LIPID CASE 271 New AHA Women's Guidelines

So let's examine a woman in this case discussion and apply the new 2011 AHA Women's Preventive CV Guidelines guideline to see how well it really works. This case comes from my own practice, the North Jersey Institute of Menopausal Women, which draws women from far and near places. The patient's husband had recently consulted me because of a significant problem with Lp(a). The patient, after being shocked that there was something called a lipidologist, decided to get my opinion on her lipids after seeing how I handled her husband (although I prefer women patients, I do see some high risk men in consultation).

The patient is a 47 y/o white menopausal female with no serious medical history who works as a CCU nurse in a large hospital. She has known about abnormal lipids for over a year but was never formally treated. Indeed a cardiologist told her last year the lipid panel (see below) did not warrant treatment even though the LDL-C was abnormal. She has had weight gain since going through climacteric changes and is now fully menopausal with no periods for a year and a high FSH. Interestingly she has dealt with polycystic ovarian syndrome (PCOS) all her life (including exploratory surgeries and ovarian resections), but was never until recently obese and was never hirsute. She had fertility problems but ultimately had two pregnancies (complicated by gestational diabetes). She has no known cardiac disease but has had some nonexertional episodes of severe, sharp, internal discomfort in her lower chest with radiation to the neck and jaw. Ultimately it was thought to be noncardiac but no real cardiac workup other than enzymes was ever done.

Family history shows her mother to be alive (69) with T2DM and her father alive (70) with HTN; 1B 1S are alive and well.

Review of symptoms revealed significant early menopausal symptoms of severe flushes, sleeplessness and psychological irritability. Her medications include: Flaxseed oil 1000 mg twice daily, Multivitamin, Vitamin E 400 IU daily, Chromium picolinate 200 mg daily, Magnesium 250 mg every other day, Vitamin B12 500 mcg daily

Vital signs: Ht: 68.75 Wt: 196 BP: 120/80 BMI: 29 Waist size 35"

Of course, she like all my patients (referral lipid clinic) had an advanced CV risk panel from Health Diagnostic Labs in Richmond VA done:

Lipid panel (#1) from 2009: (was told no drug therapy needed) (perimenopausal state)

TC = 186 LDL-C = 130 HDL-C = 40 TG = 140 VLDL-C = 28 Non-HDL-C = 146
TC/HDL-C = 4.65 TG/HDL-C = 3.5
Glucose = 98

2010 lipid panel (#2) (a year after than above) (menopausal state)

TC = 217 LDL-C = 144 HDL-C = 43 TG = 174 VLDL-C = 34.8 Non-HDL-C = 174

TC/HDL-C = 5.0 TG/HDL-C = 4.0
hs-CRP = 1.47

DAYSPRING DISCUSSION: I want to simply use the above history and lab information before I show what the advanced testing demonstrated (and of course then we will have a serious discussion of her cardiovascular risk).

Nobody in their right mind should casually dismiss this woman's history and lipid panel from either 2009 or 2010 as did the cardiologist at her hospital. A cursory review of the data shows not only an abnormal TC/HDL-C ratio but a significantly elevated TG/HDL-C ratio. I am sure he (and unfortunately for women most primary care providers or gynecologists) has no clue that data from WISE (Women's Ischemic Evaluation) revealed that women who have chest pain and a TG/HDL-C ratio > 3.0 have a significant increase in both CV and total mortality (Amer Heart J 2009;157:548-555). Indeed in this study women(with chest pain) who did not have an elevated TG/HDL-C ratio had no recurrent events. Sadly the new Women's Guidelines ignored this free, simple to understand ratio. Data in women have proven that any woman with a TG/HDL-C ratio > 3.5 has > 80% chance of having small LDL particles and as you all should know virtually all drug naive patients not on serious lifestyle who have small LDLs have a high LDL-P (coronary risk factor #1). As you know very shortly we will be discussing lipoprotein data in this woman, so we shall see.

Did all my readers make the diagnosis of 277.7 or the metabolic syndrome (TG > 150, HDL-C < 50 and increased waist size)? If not: Tisk Tisk Tisk (I am shaking my finger at you). By the way with her long history of PCOS and her gestational diabetes (a new CV risk factor in the above guidelines) is anyone shocked that she has the metabolic syndrome? As soon as the diagnosis of PCOS is made, odds are you have a lipid/lipoprotein disorder. Tragically PCOS is a very easy diagnosis to miss and therefore its associated CV risk is not treated. Even when diagnosed many providers worry more about the menstrual, cosmetic and infertility issues.

How about this data? Menopausal women with a waist size > 35" and a TG > 128 mg/dL have a marked increased risk of metabolic syndrome, CV risk and mortality compared to women without EWET (Elevated TG, Elevated Waist). Please see the paper: Enlarged Waist Combined With Elevated Triglycerides Is a Strong Predictor of Accelerated Atherogenesis and Related Cardiovascular Mortality in Postmenopausal Women by László B. Tankó, et al. Circulation.2005;111:1883-1890. They conclude: *"The combined presence of EWET may be the best indicator of cardiovascular risk in postmenopausal women. Other components of the MS-NCEP add little medical value to screening in general practices."*

So using new guideline criteria, and the risk calculator they now provide:

Age 48 = 5 points Low HDL-C of 40 = 1 point TC of 217 = 3 points. Nonsmoker, normotensive, nondiabetic = 0 points Thus she has 9 total points which gives her a ten

year risk score of 5.4% (low risk). However, using the new criteria, because she does a history of gestational diabetes, an HDL-C < 40, central obesity (BMI > 29) which she qualifies as an "at-risk" woman. Her 2011 guideline declared desirable lipids would be an LDL-C < 100 mg/dL, an HDL-C > 50 mg/dL, TG < 150 mg/dL and non-HDL-C < 130 mg/dL. So she would qualify for lifestyle therapy (nutritional and exercise).

Does she qualify for drug-lowering therapy since she would not be considered a high risk woman? The guideline (although it for sure in risk discussion section advises that an LDL-C < 100 mg/dL is optimal), in the treatment section states that her LDL-C should be less than not 100 mg/dL but rather 130 mg/dL. To achieve that goal as a patient with multiple risk factors and a ten year risk of 10-20%, nutritional therapy is indicated. But her 10-yer risk is < 10%. Amazingly unless the LDL-C is > 190 mg/dL, drug pharmacotherapy is not indicated in anyone but a high risk woman. So I guess we should send this woman (with her guideline determined "at-risk status") on her way with a referral to a nutritionist. No one would disagree with lifestyle counseling, but how many would also write a prescription? Remember with new Healthcare rules likely to come, treating off guideline recommendations, even with generics, will likely not be an option except for those who patients who can afford to pay for their own drugs. Formulary plans (so called death panels) will not likely pay for drugs issued without guideline support.

Well, let's just see what if any enticing information was provided by the HDL Advanced Panel with respect to lipoproteins.

Lipoproteins: apolipoprotein B 108 (70th percentile Framingham cut point)
Total LDL-P = 2013 very high risk (90th percentile Framingham cut point, > 95th MESA cut point)
Small LDL-P 1417 (very high)
LDL size at 20.3 nm (Pattern B or small phenotype)
Total HDL-P = 32.4 (60th percentile cut point i.e. 40% of patients would be worse)
ApoA-I = 133 (moderate reduction for a woman)
ApoB/A-I ratio abnormally high at 0.8 (should be well under 0.60-0.70
Lp(a) = 8 mg/dL

So, this woman has extremely abnormal lipoproteins (the vehicles trafficking her sterols). She has a very high LDL-P/HDL-P ratio of 62.1. Using data developed from the VA-HIT Trial (men with low HDL-C), those who had a ratio > 61 were in the upper (highest) quartile of risk (Circulation. 2006;113:1556-1563). [TD note to fellow NMR users, stop dwelling so much on whether the HDLs are large or small or how much cholesterol they carry (HDL-C or large or small HDL-C) and concentrate on the total HDL-P and take it very seriously when it is low and add the LDL/HDL-P to your flow sheet]. Atherogenesis occurs when the apoB-containing LDLs enter the arterial wall and set off the maladaptive inflammatory process (Ira Tabas: Circulation. 2007;116:1832-1844). Using the ADA/ACC consensus statement on lipoprotein Management in persons with cardiometabolic risk ((Diabetes Care 2008;31:811-822),) this lady's apoB calls for drug therapy. Using the AACC 2009 Statement (Clinical Chemistry 2009;55:3:407–

419) either elevated apoB or LDL-P, qualifies a person for drug therapy. So if this woman were your wife or a loved-one, would you insist she simply follow the 2011 AHA "Effectiveness based Guideline" and get on a better diet? As we say in Jersey, Give me a break! I do not see how anyone could be totally effective in achieving goals here without pharmacotherapy and lifestyle.

Of course I evaluated the cholesterol abnormality a bit further by ordering a sterol balance test at Boston Heart Labs (www.bostonhesartlab.com). Interestingly even though she was on no lipid modulating therapy she had suppressed markers of both cholesterol synthesis (lathosterol) and absorption (campesterol and sitosterol). This alerts me that her high apoB and LDL-P is not a cholesterol production or absorption problem per se, but may be due to a TG-related overproduction of atherogenic apoB particles which are not being cleared due to their small size (should respond nicely to better lifestyle). Her apoE genotype was E3/E3 (normal), so there are no issues there.

But wait, let's see what other information was provided in the advanced panel: Let's look at the inflammatory markers even though the Guideline folks found little use for them:

hs-CRP = 1.47 (seemingly OK but remember risk related to CRP is graded and 1.47 is not perfect (< 1.0)
Lp-PLA2 = 146 (normal) Lipoprotein associated phospholipase A2
Fibrinogen = moderate elevation at 432
Myeloperoxidase (MPO) = 998 (EXTREMELY HIGH) normal well under 400 and anything > 500 a potential big worry. Indeed until proven otherwise one should assume someone with a level > 900 to be at very high risk and likely even have CAD (potentially unstable). MPO can also attack HDL particles and render them dysfunctional. Not good for a woman who already has too few HDLs. This test is performed at Cleveland Heart Lab (www.clevelandheartlab.com)

So now we are dealing with not only a lipoprotein nightmare with equivocal lipids), but also with significant inflammation (remember the word maladaptive inflammatory process). We have to wonder when the heck is her acute coronary syndrome going to occur. I think we also have to look back her episode of undiagnosed chest pain. Data from WHI and the WISE trial showed that women (unlike men) who presented with chest pain who underwent coronary angiography had a 50% incidence of having an unremarkable angiogram (not revealing obstructive disease). Such women are said to have microvascular angina or ischemic heart disease instead of the old term obstructive coronary disease. We have to stop thinking of at-risk women in terms of do they have coronary luminal occlusions. If you are not up to date on women and CHD please read the fantastic review: Women and Ischemic Heart Disease Evolving Knowledge. Leslee J. Shaw et al. J Am Coll Cardiol 2009;54:1561–75.

Is there more? I hope you all noted in the history, this woman has been battling PCOS for her adult life and had gestational diabetes. These are a insulin resistant disorders. Let's examine some tests of insulin resistance.

Insulin level (using HDLs newer very sensitive assay) = 15 (very high) and a major CV risk predictor as well as T2DM predictor

Her free fatty acid levels were normal and she does not meet criteria for impaired fasting glucose.

Her NMR Lipoprotein Insulin Resistance score was 55 (0-100) with abnormal levels 500-100. For sure all of these IR tests, means lifestyle and perhaps insulin sensitizing therapy will be needed to avoid T2DM onset.

So we now have a long-term insulin resistant woman with metabolic syndrome, extremely abnormal lipoproteins and a disastrous MPO level. There could not be any more risk could there? Well, her omega-3 index was quite low at 3.9% (desirable > 8%). This is a measure of omega-3 FA in red blood cell phospholipids. A low index is a major risk factor, as important as any lipid abnormality in predicting adverse CV events. It is also very easy to correct with omega-3 FA supplementation (Curr Atheroscler Reports 2009;11:411-417). For test ordering info see www.omegaquant.com Please all readers - do one on yourself and your loved ones unless they are an Eskimo (not needed in anyone eating seals for breakfast). Lastly her Vitamin D level was 36 (lower limit of normal)

Did I suggest pharmacotherapy? You betcha! Here are my recommendations:

1) Contact the Healthcare coach made available by HDL.

2) Stop Flaxseed oil as it has done nothing to her Omega-3 index. Many humans do not convert much alpha linolenic acid (the major component of flaxseed oil) to EPA and DHA (the cardioprotective omega-3 FA). Part of the reason is that the omega-6 FA (linoleic acid) competes with linolenic acid for conversion enzymes. I gave her prescription strength omega-3 Lovaza 3 capsules daily (an off-label use). One could use a lesser dose, but it will take longer to normalize the index. Once normalized I can always cut back on omega-3 supplementation. By the way the 2011 AHA statement advises omega-3 FA supplementation is indicated for use in all women with elevated cholesterol or TG. Interestingly they advise 1800 mg of EPA (the dose used in the JELIS trial: an open-label Japanese trial enrolling primary and secondary prevention patients where the EPA plus a baby statin did a much better job reducing events than did the baby statin alone (Part of the reason is that the omega-6 FA (linoleic acid).

3) Even though her lathosterol level is low, she needs to start a statin (Crestor 20 mg) which by further suppressing cholesterol synthesis will hopefully upregulate LDL receptors and help lower LDL-P. She of course was warned about myalgia and muscle weakness.

4) Once her CV risk has been lessened, if vasomotor symptoms persist potential menopausal hormonal therapies can be discussed. If you think such hormonal therapy cannot be used (for quality of life issues, not CV protection) in a such a patient, read the guidelines I quoted above. Even in the Heart and estrogen replacement Study (HERS) of women with significant atherosclerosis, there was no Prempro related adversity in women who were on a statin.

5) Stop all of the other supplements listed above but take a vitamin D supplement and aspirin (not recommended for low risk women, but I do not consider her low risk.

Guess what: A follow up evaluation was just done. She has lost 9 pounds and there for whatever reason has been a significant improvement in her vasomotor and other menopausal symptoms and is tolerating the statin very well. Thank goodness she followed my therapeutic advice as the cardiologist after being confronted with the advanced panel, pooh-pooed it and stated no one uses these tests and he did not consider lipidology a real science. He said the advanced testing would not change therapy (this coming from the same guy who did not advise therapy after last year looking at her abnormal lipid panel). Beware women of America: these are the obstacles you will face in getting competent CV care.

Follow up testing:

TC = 118, LDL-C = 53, HDL-C = 37, TG = 82, Non-HDL-C = 81 VLDL-C = 16
TG/HDL-C = 2.2
Total LDL-P = 1034 (20th percentile cut point)
Small LDL-P = 400 (normal)
Total HDL-P = 30.5 (lower than previous)
ApoB = 55 (perfect) ApoA-I = 118 (remains low)
MPO = 369 (perfectly normal) LpPLA2 remains normal but is lower at 118
Insulin level reduced to 13
Omega-3 Index now at 8.4 % (perfect)
Vitamin D3 now 48 (perfect)

Wow: Those results even surprised me. But it gave me great satisfaction. It even makes me think Lipidology (actually lipoproteinology) might be a real science!

So Guidelines are nice. They bring us all into the ball park. They make you think and teach you what Level I evidence calls for. Yet the art of practicing medicine is knowing which patients need a higher level of expertise and in whom to seek additional information (readily available testing) that can help us likely do a better job. Over 14 years ago I was an overweight guy with a perfect and I mean perfect lipid panel. When it became available in 1998 I got lipoprotein testing (NMR) on myself and all of a sudden required several lipid modulating drugs to normalize the abnormal atherogenic lipoproteins. 13 years later and I am still here! I doubt that would have been true had I strictly followed NCEP ATP-II or ATP-III. Again I do not want to dismiss any guidelines. They serve a purpose. Most would do very well to actually read and understand them. Only then will you have the knowledge and insight as to who needs more!