

## **LIPID CASE 262    Healthy Woman: How much of a workup to do?**

Local media wanted to do a story on advanced testing and set up the following patient for an advanced cardiovascular assessment at Health Diagnostics Laboratory (HDL) in Richmond, VA. She has been previously healthy and active but recently her father (age early 60's) had an MI and because of extensive atherosclerotic disease required triple coronary artery bypass grafting. The case was sort of a test case: would advanced testing be any better than standard of care or NCEP evaluation and recommendations?

My readers know that I am an educational consultant for HDL and for disclosure purposes all should know that the majority of testing from my practice now goes to HDL, but I also use Boston Heart Lab and Cleveland Heart Lab for certain tests. When the work up on the above patient returned I was asked to comment (no patient names or ID provided to me). I'd like to factiously call her Rachel Jackson in memory of the "real" Mrs. Andrew Jackson who died at the Hermitage in Nashville, TN on the evening before she and President-elect Jackson were to depart for their new life in Washington DC. She experienced substernal chest discomfort with radiation to neck and arms and died within a few hours. If HDL or any of the above labs existed back then, could we have picked up her CV risk prior to the fatal event? If so, is a lipid profile all we would have needed? Those aware of Framingham Data in women have known since 2001 (Arch Intern Med. 2001;161:949-954) that 2/3 of women having a major CV event have LDL-C levels well under 140 mg/dL. Baseline HERs data also showed us that 20% of women with severe CHD have an HDL-C between 60 and 80 mg/dL (Am Heart J 2000;139:288-96). Very recent data from the Get with the Guidelines Study (Am Heart J 2009;157:111-7.e2.) showed 50% of patients requiring hospitalization for CVD have an LDL-C < 100 mg/dL and 18% less than 70 mg/dL and 44% have a perfectly normal HDL-C. The TG values of the vast majority of the patients were between 100-200 mg/dL. Bill Cromwell's analysis of Framingham Offspring long term (16 years) CV mortality showed several patients with high LDL-C with excellent survival and several patients with low LDL-C with death. What is going on? Are not we told LDL-C or even HDL-C are the keys to solving lipid disorders and reducing CV events?

The patient is 38 years old and came in with her two young sons (ages 3 and 5). She appeared quite healthy with a BMI of 24 (5'6 inches and 150 lbs) and was normotensive and did not smoke.

Her standard lab results are as follows:

TC = 213    HDL-C = 47    LDL-C = 113    TG = 172    VLDL-C = 34

Non-HDL-C = 166    TC/HDL-C = 4.5    TG/HDL-C = 3.6

So let's see if NCEP ATP-III can help us here. Using history, physical and the lipid profile she has no major cardiovascular risk factors (dad having an MI at age 60 is not considered premature heart disease: a 64 year old like me would disagree). So the reality is this woman does not qualify for Framingham Risk determination. Even if you did

FRS, she has less than a 1% risk of a CV event over the next ten years. None of the above lipid concentrations are extreme enough to justify anything but lifestyle changes - certainly drugs would not be indicated. NCEP ATP-III states a TG of 150-200 mg/dL is associated with borderline CV risk, but unless they are > 500 mg/dL, TG are not used to initiate drug therapy (only LDL-C is used for that). Astute clinicians have likely noted the patient has two criteria for the metabolic syndrome (TG > 150 mg/dL and HDL-C < 50 mg/dL in a female). But she lacks increased waist size, hypertension or elevated glucose. Even if she were a full metabolic syndrome, NCEP ATP-III advice would be lifestyle changes which she seems to have done very well.

Lipidaholics know I often allude to Szapary's and Rader's classic TG/HDL axis paper (Am Heart J 2004;148:211–21) which would conclude that the odds are this woman is at risk even though it cannot be recognized using LDL-C. The author's state: *"High TG and low HDL often occur together, often with normal levels of LDL-C, and can be described as abnormalities of the TG-HDL axis. This lipid abnormality is a fundamental characteristic of patients with the metabolic syndrome, a condition strongly associated with the development of both type 2 diabetes and CHD. Patients with high TG and low HDL-C should be aggressively treated with therapeutic lifestyle changes. For high-risk patients, lipid-modifying therapy that specifically addresses the TG-HDL axis should also be considered."* However to be considered high risk this woman would have to have an extreme elevation of some important CV risk factor (e.g. an LDL-C > 190 mg/dL) and that is not seen in her lipid profile. What are the odds advanced CV testing will discover that she is a high risk patient requiring therapy?

Vera Bittner published incredible data last year from the Women's Ischemia Syndrome Evaluation (WISE) which showed that among women with suspected ischemia, the TG/HDL-C ratio (>3.6) is a powerful independent predictor of all cause mortality and cardiovascular events (Am Heart J 2009;157:548-55). Although HDL-C has long been respected, TG have for the most part been ignored in the past by way too many providers. NCEP ATP-III in 2001 tried to give TG its proper respect by making non-HDL-C a goal of therapy when TG are > 200 mg/dL. Yet even in 2010, almost no one calculates non-HDL-C or TG/HDL-C ratios. Keep in mind as TG rise HDL particles go from a cholesteryl ester (CE)-rich, TG-poor particle to a TG-rich, CE-poor particle and this explains why so many develop low HDL-C as TG (most often due to insulin resistance) rise. HDLs carrying TG instead of CE is usually associated with reduced HDL-C values.

The patient did receive the cardiovascular panel at HDL. Again I ask, based on the above lipids are any of you even pondering the idea this is a very high risk woman? Her LDL-C value of 113 which is at the 30th percentile Framingham Population Study cutpoint (normal – this alludes to the fact that in the Framingham population 30% of people would have a better LDL-C and 70% a higher level). For Framingham cutpoints please go to: (<http://www.lipidcenter.com/pdf/Framingham.pdf>). Using the more contemporary data from the MultiEthnic Study of Atherosclerosis (MESA) cutpoints it is the 45th percentile (perhaps of value of some concern). Yet the LDL-C still does not qualify the patient for any therapy as it is an at goal NCEPATP-III value. Yet, quoting the 30 international experts from: The thirty-person/ten country panel (Journal of Internal Medicine 2006;

259: 247–258), we now know *"that apo B has been shown to be superior to LDL-C in predicting the risk of vascular events and the progression of vascular disease in a series of prospective epidemiological studies. --- Because the amount of LDL cholesterol per LDL particle varies substantially both between and within individuals, LDL cholesterol does not necessarily equal the most critical variable, the total number of LDL particles. -- total plasma apo B is, for practical purposes, a reflection of LDL apo B (i.e.LDL-P)."*

So let's review the first part of the HDL report form - it deals with lipoprotein assessment and remember there are no lipoprotein measurements in any lipid profile.

Apolipoprotein B (apoB) = 114 mg/dL (the 75th percentile Framingham Cutpoint) (MESA apoB not published)

Total LDL-P = 2116 nmol/L (90th percentile Framingham cutpoint or > 95th MESA cutpoint) In other words this is an extreme elevation of a major (perhaps the most important) cardiovascular risk factor currently available.

So my goodness: 75% of people have a lower apoB and 95% have a lower LDL-P than this lady. So despite her fairly unremarkable lipid values she has extreme elevations of her atherogenic lipoproteins and her risk category just went from low (using standard NCEP ATP-III criteria) to high, In NCEP ATP-III an extreme abnormality of a lipid value like LDL-C (> 190 mg/dL) or TG > 500 mg/dL or isolated low HDL-C would make her high risk and call for initiation of lifestyle and /or drug therapy. Well, so does such a high apoB and LDL-P. Therefore we simply cannot abide by NCEP ATP-III as we would be ignoring the very abnormal apoB and LDL-P values. Looks to me as I stated above we are beyond the days when we can bet human lives on lipid concentrations alone. Spare me the discussion that her TG/HDL ratio and recognition the TG/HDL-C axis disorder would have generated therapy. There are very few clinicians who would have prescribed medication for the above patient based on the history, physical and lipid profile. There would be patients with the same lipid values who have a normal apoB and LDL-P.

What else showed up on the HDL CV profile?

Her small LDL concentration was high risk at 54 mg/dL (optimal < 20) and the percentage small LDL was also high at 48% (normal distribution show optimal values are < 13% and very abnormal is > 23%. What matters of course is her total LDL-P and apoB. The increased small LDL should suggest to us insulin resistance may be at play and it certainly goes along with the abnormal TG/HDL-C axis. Are small LDLs more atherogenic than big: hypothetically due to several reasons, yes, but in reality the data shows once adjusted for LDL-P, small LDL parameters do not add to CV risk prediction - but predominance of small LDL are definite markers of IR and are an indication that therapeutically normalizing apoB or LDL-P may be difficult (LDL receptors are less efficacious at recognizing and removing small rather than large LDLs.

The apoA-I was 142 mg/dL which is on the low side for a woman (should be well above ~150 if not 160 mg/dL). Her HDL-P (using NMR) was excellent at 36 (~80th percentile). Is there a coherent reason her apoA-I be somewhat low but her HDL-P is excellent.

Her HDL2 concentration was quite low at 8 mg/dL. Lack of large HDL2 is considered a major risk factor in drug naive patients and a value under 12 mg/dL should until proven otherwise be considered high risk. Lack of the large, mature HDL can also be very indicative of insulin resistance. Boston Heart Lab provides the most cutting edge analysis of HDLs using a technique (2D gel electrophoresis) called HDL mapping. HDL species exist as unlipidated apoA-I, phospholipidated or minimally cholesterol lipidated species called prebeta HDLs. After additional lipidation and esterification of the acquired cholesterol the HDL becomes larger and more mature. Such HDLs are called alpha 1-4 (with 4 being the smallest and 1 being the largest). Anyone with a low HDL2 concentration would lack the larger alpha HDL 1 and 2 particles which would (in a drug naive patient) be considered indicative of impaired HDL-mediated trafficking of cholesterol. HDL particles can have from one (an unlipidated apoA-I particle) to four apoA-I molecules with the large HDLs carrying increased numbers of HDLs. So one could have a normal HDL-P by NMR, but if most of the HDLs were small (and thus carrying less apoA-I per particle) there might be somewhat of a disconnect (discordance) between apoA-I and HDL-P measurements. Note HDL-P via NMR cannot assay unlipidated apoA-I or prebeta HDLs but because of their extremely short half life (minutes) they contribute little to total HDL-P. Clearly HDL mapping at Boston Heart Labs is extremely useful in making accurate diagnoses in patients with hypoalphalipoproteinemia. However, the patient at hand has a normal HDL-C level using NCEP ATP-III criteria. Using AHA Women's Guidelines from 2007, an HDL-C < 50 mg would be below the desirable level of 50 mg/dL.

I want you to think about why this drug naive lady lacks large HDL particles. Her TG/HDL-C axis disorder with a high TG/HDL-C ratio, increased small LDL and lack of large HDL are strong indicators that despite her perfect BMI she is insulin resistant (IR). NHANES data showed 20% of persons with full metabolic syndrome have a BMI < 26 (Diabetes Care 27:2222-2228, 2004). With a high TG and IR there is likely increased CETP activity allowing TG from apoB particles to swap with CE from HDL particles. The HDL becomes TG-rich and CE-poor, and once it enters the liver hepatic lipase hydrolyzes the TG and surface phospholipids and the HDL becomes small: hence there will be reduced levels of large HDL and increased amounts of smaller species in IR patients. The key point is that the TG, that caused the HDL core composition abnormalities, came from increased numbers of apoB particles (vast majority of which are LDL particles) and therefore in drug naive IR patients who lack large HDL (explaining her HDL-C < 50 mg/dL) much of the risk is simply due to high apoB and LDL-P. Clearly that is the case in this woman: moral of the story: much of the risk seen with low HDL-C and in those lacking large HDLs is related to very high apoB and LDL-P levels (atherogenic particles). First line treatment must be directed at LDL-P, not any HDL parameter.

This woman is turning into a real CV challenge! What else did the HDL CV profile come up with?

Lp(a) mass was somewhat high at 41 mg/dL (normal being < 30 mg/dL) and her Lp(a)-cholesterol or Lp(a)-C was also high at 6 mg/dL (normally nonexistent or < 2 mg/dL). She is a Caucasian and likely has the apo(a) isoform that is more likely associated with CVD risk. There is data that Lp(a)-C may be a better indicator of risk than Lp(a) mass. Lp(a) abnormalities are always of more concern in patients with high or very high apoB and LDL-P than in patients with unremarkable numbers of atherogenic particles as is the case here.

Her apo E genotype is normal at 3/3. CV and LDL-C risk with respect to apoE isoforms goes from low in E2/E2 through high at E4/E4. The fact that this lady with a normal BMI had such terrible atherogenic particle numbers with a normal apoE genotype suggests treatment will be difficult. Despite her BMI, a Mediterranean diet and supplementing N-3 FA may be needed. Most E3's with terrible lipids are poor eaters. For sure I would do an omega-3 index on her (see [www.omegaquant.com](http://www.omegaquant.com)) to guide her omega-3 FA status.

Her coagulation evaluation included Factor V leiden testing and prothrombin mutation: which were normal. Inflammatory markers revealed an elevated hs-CRP of 2.75 mg/L but normal Lp-PLA2 of 121 ng/ml. I suspect the elevated hs-CRP is simply another marker of insulin resistance and the normal Lp-PLA2 (an atheroma specific inflammatory marker) is reassuring. A myeloperoxidase level at Cleveland Heart Lab (but also now available through HDL) would add further insight and might provide some information on HDL functionality.

A fibrinogen level, a proven independent CV risk factor, was elevated at 461 mg/dL. Homocysteine testing, another potential independent CV risk factor, was normal as was a vitamin D level. Her insulin level was normal at 5, but her NMR derived Lipoprotein-related Insulin resistance score was abnormal at 52.

So does this woman have insulin resistance or not? Against it but certainly not ruling it out are the normotension, BMI and insulin level but for it are the high TG/HDL-C ratio, elevated hs-CRP, high total LDL-P with a predominance of small LDL, lack of large HDL species and an elevated LP-IR score by NMR. IR is not only associated with CV risk, but also dramatically increases the risk of developing T2DM.

So let's dumb this down and answer my question – Did this woman need advanced cardiovascular testing.

(1) Using NCEP ATP-III or conventional old time standards no treatment is called for other than perhaps some dietary recommendations (and that is a stretch): a 38 year old thin woman who does not smoke or have high BP with no premature family history of CVD and an LDL-C of 113 mg/dL with a normal HDL-C and borderline TG is typically ignored and given no CV advice.

(2) Using the CV profile available in sophisticated labs like HDL. Oh my God! We have an insulin resistant woman who despite her young age has an extreme elevation of atherogenic particles who clearly needs to consult with a Health Care Coach (nutrition/exercise expert) and who for sure needs lipid-modulating drug therapy.

So the step (2) using more sophisticated testing identified the very increased CV risk where step (1) would have missed it and she would not receive adequate therapy in the vast majority of clinics in the world. If the Rachel Jackson's of today's world could have had this type of testing odds are they would live to celebrate their lives a lot longer. One might think today's presidents and their loved ones routinely get sophisticated testing. WRONG: Neither President Clinton, GW Bush or Obama (their records are public) ever had testing beyond a lipid profile. To all my readers: please avail yourself and your loved ones of this type of work up! Guidelines are Guidelines and you can go beyond them. Indeed the ADA/ACC Consensus Statement on Lipoprotein Management in those with Cardiometabolic risk (2008) and AACC statement (2008) now want us to use apoB and LDL-P on our patients.

If this woman were my patient how would I treat beyond the lifestyle?

Many would do CIMT testing to look for subclinical disease but because of the extreme LDL-P and apoB she needs drug therapy so in reality the CIMT will not change therapy. Coronary calcium testing is not indicated at her age as it will likely be negative. A CORUS gene expression test (<http://www.cardiodx.com/diagnostic-programs/genomic/gene-expression/>) for obstructive CAD might be interesting and if positive lead to a stress/echo.

Therapeutically, we need to upregulate a lot of LDL receptors and we need to lessen her emerging IR and prevent or delay the onset of T2DM. Despite their possible relation to T2DM onset, statins are the best drugs capable of lowering LDL-P. No generic statin is likely to get a patient with extreme LDL-P to goal (which would be an LDL-P of ~ 12-1300 nmol/L or apoB < 90 mg/dL). Likewise achieving goal might be beyond Livalo (pitavastatin) 4 mg) or Lipitor (atorvastatin) 40 mg. No one is going to start her on Lipitor 80 mg as a first line drug. I'd reach for Crestor 20 mg (rosuvastatin) here (proper on-label use of Crestor does not advise starting 40 mg dose). This lady's profile looks a lot like those from the JUPITER trial where Crestor significantly reduced events in women with low Framingham Risk, normal LDL-C and high hs-CRP. However the age of this patient was well below those studied in JUPITER. How about a nonsystemic drug like Welchol (colesevelam) which would help lower apoB and LDL-P and perhaps help with IR? Welchol is just not powerful enough by itself to get this woman to goal. However, if the Crestor 20 mg did not get her LDL-P to goal then Welchol could be added. Adding Zetia (ezetimibe) would also be an option. Keep in mind statins are category X and contraception would have to be discussed.

If one got the cholesterol balance test at Boston Heart Lab, the markers of cholesterol absorption and synthesis could guide treatment, with statins having far less effect in hyperabsorbers (increased sitosterol and campesterol levels) and ezetimibe being far

better in hyperabsorbers. Statins do a lot better in over producers (high lathosterol or desmosterol levels). Several authors using solid data have suggested we all should get absorption/synthesis markers before picking a therapy (J. Lipid Res. 2009;50:730–739).