial glucose level and urine microalbumin? What about a PLAC test (lipoprotein associated phospholipase A2)? The additional testing was done and my suspicions were confirmed. The repeat lipids also showed a big jump in TC and LDL-C:

Total-C = 202 mg/dL
LDL-C = 160 mg/dL
HDL-C = 27 mg/dL
TG = 73 mg/dL
Non-HDL-C = 175 mg/dL

Most providers would probably start a statin or statin ezetimibe combination with an LDL-C > 160. Looking at the LDL-P would also be helpful before deciding on therapy.

Total LDL Particle Number (LDL-P) = 1982
(desirable for high risk patient < 1000)
Small LDL-P = 1363 (< 600 in normal patients)
LDL particle size is 20.6 (Pattern A: Large)
Large HDL-P = 6.9 µmol/L
(intermediate risk in a drug naive patient)
Large VLDL-P = 0.0 nmol/L (perfect)
Hemoglobin A1c = 5.1
Creatinine =1.0 mg/dL
Postprandial glucose = 94 mg/dL

Not much supporting insulin in the glucose values. But still I wonder... Noted lipidologist William Cromwell, MD has long spoken of the "three amigos" as flags of insulin resistance: large VLDLs, small LDLs and reduced large HDLs—this patient has two of the three. Looking at his LDL particles, the patient has very high risk numbers: He has more LDL particles than almost 90% of those in studies like Framingham and MESA. Hepatic LDLr are not great at removing small LDL of which this man has too many. If the liver is not clearing LDL particles, he by definition has impaired indirect reverse cholesterol transport (LDLs can't return cholesterol to the liver which is one of their main functions). If they are not cleared by the liver, guess where the LDLs bring the cholesterol—right into an artery. Therapeutically, we need to upregulate lots of LDL receptors in an attempt to reduce LDL-P. Rosuvastatin 20 mg or other statin plus ezetimibe 10 mg are reasonable first choices. However, in view of the low HDL-C, using statin and extended release niacin is also appropriate (not to raise the HDL-C per se, but niacin can help a statin further lower apoB and non-HDL-C). Because of the risk I'd also add low dose aspirin plus 1000 mg N-3 FA. The NMR should be repeated in 8 weeks. I suspect he might need even additional therapy to normalize the LDL-P. If so, a recent study attested to the powerful efficacy of statin/extended-release niacin/ezetimibe combination.[12] My final quote comes from a recent, powerful editorial from Alan Sniderman, MD: "Take away the apoB particles and you take away atherosclerosis."[13] The moral of the story was a final note from the rep: "Awful as it may be, I am learning a lot from this case and so many of my doctors that I work with were saying my brother was fine without any meds!"

References:

1. Targher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. *Atherosclerosis*. 2007;191 235-240.

2. Brewer HB Jr. Hypertriglyceridemia: Changes in the Plasma Lipoproteins Associated With an Increased Risk of Cardiovascular Disease. *Am J Cardiol*. 1999;83:3F-12F

3. Dunbar RL, Rader DJ. Demystifying triglycerides: a practical approach for clinicians. *Cleve Clin J Med*. 2005;72:661-680.

4. Caslake MJ, Packard CJ. Phenotypes, genotypes and response to statin therapy. *Curr Opin Lipidol*. 2004;15:387-392.

5. Kathiresan S, Otvos JD, Sullivan LM et al. Increased Small Low-Density Lipoprotein Particle Number a Prominent Feature of the Metabolic Syndrome in the Framingham Heart Study. *Circulation*. 2006;113:20-29.

6. Phinney SD, Tang AB, Waggoner CR et al. The Transient Hypercholesterolemia of Major Weight Loss. *Am J Clin Nutr*. 1991;53:1404-1410.

7. Capell WH, Eckel RH. Severe hypertriglyceridemia with a history of treatment failure. *Nat Clin Pract Endocrinol Metab*. 2005;1:53-58.

8. Takano T, Yamakawa T, Takahashi M et al. Influence of statins on glucose tolerance in patients with T2DM. *J Atheroscler Thromb*. 2006;13:95-100.

9. Brunzell JD, Davidson M, Furberg CD et al. Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* 2008;31:811-822.

10. Liu J, Sempos CT, Donahue RP et al. Non-High-Density Lipoprotein and Very-Low-Density Lipoprotein Cholesterol and Their Risk Predictive Values in Coronary Heart Disease. *Am J Cardiol*. 2006;98:1363-1368.

11. Kontush A, Chapman J. Functionally Defective High-Density Lipoprotein: A New Therapeutic Target at the Crossroads of Dyslipidemia, Inflammation, and Atherosclerosis. *Pharmacol Rev.* 2006;58:342-374.

12. Guyton JR, Brown BG, Fazio S et al. Lipid-Altering Efficacy and Safety of Ezetimibe/Simvastatin Coadministered With Extended-Release Niacin in Patients With Type IIa or Type IIb Hyperlipidemia. *J Am Coll Cardiol.* 2008;51:1564-72.

13. Sniderman A. We Must Prevent Disease, Not Predict Events. *JACC*. 2008;52:300-1.

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Treatment Options for Lowering LDL-Cholesterol in Patients Intolerant to Statins and Niacin

We all find situations in which conventional lipid-lowering therapy will not be tolerated by our patients. The challenge, then, is to find alternative solutions to bring their lipid levels to the desired goal. I tend to come across a relatively higher percentage of patients with intolerance to conventional lipid-lowering therapy, because I see patients mostly by referral. Therefore, I decided to write this column to relate the approaches I've found effective in some of these difficult cases.

The majority of the cases I routinely see include patients who present with "intolerable muscle aching" with CPK levels mildly elevated or within normal limits, and patients with slightly abnormal levels of liver transaminases but asymptomatic. These patients are usually easy to handle by optimizing lifestyle modifications and using simple or combined therapy at very low dosages, frequently below the starting dosage. Although lipid goals are not attained in some cases, the improvement in lipid levels is considerable and significantly minimizes CVD risk factors. Somewhat of a greater challenge are patients with chronic hepatitis who experience cyclic acute episodes with an increase in liver transaminases, and this frequently leads to discontinuation of lipid-lowering drugs and refusal by the patient to restart the prescribed medications. In these cases, it is crucial for the patient to observe the cyclic nature of the increase in liver transaminases and their lack of correlation to drug intake. Once this is achieved, the patients usually agree to be treated and they are quite compliant with the medications.

In some cases, however, the problem is much more complex and worthy of discussion. In the rare cases when statin intolerance is associated with rhabdomyolysis or markedly elevated CK levels, obviously the statin being used needs to be discontinued. Elevated CK levels need to be assessed carefully, taking into consideration the lifestyle of the patient, gender and race. CK levels reflect the muscle mass of the patient and his/her daily degree of physical activity. Black males in general are known to have higher levels of CK in normal conditions. Once a decision to stop a specific statin is made and CK levels are back to normal, both the patient and the physician can be uneasy about starting treatment with a different statin, although this is the most logical approach in the majority of cases. Rhabdomyolysis or elevated CK levels occur as an individual reaction to a specific statin and a different statin will not necessarily reproduce it. Although it is perfectly natural after an episode of rabdomyolysis to be extremely careful when prescribing another statin, this can be quite successfully accomplished. Several precautions are essential if this course of action is followed, and they involve advising the patient to stop the medication immediately if muscle pain or muscle weakness occurs and monitoring closely the increase in CPK. I perform weekly monitoring of CK levels during the first couple of months and monthly thereafter until an entire year has elapsed. Also, statins should be initiated at the starting statin dosage or below the starting dosage and taken on alternating days. I have successfully managed to treat several patients after an episode of rhabdomyolysis with a different statin and reached the necessary lipid goals without any major complications.

In some cases, however, the patient is statin intolerant and, after the third trial of statins with different characteristics (composition, solubility, circulating half-life, etc.), alternative therapies need to be considered. Depending on the type of lipid disorder—hypercholesterolemia, combined hyperlipidemia or dysbetalipoproteinemia—I use different combinations of medication. I have found some interesting combinations that are worth mentioning. One of them is ezetimibe and colesevelam. This is a combination that I use in patients with hypercholesterolemia who are intolerant not only to statins but also to niacin (these patients when on niacin have markedly elevated levels of liver transaminases and nausea or nausea/vomiting). Therapy with ezetimibe or colesevelam alone often leads to the expected decrease in LDL-cholesterol (LDL-C) but seldom brings LDL-C levels to goal. Association of colesevelam and ezetimibe considerably improves LDL-C levels and LDL-C goals are more consistently attained. Considering the difference in the mechanism of action of both drugs, the additive effect

Continued on page 25

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Navigating Stormy SEAS

The impact of a clinical trial may be quite unpredictable. An example is the recently reported SEAS (Simvastatin and Ezetemibe in Aortic Stenosis) trial.[1] The background to the study is that aortic valve stenosis (AS), a condition with a prevalence of 3–5% in those over 75 years is increased in subjects with hyperlipidemia, and has a histopathological appearance that resembles atherosclerosis. Several small studies suggested that statins are beneficial, but one prospective study did not demonstrate a benefit. The SEAS trial was accordingly designed to study the effects of long-term intensive cholesterol lowering using simvastatin plus ezetimibe (S+E) on clinical and echocardiographic outcomes in patients with AS. The study examined 1873 Caucasian men and women (61/39%), with mild-to-moderate AS (peak aortic-jet velocity of 2.5–4 m per second), average age of 67–68 years, 51% with hypertension, who were randomized to simvastatin 40 mg plus ezetimibe 10 mg daily or placebo for a median follow-up period of 52 months at 173 study sites in Europe. Diagnosed atherosclerotic vascular disease or diabetes were excluded to allow for a placebo treated control group. Mean LDL-C was 139/140 mg/dL, HDL-C was 58 mg/dL and triglyceride was 126 mg/dL. The mean LDL-C level decreased by 53.8% in the S+E group versus a reduction of 3.8% in the placebo group over the entire follow-up period. The primary outcomes of the study were major cardiovascular (CVD) events, which included aortic valve-related clinical events. Secondary outcomes were aortic valve events (valve replacement, congestive heart failure due to AS, or CVD death), echocardiographic progression of AS, and safety of study drugs. The primary outcome occurred in 333 (35.3%) patients of the S+E and 355 patients in the placebo group (hazard ratio 0.96, p<0.59). There was no difference in the secondary outcomes of aortic valve-related clinical events or progression of aortic stenosis, nor in overall mortality. Importantly, there were fewer patients with ischemic CVD events in the S+E (148 or 15.7%) compared to the placebo (187 or 20.1%) group (hazard ratio 0.78, p<0.02), mostly related to a reduction in need for CABG. There were more patients with elevated liver enzymes in the S+E group (16 versus 5). An unexpected finding was that there were significantly more incident cancers in the S+E group (105 or 11.1%) compared to the placebo group (70 or 7.5%), p<0.01. In addition, there was a borderline significant increase in cancer deaths in the S+E group (39 versus 23, p<0.05). The excess cancers were not clustered at any particular site.

The primary outcomes of the study were major cardiovascular (CVD) events, which included aortic valve-related clinical events.

With respect to the cardiac outcomes, the authors point out that the lack of effect on AS is in agreement with findings in the only other randomized but smaller clinical trial (SALTIRE) in patients with AS, which used atorvastatin. They also emphasize that these results cannot be generalized to higher risk patients with AS such as those with severe hyperlipidemia, evident atherosclerotic disease or diabetes, in which AS may progress more rapidly. Regarding the increased cancer incidence, the authors refer to the results of a meta-analysis of 14 statin trials of approximately 90,000 patients showing no evidence of increased cancer risk, but state that there is less experience with ezetimibe. In an accompanying article, Peto et al[2] point out that in two of the statin trials, the incidence of breast cancer (CARE – pravastatin) and of cancer in those >69 years of age (PROSPER – pravastatin) was increased in the statin-treated group, yet no differences were found in the larger meta-analysis. They emphasize that unexpected results warrant independent testing of a separate database larger than the one that generated the findings in the first place. To that end, they analyzed unblinded data (for cancer outcomes only) from 2 large ongoing trials currently in progress utilizing simvastatin plus ezetimibe. One was the Study of Heart and Renal Protection (SHARP) comparing 10 mg of ezetimibe plus 20 mg of simvastatin daily versus placebo in patients with chronic kidney disease (9264 randomized patients), mean age 61 years with a mean follow-up period of 2.7 years at the time of unblinding (24,937 person-years). The other was the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study which is comparing 10 mg of ezetimibe plus 40 mg of simvastatin daily versus 40 mg of simvastatin daily in patients with

Continued on page 25

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Therapeutic Lifestyle Changes—Lost Horizons ?

TLC's Pleiotropic Benefits

James Hilton's 1933 novel *Lost Horizons* portrays a group of plane crash survivors from Asia who find themselves in a forced dichotomy between the war-torn world from which they came and the peaceful idyllic high-mountain Tibetan world of "Shangri-La." Their experiences in Tibet reframe many of their life values forever. Such is the dilemma many of us face with invoking meaningful lifestyle changes for ourselves and our patients in the current era of lipid-altering drug therapy. Most clinicians are fully aware that therapeutic lifestyle changes (TLC) most often underachieve lipid and lipoprotein target goals, e.g., LDL-cholesterol (LDL-C) <70 mg/dL, for the majority of their patients. Much the same applies to adherence to TLC in achieving lasting body

weight reductions. One of the longest standing statin promotional advertisements reads "When diet and exercise fail—meet another candidate for lipid-lowering therapy…" It's almost a subliminal message that we fail before we start. Indeed, TLC often fails to achieve more aggressive laboratory goals—but most often does not fail to reduce risk. Except for those with major heritable lipid and metabolic problems—a disordered lifestyle is most probably responsible for the majority of lipid and metabolic disorders we see in the clinic. If we look at TLC outcomes with regard to cardiometabolic (CMR) disease risk reduction, particularly reduction in diabetes risk, there are a plethora of very beneficial physiological changes which occur with or without significant changes in lipids or body weight. The point is that small incremental changes in lifestyle habits are clinically quite beneficial and this *frame-of-reference* or *new horizon* has been lost merely because the patient's modest lifestyle changes are not perceived to be sufficient to reach laboratory-driven targets. I am in no way disregarding more aggressive and holistic lifestyle changes for those who are motivationally ready to change but there are options for those who are more ambivalent and otherwise not ready for a complete lifestyle makeover.

Question: Is it not our overall clinical (and public health) mission to reduce risk of cardiometabolic disease? And, if so, are there not metabolic mechanisms by which lifestyle changes interact to do just this—many of which are not uniquely married to blood lipid changes?

The advent of at least 7 classes of drug therapies to manage dyslipidemia has for many providers created a convenient but evidence-based defense for spending less time on more thorough teaching and exhibition of dietary and physical activity changes. To be sure, the level and magnitude of dietary and physical activity intervention to aggressively lower LDL-C for many requires gladiator-level commitment to achieve current LDL-C target thresholds.

Systematic, even modest behavioral vested lifestyle change reduces risk and, perhaps more importantly, improves quality of life well beyond their influence on cellular metabolic dynamics. For example, in perhaps the most important lifestyle trial conducted in the last decade, after 3 years those in the lifestyle arm of the Diabetes Prevention Program lost just 8.8 lbs (202 to 195 lbs or ~ 4.5% weight loss) yet new onset diabetes was reduced 58% compared with 31% in those taking metformin. Those over 60 years of age reduced diabetes risk by over 70%.[1] These outcomes were achieved with very modest dietary intervention and approximately 1000 kcal of exercise a week. A recent 20-year follow-up analysis of the Da Qing Chinese Diabetes Prevention Study using TLC to manage diabetes risk indicated that the TLC group had a 51% lower incidence of diabetes during the active intervention period and a 43% lower incidence

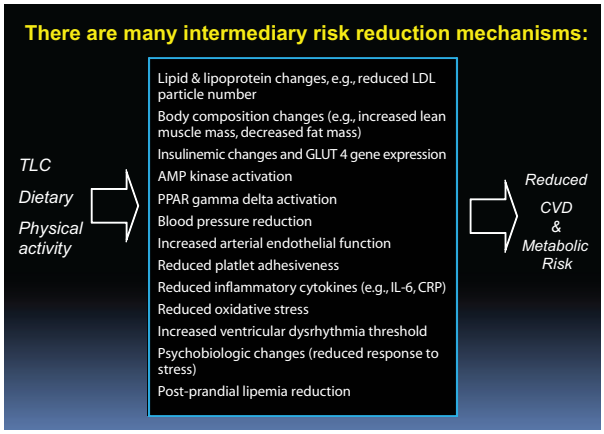


Figure 1
TLC Pleiotrophy

controlled for age.[2] These results were attained with very modest changes in blood lipids and body weight.

The "Pleiotropic" Effects of TLC: A Brief Look at the Evidence Base

Figure 1 depicts some of the core mechanisms by which sufficient dietary and physical activity behavior can improve cardiometabolic health, including—but not limited to—anthropometric and blood lipid changes. This concept of TLC pleiotropy is not new to NLA members and was most expertly posited in an elegant presentation in Orlando, Florida, by Thomas Barringer, MD, at the 2004 SELA Scientific Forum.

One of the most cogent examples of laboratory evidenced-based TLC pleiotropy is the response to Mediterranean diet therapy. The Mediterranean diet is one of the most studied dietary regimens to combat cardiovascular disease risk and it represents a "whole" dietary pattern in that it emphasizes good sources of carbohydrates (whole grains), fats (unsaturated plant oils and omega-3 fatty acids), and proteins (nuts, legumes, fish, and poultry); an abundance of fruits and vegetables; and minimal intake of refined grains, sugar-sweetened beverages, and red meat. Esposito[3] in several studies demonstrated significant increases in HOMA derived insulin sensitivity, improved arterial endothelial function and decreases in inflammatory markers—C-reactive protein (CRP), IL-6, IL-7, and IL-18 in 90 patients in response to 2 years of Mediterranean dietary intervention. Olive oil and red wine antioxidant polyphenols at nutritionally relevant concentrations transcriptionally inhibit endothelial adhesion molecule expression, thus partially explaining atheroprotection from these selected nutrients in Mediterranean and other dietary regimes.[4] More recent evidence has also demonstrated similar reductions in both CRP and fasting glucose, with soy protein based dietary intervention particularly effective in patients with type 2 diabetes (T2D).[5]

Dietary patterns that incorporate Mediterranean elements also show favorable effects on other cardiovascular risk factors—particularly blood pressure (BP). For example, among 459 US adults in the Dietary Approaches to Stop Hypertension (DASH) trial, significantly lower BP was observed after 3 weeks on a carbohydrate-rich diet that emphasized fruits, vegetables, and low-fat dairy products; included whole grains, poultry, fish, and nuts; and limited fats, red meat, sweets, and sugar-containing beverages.[6] When some of the carbohydrates in the DASH diet were replaced with either protein (about half from plant sources) or unsaturated fat (mostly monounsaturated fat) there was an even greater reduction in BP.[7] In 2006 we conducted a trial where 19 weeks of TLC, 1200 kcal/week of aerobic exercise and decreased energy intake, in 37 overweight insulin resistant patients showed greater efficacy in improving insulin sensitivity and fasting glucose compared to 30 mg of pioglitizone.[8] Such findings are not isolated discoveries as over 150 published TLC efficacy trials have been published since 2000.

Modest Increases in Physical Activity Are Beneficial

Exercise is not generally considered primary therapy for lipid disorders, especially in the current era of lipid-altering drug therapy. This is unfortunate, because exercise of appropriate quality and quantity can clearly reduce cardiometabolic risk through nonlipid mechanisms. Exercise can also induce significant favorable changes in the lipid and lipoprotein profile, in part as a result of moderate reductions in adiposity. If a patient is only able to add 9 or 10 miles a week (~1.2 miles/day) to their weekly activity they have essentially expended the same weekly energy expenditure as those who completed the Diabetes Prevention Program with impressive results. Kraus was among the first to show in a well controlled trial comparing various weekly volumes and intensities of exercise on lipids and lipoproteins that regular exercise with minimal weight change has broad beneficial effects on the lipoprotein profile—even without changes in total cholesterol and Friedewald predicted LDL-C.[9] Kraus demonstrated that moderate volumes and intensities (walking ~12 miles per week at 40–55% of aerobic capacity) can significantly reduce nuclear magnetic resonance spectrometry-measured LDL-particle concentration when total cholesterol and Friedewald-predicted LDL-C remained unchanged. Such patients on a

return clinic visit would be considered unresponsive to exercise therapy when a conventional lipid profile was used to score the patient's progress.

Most studies also show improved arterial endothelial function with exercise training. Endothelial dysfunction contributes to the initiation and

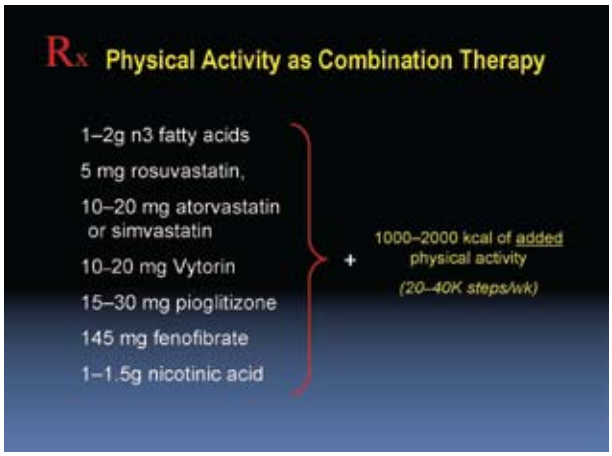


Figure 2
Exercise as Combination Therapy

progression of atherosclerotic disease and improved endothelial function is thought to be one of the primary mechanisms responsible for reduced CVD morbidity and mortality.[10] Numerous trials have demonstrated improvements in arterial endothelial function with sufficient exercise training.[11,12,13] Dietary elements such as omega-3 fatty acids, walnuts, and olive oil have also been shown to significantly improve endothelial function and reduce postprandial lipemia.[14,15] Postprandial lipemia also affects arterial function. When postprandial triglyceride-rich lipoproteins are significantly elevated, especially after a fat-rich meal, arterial walls are exposed to a variety of atherogenic lipoproteins (e.g. IDL) and there is a transient reduction in endothelial function. Single 30–45 minute exercise sessions, for example a 45-minute moderate pace walk, can significantly reduce postprandial triglyceride levels.[16]

Similar Mechanisms as Biquanides and TZDs

Both moderate and intensive exercise bouts utilize similar metabolic mechanisms as several diabetes drug classes, the Biquanides (Metformin) and Thiazolidinediones (pioglitizone, rosiglitizone) but without many of the side-effects, e.g., fluid retention of the glitizones. The value of brief acute bouts of physical activity, e.g. 2–5 minute intentional bouts of physical activity at moderate intensities activate AMP kinase, glucose transport mechanisms, and insulin signaling. Each intentional walking step is an AMP kinase activator (AMP-activated protein kinase is an enzyme that works as a fuel gauge that becomes activated during physical activity), which works similarly to glucophage and the PPARγ activating diabetes drugs.[17] Both aerobic and resistance exercise training improve insulin sensitivity and glucose transport mechanisms that help to improve cardiometabolic health and are involved in deterring diabetes in prediabetic subjects. In a recent study of 78 Australian children, 2 sets of 11 resistance exercises twice a week for only 8 weeks improved HOMA measured insulin sensitivity and decreased both waist circumference and total fat mass.[18] There is also emerging evidence that exercise training can reverse skeletal muscle mitochondrial abnormalities from lipid overload induced by high fat load diets and inactivity.[19]

Is It the Weight Loss Or Physical Activity Itself?

In one of the most elegant clinical exercise science reviews recently published, Richard Telford, physiologist at the University of Melbourne, revealed that the scientific literature indicates consistent findings of strong associations of physical activity (PA) with mortality and with morbidity associated with T2D, *after* controlling for obesity and other potentially confounding factors.[20] Collectively, these findings indicate that low PA is not just a predictor, but a direct cause of metabolic dysfunction and the morbidity and mortality associated with T2D. Considering the many cellular mechanisms that can help explain this, the finding is not difficult to justify. By contrast, Telford argues, there is little evidence that overfatness and obesity (adjusting for any effect of reduced PA) actually

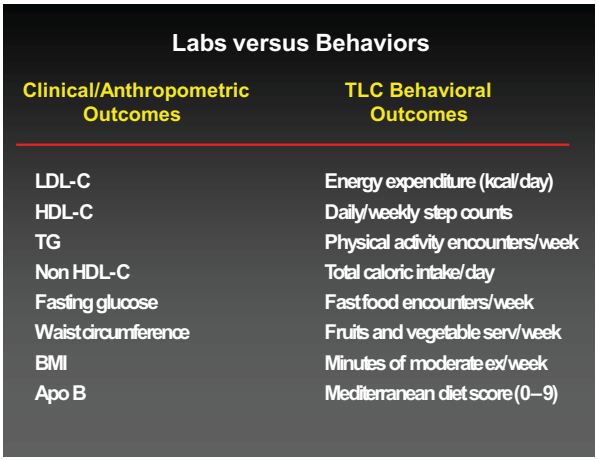


Figure 3
Labs vs. Behaviors

cause T2D. Observational studies suggest that obesity, including viscerally sited obesity, is most appropriately categorized as a marker or predictive (noncausal) risk factor for T2D, although, in contrast to PA, several studies were not able to detect any significant correlation after controlling for PA. The findings are consistent with the premise that PA is of direct benefit, perhaps even essential to preventive and curative medicine in relation to insulin resistance and T2D. In support of Telford's argument, Church's investigation of 2316 men with diabetes over 16 years found that low-fit individuals were at 2.7 times the risk of dying of CV disease compared with normal-weight men of high fitness, irrespective of whether they were of normal weight, overweight, or obese.[21] Lastly, Lopez-Soriano and colleagues in Spain and France who have focused their work on exercise induced PPAR activation, cogently argue that physical activity is afforded little attention in recent studies and reviews evaluating the link between insulin resistance, inflammation and obesity.[22] They insist that physical activity is a potentially confounding factor which has been overlooked by many attempting to understand the role of obesity.

Regaining Our Horizons

So, for those of us who have lost our TLC horizon, our frame of reference with respect to genuinely valuing lifestyle changes—even small changes—what incremental TLC changes should we value for ourselves and our patients? What pragmatic forms of TLC can reduce cardiometabolic risk with or without dramatic changes in LDL-C or reduced body weight? The following are several examples:

1. Give your patients credit for each and every step they take (e.g. as recorded with well-engineered reliable pedometers) irrespective of laboratory measures or body weight changes. Prescribe walking programs through the systematic use of clinical pedometry. Have patients record weekly step-count (some pedometer models have 7-30 day memories, e.g. Accusplit 120XLM). At patient's return visit chart and give credit for each and every recordable walking step much as you would for charting their glucophage or statin. There is good reason to believe that each intentional walking step is an AMPK and PPAR activator working very similar to many of the antidiabetic agents.

   For example: add at least 1000 kcal of exercise per week to existing weekly activity pattern.

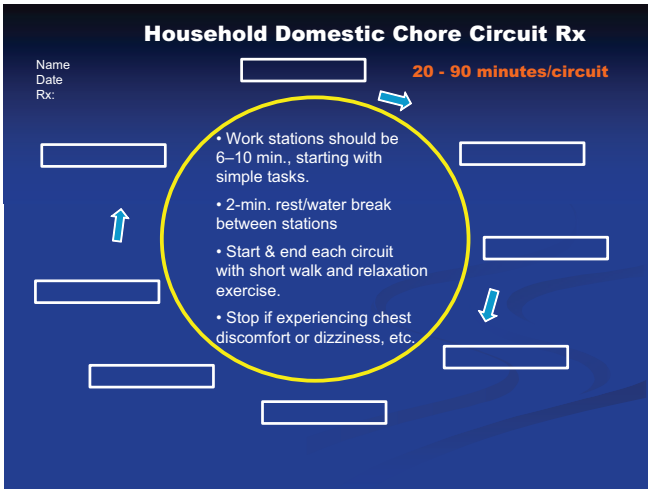


Figure 4
Household Circuit Activity Rx Form

   This would be the equivalent of adding approximately 10 miles of walking a week or ~20,000 stepcounts on a reliable pedometer. Ideally, graduating to at least 1500 kcal week over time would be near optimal (~15 miles/wk) depending on goals.*

2. When asking patients to change their diets, assess their intake of major food groups with one of the many simple food frequency assessment tools (e.g. NCEP's MEDFITS) first and make changes in one food-group at a time (e.g., each return visit), or even one food within a food group – rather than wholesale dietary changes. The Mediterranean and DASH dietary elements are perhaps the most useful here. Individual and incremental changes in nut, soy, legume, fruit, and fish consumption can be translated to some level of risk reduction.

3. Write exercise prescriptions as combination therapy. Clinicians need to quantify and prescribe physical activity (in terms of kcal/day or /week or stepcount/week) as prescribed combination therapy with drug therapy when applicable (see figure 2). For example, 1500 kcal of weekly exercise when added to omega-3 fatty acid therapy would further reduce triglycerides and VLDL knowing that 1500 kcal of energy expenditure at moderate exercise intensities will oxidize intramuscular and adipose tissue stores of triglycerides and fatty acids.

4. Begin to objectively score and chart TLC behaviors in the same way you would objectively chart laboratory measures on each patient visit. Each TLC measure in Fig. 3 can be serially scored on a numerical or Likert scale (e.g., 0–10) and translated into some meaningful level of CMR risk reduction with or without changes in lipids or body weight.

5. Systematize household domestic chores into a circuit of short utilitarian activities such that the patient expends 200–350 kcal during one household circuit session. This would provide a sense of accomplishing both household/yard tasks as well as generating increased daily energy expenditure. Figure 4 depicts a patient household circuit prescription form for which the patient rotates between 6–10 minute work stations.*

*Interested readers may email the author for example protocols for: (1) systematic clinical pedometry instructions for those at high CMR risk, (2) household circuit activity protocol instructions, or (3) a 15-month metabolic syndrome/CMR TLC flow-sheet. Email: rlaforge@nc.rr.com.

References

1. Knowler WC et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.

2. Guangwi L, Zhang P, Wang J et.al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*. 2008;371:1783-1789.

3. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004;292:1440-1446.

4. Annunziata-Carluccio M, Siculella L, Ancora MA et al. Olive Oil and Red Wine Antioxidant Polyphenols Inhibit Endothelial Activation: Antiatherogenic Properties of Mediterranean Diet Phytochemicals. *Arterioscler Thromb Vasc Biol.* 2003;23:622-629.

5. Azadbakht L et.al. Soy Protein Intake, Cardiorenal Indices, and C-Reactive Protein in Type 2 Diabetes With Nephropathy. *Diabetes Care.* 2008; 31:648-654.

6. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med.* 1997;336:1117-1124.

7. Appel LJ, Sacks FM, Carey VJ, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294:2455-2464.

8. Shadid S, La Forge R, Otvos JD, Jensen M. Treatment of obesity with diet/exercise versus pioglitazone has distinct effects on lipoprotein particle size. *Atherosclerosis.* 2006;188:370-376.

9. Kraus WE, Houmard JA, Duscha B et al. The effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med.* 2002;347:1483-1492.

10. Esper RJ, Nordaby R, Vilarino JO et al. Endothelial dysfunction: a comprehensive appraisal *Cardiovasc Diabetol.* 2006;5:1-18.

11. Clarkson P, Montgomery HE, Mullen MJ et al. Exercise training enhances endothelial function in young men. *J Am Coll Cardiol.* 1999;33:1379-1385.

12. Hambrecht R, Wold A, Gielen S et al. Effects of Exercise on Coronary Endothelial Function in Patients with Coronary Artery Disease. *N Engl J Med.* 2000;342:454

13. Sonne MP, Scheede-Bergdahl C, Olsen DB et al. Effects of physical training on endothelial function and limb blood flow in type 2 diabetes. *Appl Physiol Nutr Metab.* 2007;32:936-941.

14. Goodfellow J, Bellamy M, Ramsey M et al. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. *JACC.* 2000;35:265-270.

15. Cortes B, Nunez I, Cofan M et al. Acute effects of high fat meals enriched with walnuts or olive oil on postprandial endothelial function. *JACC.* 2006;48:1666-1671.

16. Malkova D, Gill JM. Effects of exercise on postprandial lipoprotein metabolism. *Future Lipidology.* 2006; 1:743-755.

17. Schimmack G, DeFronzo RA, Musi N. AMP-activated protein kinase: role in metabolism and therapeutic implications. *Diabetes Obes Metab.* 2006;8:591-602.

18. Benson AC, Torode ME, Singh MA. The effect of high-intensity progressive resistance training on adiposity in children: a randomized controlled trial. *Int J Obes.* 2008;32:1016-1027.

19. Muoio DM, Koves TR. Skeletal muscle adaptation to fatty acid depends on coordinated actions of the PPARs and PGC1α: implications for metabolic disease. *Appl Physiol Nutr Metab.* 2007;32:874-883.

20. Telford RD. Low Physical Activity and Obesity: Causes of Chronic Disease or Simply Predictors? *Med & Science in Sports & Ex* 2007;39:1233-1240.

21. Church T, LaMonte M, Barlow C, Blair SN. Cardiorespiratory Fitness and Body Mass Index as Predictors of Cardiovascular Disease Mortality Among Men With Diabetes *Arch. Intern. Med*. 2005;165:2114-2120.

22. Lopez-Soriano J, Chiellini C, Margherita M et al. Roles of skeletal muscle and PPARs in the development and treatment of obesity. *Endocr Rev.* 2006; 27:318–329.

JUPITER Results Reinforce Benefits of Therapy

There has been much speculation and interest in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study.[1] The results of this landmark primary prevention trial were presented at the American Heart Association (AHA) 2008 Scientific Sessions in New Orleans, Louisiana, on November 10, 2008, by Paul Ridker, MD.

Speaking to a crowded, standing-room-only hall filled with over a thousand attendees, Ridker explained the methodology and intent of the trial and offered a detailed look at the results. The study, published simultaneously on-line in the *New England Journal of Medicine*, showed that treating healthy men 50 years or older and women 60 years or older who have elevated levels of high-sensitivity C-reactive protein (hsCRP) with rosuvastatin (Crestor), 20 mg daily, almost halved the study's primary end point consisting of nonfatal MI, nonfatal stroke, treatment for unstable angina, revascularization, or death from cardiovascular disease.

The 17,802 participants chosen for the study were divided into a treatment and a placebo group. Patients in the above age range were eligible for inclusion if they had no history of cardiovascular disease, baseline LDL cholesterol (LDL-C) below 130 mg/dL, triglycerides below 500 mg/dL, and were not prior or current users of lipid-lowering therapy. Participants were selected if they met these and other criteria, and had hsCRP levels ≥ 2.0 mg/L in the absence of overt causes of inflammation such as severe arthritis or lupus.

The study hypothesis was that individuals with elevated hsCRP would be at risk of atherothrombosis, and that treatment with rosuvastatin would be of benefit. After a 4-week placebo run-in to gauge compliance, the subjects were randomized to receive rosuvastatin, 20 mg daily, or placebo for a scheduled followup period of 5 years or until 520 confirmed primary endpoint events occurred. Enrollment began in February 2003 and was completed by December 2006. JUPITER's prespecified monitoring plan called for two interim efficacy analyses, and at the first one held on March 29, 2008, the independent safety and monitoring board recommended that the study be terminated. The recommendation was based on the observed treatment benefit of rosuvastatin on the primary endpoint, and secondary endpoints including total mortality.

The median period of follow-up was 1.9 years when the study was stopped. There had been 142 primary endpoint events in the treatment group compared to 251 in the placebo group. The number needed to treat (NNT) to prevent one primary endpoint event over 2 years was 95, and projection models suggest that the NNT at 4 years and 5 years would be 31 and

Editorial by Thomas Bersot, MD, PhD

The results of the JUPITER study are drawing considerable interest and speculation among medical professionals. In considering what the outcomes may mean for patient management, there are a number of issues that should be considered. A few of these are described below.

First of all, further analyses of the JUPITER data are required to learn if measuring hsCRP improves upon existing cardiovascular disease event risk prediction and treatment guidelines. Updated ATP III guidelines suggest that hsCRP levels be assessed in primary prevention patients if the 10 year Framingham risk is ≥ 10 percent, but below 20 percent.[1] Values of hsCRP ≥ 3.0 mg/L reclassify these patients as secondary prevention patients with a goal for LDL-C < 100 mg/dL. In JUPITER there was a treatment benefit of rosuvastatin compared to placebo among the 36 percent of subjects in whom age was the only ATP III "major risk factor." In this 36 percent of trial subjects, 10-year-risk must have been below 10 percent since age was the only major risk factor. According to the updated ATP III guidelines, measurement of hsCRP would not be recommended for patients with only one major risk factor.[1,2]

It is also important to keep in mind that the entry criterion for hsCRP in JUPITER was a value ≥ 2.0 mg/L, not 3.0 mg/L, which is the suggested value for reclassifying patients as secondary prevention patients in the updated ATP III guidelines.[1,2] It is possible the 36 percent of patients with age as their only "major risk factor" could have been enriched with those affected by metabolic syndrome (42 percent of participants in JUPITER met criteria for metabolic syndrome). The 5 criteria defining metabolic syndrome include only one ATP III "major risk factor," HDL-C < 40 mg/dL in men. Blood pressure is not a "major risk factor" unless the value exceeds 140/90 mm Hg, but in defining the metabolic syndrome criteria for hypertension are systolic

Continued on page 20

25, respectively. Total mortality was reduced by 20%. Reductions in risk of having a primary endpoint event were observed in every subgroup reported on including those based on gender, race, BMI, geographic region and other factors. Benefits were seen even in patients who would normally be classified as "very low risk."

Treatment effects at 12 months of rosuvastatin, 20 mg/day, vs. placebo on lipids included a 50 percent lower median LDL-C (mean difference of 47 mg/dL), a 17-percent reduction of median triglyceride levels and at the end of the study no effect on the median HDL-C level. The hsCRP level at 12 months was 37 percent lower in the rosuvastatin group compared to the placebo group (2.2 mg/L vs. 3.5 mg/L, respectively).

"We can no longer assume that patients with low cholesterol are at low risk," says Ridker. "This does not mean that cholesterol isn't important. We want our high-cholesterol patients to be treated very aggressively. But in this study, we found that patients with low cholesterol but high CRP benefited greatly from statin therapy." The study authors suggest that the data obtained will trigger further studies on the effects of anti-inflammatory drugs as potential therapeutic agents and that the mechanism of action of statin drugs will continue to be explored. Because the rates of hospitalization and revascularization were reduced by 47% in a 2-year period, the strategy employed by the study could be cost-effective.

"We have so many patients who continue to be nervous about taking these therapies, and we want to give out a message to continue with exercise, diet, and smoking cessation, but now we have very overwhelming evidence that this class of drug, this method of lowering surrogate end points, reduces hard clinical end points," says Ridker.

Further analysis of the implications of this research with subpopulations, including different age groups, those with metabolic syndrome, primary prevention patients with low Framingham risk scores and others may reveal the need to look again at current guidelines. This trial suggests that certain patients are being overlooked and hsCRP levels may be useful in identifying those at risk of developing CVD even in the absence of abnormal lipid levels. The results obtained in JUPITER reinforce the lipid hypothesis and show that statin medication appears to have a dual effect on both lowering LDL-C and inflammation.

References:

1. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Eng J Med.* 2008;359:2195-2207. www.nejm.org, November 20, 2008.

BP ≥ 130 or diastolic BP ≥ 85 mm Hg. Perhaps when the JUPITER data is further analyzed the presence of metabolic syndrome, even if age is the only ATP III major risk factor of a patient, may be sufficient to reclassify a patient as a high risk coronary heart disease equivalent patient.

In conclusion there are several points of this important trial that require further thought with regard to the implications of JUPITER for patient management.

a. Who should be tested? Does a value of hs CRP ≥ 2.0 mg/L in persons substantially below the age entry criteria (50 years for men; 60 years for women) carry with it the same future risk of a CVD event as was observed in the JUPITER cohort? Should these younger primary prevention patients be treated with a lipid lowering drug based only on a value of hsCRP?

b, Should the value for reclassifying patients from a lower level of risk to CHD equivalent status be changed to 2.0 mg/L from the current value of 3.0 mg/L?

c. Keep in mind that guidelines for accurate assessment of hsCRP require two separate determinations of hsCRP separated by 2 weeks and averaging the values. In JUPITER the two measurements were obtained 4 or more weeks apart.[3,4]

d. The LDL-C levels of subjects in JUPITER were reduced by about 50 percent to on-treatment values of ~ 55 mg/dL. Should these treatment goals apply only to those primary prevention patients who meet the entry criteria of this trial? Existing ATP III guidelines suggest that if lipid lowering therapy is prescribed a dose that lowers LDL-C a minimum of 30–40 percent should be utilized.[1]

References:

1. Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation.* 2004;110: 227-239.

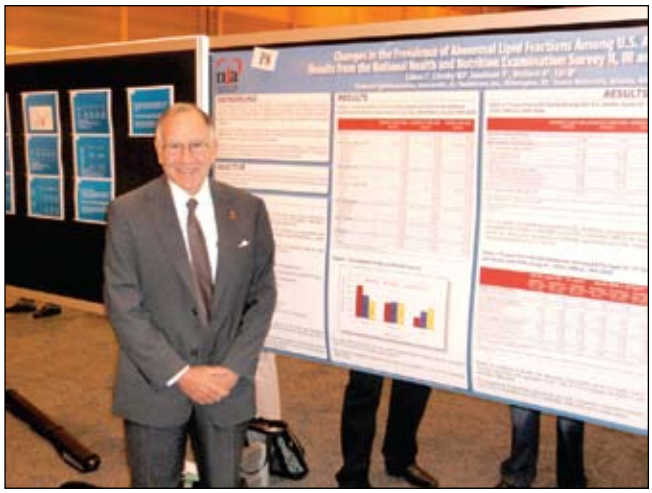
2. Smith SC et al. CDC/AHA workshop on markers of inflammation and cardiovascular disease. Application to clinical and public health practice. Report from the Clinical Practice Discussion Group *Circulation.* 2004;110: e550-e553.

3. Myers GL et al. CDC/AHA workshop on markers of inflammation and cardiovascular disease. Application to clinical and public health practice. Report from the Laboratory Science Discussion Group. *Circulation.* 2004;110: e545-e549.

4. Ridker PM et al. Baseline charactetristics of participants in the JUPITER Trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol;* 2007;100: 1659-1564.

NLA Completing NHANES Research Project

The NLA received a research grant to examine the changes in the typical American lipid profile over the past 3 decades. We teamed with HealthCore Inc. to examine the past 30 years of National Health and Nutrition Examination Survey (NHANES) database content, looking at lipid levels, trends in BMI, and dyslipidemia across various populations and arrived at some surprising conclusions. As you might expect, Americans are making progress in some areas, but in others there are grounds for concern. A press release issued at the American Heart Association annual meeting this month in New Orleans



presents a first look at some of our findings. Titled New Analysis Shows Troubling Trend in Triglyceride Levels May Be Linked to Rising Rates of Obesity, it is given in this issue of the Lipid Spin. We are now completing a full manuscript that details the results of this research effort. In addition, we presented a first-look at our research in the form of a poster which we exhibited at AHA. The lead author, Jerome D. Cohen, MD, was on hand to answer questions from meeting attendees. View the poster online at www.lipid.org/press.

Take the Survey Today

The NLA needs your help. We have two surveys posted at our homepage that are designed to give us demographic data on our membership. Your input is anonymous and each survey only requires a minute or two to complete. With this critical information, the NLA can better tailor our conference agendas and our educational programs to best meet your needs. In addition, when the collection period is complete, we will publish the results so you can see where you stand with respect to the rest of our membership. Future surveys will gather other data, such as practice composition and salary. Your participation is greatly appreciated. Take one or both surveys today at **www.lipid.org/survey**.

Lipid.org 2.0 Is Almost Here

After nearly a year in development, we are preparing to roll out a demonstration of Lipid.org 2.0. You will be amazed and delighted at our new look and tools designed to make being a member of the NLA even more empowering. Content from our current site will still be available, but in the months to come, you'll find new elements added on a regular basis. In offering you, our membership, a virtual workspace to meet and share ideas with one another, we are accomplishing several of our strategic objectives and "going green" by reducing paper and mailing resources. Visit www.lipid.org regularly to stay apprised of our progress. Lipid.org 2.0 is all about you.

Cholesterol Awareness Month a Success

Our press release on Cholesterol Awareness Month was quickly picked up by publications across the country. Over 100 publications and major media outlets distributed our advice regarding the importance of knowing one's total lipid profile and the necessity of achieving lipid goals as lifelong activity. Recent events have underscored the relationship between nutrition, exercise, and a healthy heart. We were happy to represent you in the public arena with positive messages during Cholesterol Awareness Month. Our press release is available for viewing and download at the press page at lipid.org and also at our patient website, **www.learnyourlipids.com**.

SELA Teaming with Georgia Division of Public Health

We are extremely pleased to report that the Georgia Division of Public Health has asked the NLA, and our Southeast chapter, specifically, to present a tailored version of our Lipid Management Training Course to Georgia's rural healthcare providers. This is part of the country known as the "stroke belt" because rates of stroke and heart attack are especially high due to environmental and lifestyle factors. This special educational program is called "The Georgia Lipid Academy," it features SELA members as faculty, and will be given a total of 6 times over a 2-year period. We hope that Georgia's physicians and allied health professionals take advantage of this complimentary program designed to help them combat morbidity and mortality stemming from dyslipidemias. Health care professionals who reside and practice in Georgia can register online and learn more about the program at **www.lipid.org/georgialipids**.

From the NLA Office

Lipid Luminations Podcasts Are Available
NLA members can listen to podcasts of our XM Radio program on ReachMD, Lipid Luminations. It's easy—just click on the story on our homepage under "News," titled "ReachMD and Lipid Luminations," or go directly to www.reachmd.com/xmradioseries.aspx?sid=7. Register and use promo code "NLAReachMD" to download the podcasts for listening at your convenience or stream them directly from the site. These are popular broadcasts featuring top NLA thought leaders speaking on breaking and critical issues in clinical lipidology. We hope to have these available at our site (lipid.org) directly in the near future. Keep an eye open for them.

Cholesterol Ratio Questionnaire—Your Input Is Needed
Right now at www.lipid.org, we have posted a new survey to gain your input on the question of using HDL-C/LDL-C ratios for assessment of risk. This subject was the focus of our clinical article in this issue of the *Lipid Spin* and we'd like to get your feedback. The survey is brief and can be completed quickly—there are only 7 questions in multiple-choice format. Your insights will be greatly appreciated. Take the questionnaire online at: **www.lipid.org/encsurvey.**

Contribute to the *Lipid Spin:* Calling All Authors
By now you've undoubtedly noticed the new look of the *Lipid Spin.* In addition to our regular informative articles, we are branching out to cover a wider variety of topics. This means we also need a wider variety of contributors. We welcome member submissions on such topics as:

- Clinical articles
- Review articles
- Case studies
- Practical pearls
- How-to features
- Profiles of notable members
- Reader opinions
- Letters to the editors

If you have thoughts on lipidology, medicine, or even how to build your practice, share them with your fellow NLA members. This is a great way to introduce yourself and your work to your colleagues. If you'd like to contribute, contact Daniel Sosnoski at the NLA head office or send in an article directly (ph. 904-309-6203 or e-mail: dsosnoski@lipid.org).

Letter to the Editor

Editors' Comment:
As the *Lipid Spin* has previously published a letter from Dr. Feeman in which he presents and discusses his ATD risk index in some detail, and due to imitations in space, it will not be possible to publish again that section of his current letter dealing with his own work.

His major question about Dr. Richman's article printed in the *Lipid Spin* is indicated below. We also thank him for the comment on his patient taking Red Yeast Rice.

Ronald B Goldberg MD
Maria Lopes-Virella MD

Editors:
Michael Richman's article on Advanced Lipoprotein Testing advocates VAP testing because traditional LDL testing may miss up to 50% of people who will have an acute atherothrombotic disease event, such as acute myocardial infarction.

However, there have been no randomized controlled clinical trials to demonstrate that VAP testing offers anything of value over known atherothrombotic risk factors.

Sincerely,
William E. Feeman, Jr., MD

Michael Richman Responds:

Dear Dr. Feeman:
In response to your letter to the editor, the article titled *Advanced Lipoprotein Testing* was a brief general overview of the topic. I did not advocate any specific type of testing but merely outlined the different types available.

Cordially,
Michael F Richman MD, FACS

New Analysis Shows Troubling Trend in Triglyceride Levels May Be Linked to Rising Rates of Obesity

While LDL control has improved, there is an urgent need for more comprehensive lipid control to protect against heart disease

A new 30 year analysis of the National Health and Nutrition Examination Survey (NHANES) database conducted by the National Lipid Association (NLA) indicates that while Americans are doing a better job of managing LDL or "bad" cholesterol, the percentage of adults with high triglycerides, a blood fat linked to heart disease, has doubled, leaving many people at risk for potentially life-threatening events such as heart attack or stroke. Results of the analysis were presented today at the American Heart Association's Annual Scientific Sessions in New Orleans.

Between 1976 and 2006 the number of Americans with unhealthy isolated LDL levels dropped from 43 percent to 40 percent, an improvement that researchers attribute to more aggressive educational initiatives and treatment. However, far less emphasis has been placed on controlling triglycerides. The rising rates of isolated high triglycerides seen over the last three decades underscore the need for physicians and patients to understand and treat all three key lipids, which include LDL, HDL or "good" cholesterol and triglycerides.

"Studies have shown that unhealthy levels of triglycerides and HDL can lead to heart attack and stroke," said study author Jerome D. Cohen, M.D., chairman of the National Lipid Association's consumer affairs
committee and director of Preventive Cardiology Programs at St. Louis University Health Sciences Center. "As we continue in our efforts to reduce the toll of heart disease in America, this study clearly shows the need for increased focus on controlling triglycerides, in addition to the other components of the lipid profile."

Along with LDL and HDL, triglycerides are the third component of the lipid profile and are an independent and compounding risk factor for heart disease, the leading cause of death in the U.S. Studies have shown that the risk of developing heart disease doubles when triglyceride levels are above 200 mg/dL. When triglycerides are above 200 mg/dL and HDL cholesterol is below 40 mg/dL, a person is at four times the risk of developing heart disease. Other studies have shown that low HDL is predictive of cardiovascular events even when LDL is at goal.

While the percentage of the population with unhealthy HDL levels has remained relatively consistent over the past 30 years, the percentage of adults with a combination of high triglycerides and low levels of HDL doubled from two to four percent, further highlighting the need to simultaneously treat multiple lipids.

Obesity, Age and Triglycerides

The analysis cited dramatic increases in the number of obese Americans as one possible explanation for the spike in triglycerides over the last three decades. Data indicate a strong correlation between obesity (defined as a BMI > 30) and high triglycerides. Rates of obesity more than doubled from 15 percent in 1976 to 33.7 percent in 2006, while the percentage of Americans with isolated high triglycerides also doubled from 2.4 to 5.5 percent.

The study also revealed a strong increase in elevated triglyceride levels among people over the age of 60, with the likelihood of having unhealthy triglycerides increasing nearly five-fold from 1.8 percent in 1976 to 8.7 percent in 2006. This extensive analysis provides strong evidence of the connections between age, weight and lipid levels over the last 30 years.

"As Americans age and rates of obesity continue to grow exponentially, it is becoming increasingly important to monitor and manage HDL and triglycerides, along with LDL," said Thomas Bersot, M.D., president of the National Lipid Association. "By elevating the need to address all three lipids, we hope to improve heart health in America."

Conclusions

Researchers involved with the study concluded that the basis of these findings, physicians and other healthcare professionals should closely monitor patient triglyceride levels in an effort to improve preventive care. Patients, for their part, should be aware of all three lipids and work with their healthcare providers to reach optimal lipid levels.

Continued on page 25

Save the Date

Online Courses

Online: Through December 2008
CME Newsletter: Cardiovascular Disease & Dyslipidemia
Sponsored by SCEPTER
Endorsed – CME, CE
Available at www.lipid.org/education/masters

Online: Through January 2009
2007 NLA Masters Summit Webcast: The Role of the Digestive Tract in Lipid Metabolism and CV Risk
Sponsored by the National Lipid Association
Available at www.NLACME.com

Make plans now to attend the National Lipid Association Annual Scientific Sessions to be held in Miami, FL April 30–May 3, 2009

Meetings and Events

Friday, December 12, 2008
Duke Challenges in Diagnosis and Management of Dyslipidemia: 2009
One-Day Multi-Topic Intensive Update CME Course at Duke University
Durham, NC
Sponsored – CME
E-mail: rlaforge@nc.rr.com

February 5–7, 2009
Cardiovascular Disease Prevention 2009: Seventh Annual Comprehensive Symposium
Coral Gables, Florida
Sponsored by Baptist Health South Florida
Endorsed – CME, CE
E-mail: meded@baptisthealth.net

February 20–22, 2009
PLA 3rd Annual Scientific Forum
Salt Lake City, UT
Sponsored – CME
www.lipid.org

April 30–May 3, 2009
2009 NLA Annual Scientific Sessions (In Participation with Southeast Lipid Association)
Miami, FL
Sponsored – CME
www.lipid.org

June 12–14, 2009
NELA 5th Annual Scientific Forum
Boston, MA
Sponsored – CME
www.lipid.org

The President's Dinner and Dance at the Pacific Lipid Association's 3rd Annual Scientific Forum will be held at Salt Lake City's stunning La Caille, Saturday, Feb 21, 2009. This will be an evening to remember!

June 14-18, 2009
XV International Symposium on Atherosclerosis
Boston, MA
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This Symposium, held triennially under the auspices of the International Atherosclerosis Society, offers the world's largest and most prestigious forum for the presentation of new research and clinical findings on arterial disease.

Who Should Attend
Practicing physicians and clinical researchers involved in the diagnosis and treatment of lipid, cardiovascular, metabolic diseases, and disorders, basic scientists, epidemiologists, nutritionists, geneticists, public health specialists, general practitioners, and other healthcare professionals.

The XV International Symposium on Atherosclerosis – Boston 2009 is jointly sponsored by National Lipid Association and Giovanni Lorenzini Medical Science Foundation.

Practical Pearls *cont. from page 13*

is not surprising but the degree of LDL-C lowering can be higher than expected (approximately 40% in some of the patients with whom this combination therapy was used).

Another combination therapy that is quite useful in patients with diabetes and combined hyperlipidemia who are intolerant to statins and niacin is the association of colesevelam and fibrates (fenofibrate and gemfibrozil). This combination is well tolerated and the decrease in lipid levels quite adequate. I seldom use colesevelam in diabetics to avoid the risk of enhancing hypertriglyceridemia. However, in combination with a fibrate this side effect is not observed and the degree of glycemic control improves. Although the mechanism of action of colesevelam in lowering glucose levels is not known, the hypoglycemic effect of colesevelam has been described and the drug is now approved for treatment of type 2 diabetes in addition to other medications.

Although I am using colesevelam more often in type 2 diabetics than I have in the past, there are a couple of issues to consider in addition to the excessively high cost of colesevelam: using it in patients with autonomic neuropathy or with high levels of triglycerides. I have used the combination in patients with triglycerides below 300 mg/dL and carefully excluded the presence of autonomic neuropathy. One of the major problems of administering the drug in patients with autonomic neuropathy besides nausea and vomiting is fecal impaction, which in some patients leads to bowel obstruction and requires hospitalization.

The hypoglycemic effect of colesevelam has been recently described and it is not widely known, but it has certainly opened new therapeutic options in diabetes that until recently were seldom considered. This may lead to a decrease in the price of the drug either by increasing its usage or making the field more competitive.

Lipid Luminations *cont. from page 14*

acute coronary syndrome (11,353 randomized patients, median age 62 years, and a mean follow-up period of 1.0 year (11,564 person-years) at unblinding. Combining these 2 databases with 4 times the person-years of follow-up available in SEAS (36,501 vs. 7636), 313 cancer cases were recorded among the patients who had been assigned to receive ezetimibe, as compared with 326 among those who had not (P = 0.61). However of these, 97 in the ezetimibe group versus 72 in the control group died of cancer (mainly of the lung, p<0.07) and if the SEAS database is added, total cancer deaths were 134 versus 92 (risk ratio 1.45, p<0.007).

Peto et al conclude that the currently available results do not provide credible evidence for any adverse effect on cancer from the addition of ezetimibe to statin therapy, and that attributing an increase in cancer deaths in the absence of an increase in cancer incidence to an adverse drug effect is implausible, and is most likely explained by a play of chance. In an editorial on these studies Drazen et al[3] conclude nevertheless that it is appropriate to raise a note of caution and that the completion of SHARP and IMPROVE-IT may shed further light on this. In the meanwhile, physicians and patients are unfortunately left for now with uncertainty about the efficacy and safety of ezetimibe.

References:

1. Rossebø AB et al. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. *N Engl J Med*. 2008;359:1343-56.

2. Peto R, Emberson J, Landray M, et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008; DOI: 10.1056/NEJMsa0806603.

3. Drazen JM, D'Agostino RB, Ware JH, et al. Ezetimibe and cancer—an uncertain association. *N Engl J Med* 2008; DOI: 10.1056/NEJMe0807200.

NLA Research Report *cont. from page 23*

Study methodology

Adults aged 20 to 74 years who took the blood lipid examination were selected from NHANES II (1976-1980), NHANES III (1988-1994), and NHANES 1999-2006. Adults missing values on total cholesterol, HDL cholesterol or triglycerides were excluded. Where LDL was missing, the Friedewald equation was used to calculate LDL for patients with TG<400 and the Hattori equation was used to calculate LDL for patients with TG ≥ 400.

Lipid levels were measured for the sample of adults with laboratory data who were examined in the morning and had fasted for 8.5 to 23 hours. High triglycerides and LDL and low HDL levels were characterized in the analysis as non-optimal, defined as ≥150 mg/dL for triglycerides, <40 mg/dL for HDL and ≥100 mg/dL for LDL. Obesity was defined as BMI ≥ 30 kg/m2

This study was conducted by the National Lipid Association Consumer Affairs Committee and analysis and research were performed by HealthCore, with the support of an independent grant from Abbott Laboratories.

ABCL Congratulates the 2008 Diplomates

In 2008 the American Board of Clinical Lipidology officially awarded Diplomate status to the following physicians who qualified for this distinction. The diplomates will be honored at the Convocation Ceremony to be held at the NLA 2009 Annual Scientific Sessions at the Fontainebleau Hotel in Miami, Florida, on Saturday, May 2. The National Lipid Association congratulates these dedicated professionals.

Fadi Alfayoumi, MD
Brownsville, TX

Naji Aljohani, MB.ChB.
Toronto, ON

Saadah Alrajab, MD
Visalia, CA

Khalid Alrasadi, MD
Verdun, QC

Bruce Andrus, MD
Lebanon, NH

Brian Asbill, MD
Asheville, NC

Karen Aspry, MD, MS
East Greenwich, RI

Zuhier Awan, MB.ChB
Westmount, QC

Khalid Aziz, MD
Bunnlevel, NC

Matthew Beasey, MD
Bristol, TN

David Blank, MD
Westmount, QC

William Borden, MD
Chicago, IL

Maria Castro, MD
Rochester, MN

Michael Cecil, MD
Covington, GA

James Chaney, DO
Hazard, KY

Michael Conlin, MD
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Khaleel Deeb, MD
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Nicholas DePace, MD
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Jamshid Faraji, MD
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Ramprasad Gadi, MD
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Jose Garcia, MD
Ponce, PR

Julian Gonzalez, MD
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John Homan, MD
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Michael Lenz, MD
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Louis Malinow, MD
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Gerald Youker, MD
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Thomas Zoch, MD
Neenah, WI

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Albany, NY

ACCL Congratulates the 2008 Diplomates

In 2008 the Accreditation Council for Clinical Lipidology officially awarded Diplomate status to the following allied health professionals who qualified for the distinction of Clinical Lipid Specialist. The diplomates will be honored at the Convocation Ceremony to be held at the NLA 2009 Annual Scientific Sessions at the Fontainebleau Hotel in Miami, Florida, on Saturday, May 2. The National Lipid Association congratulates these dedicated professionals.

Ruth R. Bertsch, RN
Virginia Beach, VA

Becky Captain, MSN, NP
Kansas City, MO

Travis J. Cork, PharmD
Sheridan, WY

Marina Donahue, MS, NP
West Bridgewater, MA

Jessica Durham, MA, ARNP
Seattle, WA

Eric K. Gupta, PharmD
Pomona, CA

Sherri T. Lloyd, PA-C
Colorado Springs, CO

Cheri L. Hayes, MSN, NP
Avon, OH

Kathleen Hill, MSN, CRNP
Wallingford, PA

Teresa Hoffmann, PharmD
Lima, OH

Kris Komosa, MSN, NP
Elyria, OH

Leslie A. Machos, PharmD
Appleton, WI

Joel Marrs, PharmD
Portland, OR

Stacy L. Martin, PharmD
Charlotte, NC

Janet McAlister, MSN, NP
Smyrna, GA

Deborah Miller, MSN, NP
Bricktown, NJ

Yen B. Nguyen, PharmD
Richmond, VA

Jessica L. O'Neill, PharmD
Belleville, MI

Debra L. Parker, PharmD
Findlay, OH

Roda Plakogianis, PharmD
Whitestone, NY

Danielle Raymer, PharmD
Winston-Salem, NC

Kristen Rodeheaver, MS, NP
Green Bay, WI

Cynthia G. Rodriguez, MS, ARNP
Odessa, FL

Paulette C. Schreiber, MSN, CRNP
St. Marys, PA

Doyle Shelton, PA-C, MS
Wesley Chapel, NC

Eric E. Shoup, MS, PA-C
Columbia, SC

Melissa J. Snider
Hilliard, OH

Nicole Spaeth, MSN, ARNP
De Pere, WI

ToniMarie Swartz, PharmD
Timberlake, OH

Karen A. Tisdel, PharmD
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