

## **LIPID CASE 251 Treating HDL Size**

Hi Lipidaholics: This week case is a very common lipid disorder, but what are the medications needed to achieve goals of therapy.

I was asked about a 44 year old physically fit Caucasian man with a history of hypertension, dyslipidemia, metabolic syndrome, father with MI at age 65, non-smoker grandfather with an MI at age 50 (both of whom were were heavy smokers and drinkers). At the time of the first visit the medications included metoprolol and amlodipine.

Prior labs:

TC = 195, TG = 201, HDL-C = 34, LDL-C = 121, glucose = 115. (all in mg/dL)  
TC/HDL-C = 5.7 TG/HDL-C = 5.9 non-HDL-C = 161

The above medications were stopped: he was started on Lotrel and sent for NMR testing

Next labs:

TC 219, TG = 173, HDL-C = 40 LDL-C = 144 TC/HDL-C = 5.4 TG/HDL-C = 4.3  
non-HDL-C = 179

Total LDL-P 1842 nmol/L (high risk)  
Small LDL-P 1158 nmol/L (elevated)  
LDL size 20.1 nm (small or Pattern B)  
Total HDL-P 33.2 umol/L (low)  
Large HDL-P 1.1 umol/L (very low)  
HDL size 8.3 (small)  
Large VLDL-P 7.8 (increased)  
LP-IR score 80 (high)

No emerging markers or imaging studies have been done or ordered.

The provider stated:, I am undecided whether to start a high dose statin with niacin or Trilipix, though I'm leaning towards Niaspan. On the one hand, Trilipix (fenofibric acid) seems like a good choice based on his insulin resistance/pre-diabetes (and FDA indication to use with a statin), but has benefit of fibrates been established with triglycerides under 200? I'm also aware that fibrates increase HDL particle number more than Niaspan, but the main problem, it seems to me, is the paucity of large HDL particles, which Niaspan will definitely improve. Then, there's the issue of Niaspan pushing the patient from pre-diabetes to T2DM. As you see, I'm confused. What treatment and further evaluation (including imaging, if any) would you recommend?

## **DAYSRING DISCUSSION**

Case looks like a typical metabolic syndrome patient with dyslipidemia or more accurately dyslipoproteinemia. Of interest is the caveat that the patient is physically fit: does that mean normal BMI and waist size or a obese NFL lineman who is certainly physically fit? NHANES data has shown 20% of full blown metabolic syndrome patients have a BMI < 26 and are referred to as metabolically obese. Using Framingham Risk Scoring he is low risk for a CV event within ten years. The metabolic syndrome adds to that risk (many would boost the patient up to the moderate risk category: but he does not qualify for the moderately high risk category) and NCEP would suggest treatment with therapeutic lifestyle to get the LDL-C < 130 mg/dL and if the TG were still high to get the non-HDL-C < 160 mg/dL (using NCEP 2004 addendum there is an option for an LDL-C of < 100 and non-HDL-C < 130 mg/dL). The clinician wants to use a high dose statin and then needed help deciding between adding a fibrate vs. niacin. Is monotherapy or combination therapy indicated or too aggressive?

NCEP wants us to get patients to goal using lifestyle and drugs if needed: They advise starting therapy with drug(s) capable of achieving goal. Thus they give two options: Start the dose of statin that will likely achieve the LDL-C goal (we'll assume in this case one should go for the optional LDL-C goal of 100 mg/dL). A 44% drop in LDL-C will be needed: So the provider is correct in suggesting a high dose statin (Crestor 20 mg. Lipitor 40-80 mg). However NCEP also gives option 2: start a low dose statin in combination with niacin, ezetimibe or sequestrant (like colestevlam or Welchol which is now available in a powder that is turned into liquid drink form). Note that NCEP did not list adding a fibrate which is very interesting because there is primary prevention outcome data with a fibrate (Helsinki Trial) and no primary prevention data with ezetimibe or niacin. There is primary prevention data with a sequestrant (cholestyramine in the LRC-CPPT). So the clinician with NCEP recommendation could instead of potent statin use lower dose Advicor, Simcor or Vytorin or statin/Welchol.

I suspect the clinician is looking at the high risk (>80<sup>th</sup> percentile population cutpoint) LDL-P and knows it will take a strong therapy to drop the LDL-P from >1800 to < 1000 nmol/L (the 20th percentile population cutpoint in MESA), although the recent AACC statement would call for an LDL-P of < 1100 nmol/L for high risk and < 1400 nmol/L for moderate risk patients. Thus the provider is seeking advice on adding Niaspan or fenofibric acid (Trilipix). If LDL-P is the goal of therapy with have no head to head studies comparing the above choices. Individually statins, ezetimibe, niacin and fenofibrate all lower LDL-P. Statins are the best and the others as monotherapy are fairly similar depending on which study you look at (most of the data looks at apoB not LDL-P). With respect to combo therapy: statin/ezetimibe and statin/niacin are better at lowering apoB than is statin/fenofibrate or statin/fenofibric acid. In the case above the clinician seems to favor niacin because he knows HDL size will likely increase and he seems to think it is beneficial to increase HDL size. This is the part of the case I really want to discuss. We all know that in general low HDL-C is a powerful, independent predictor of risk, although there are exceptions to that generalization. Why the risk with low HDL-C?

Does low HDL-C mean there are very few HDL particles? The answer is maybe or maybe not. HDL-C is simply the cholesterol trafficked by all of the HDLs within a dL of plasma. With high HDL-C, one could have very large HDL particles without a very high HDL particle count (HDL-P) or one could have small HDL particles with a very high HDL-P. With low HDL-C one could have a normal HDL-P consisting of numerous small HDLs. Cromwell has nicely shown (*Journal of Clinical Lipidology* (2007;1:57–64) that above an HDL-C of 40-45 mg/dL, the HDL-C is a function of HDL size not HDL-P. So it is not a given that a person with an HDL-V has a terribly reduced HDL-P.

Does low HDL-C mean the HDL particles are not functional - absolutely not. HDL functionality studies show that functionality has little relationship to HDL size or cholesterol content. Likewise the constant dynamic remodeling or flux of HDLs had little relationship to HDL-C. Indeed total HDL-C has no relationship to either macrophage RCT or total RCT. HDL-C has no relationship to HDL proteomics (the critical surface proteins adding to HDL functionality).

Is the lack of large HDLs an independent predictor of risk? It sure is in studies of DRUG NAIVE PATIENTS. Why? Like increased numbers of small LDL, large VLDL-P, VLDL size, both small HDL size the lack reduced large HDL-P is often a marker of insulin resistance (note the high lipoprotein-associated insulin resistance score or LP-IR of 80). Let me explain why the lack of large HDL-P or reduced HDL size is a risk factor, but only in drug naive patients. The answer is in understanding what process causes a reduction in both HDL size and large HDL particles at the same time it increases apoB. Of course the answer is insulin resistance and elevated TG. Keep in mind that total HDL-P = Large HDL-P plus small HDL-P. In such patients who typically have high TG/HDL-C ratios (as the above patient), the liver over secretes very large TG-rich VLDL particles. The NMR as in this case reports increased large VLDL-P (a powerful marker of insulin resistance). The large TG-rich VLDL(the predecessor of LDL-P) interacts with the normally composed cholesteryl ester (CE)-rich HDLs and LDLs. Using cholesteryl ester transfer proteins (CETP) there is an exchange of TG for CE between the TG-rich and the CE-rich lipoproteins. The VLDLs become TG-poor and CE-rich (raising VLDL-C) but the HDLs and LDLs became TG-rich and CE-poor (both the LDLs and HDLs are still large, but simply carrying TG instead of CE) leading to a reduction in both HDL-C and LDL-C. Because the rise in VLDL-C is more than the reduction in LDL-C, non-HDL-C (an apoB or LDL-P surrogate) also rises. Once the large, TG-rich, CE-poor LDLs and HDLs are exposed in hepatic sinusoids to hepatic lipase, they transform into small, dense HDLs and LDLs. The former are so small they break up and the apoA-I is excreted in the urine leading to a dramatic reduction in large and less dramatic reduction in total HDL-P (as there is actually an increase in small HDL-P). In essence TG converts larger HDLs into small ones, many of which are on the catabolic path to excretion. Thus in IR patients, as TG rise, CETP activity increases and ultimately both LDL and HDL size significantly shrinks. However, just as TG lead to reduction in HDL size, they also lead to reduction in LDL size: small LDLs are less likely to be removed from plasma by hepatic LDL receptors and thus small LDL size is almost always associated by increase in small and Total LDL-P or apoB (coronary risk factor #1).

Thus the answer is: in drug naive, IR patients the absence of large HDL particles is a simply a surrogate of apoB: lack of large HDL-P is almost always associated with elevated apoB: too many TG-rich apoB particles (remnants, large TG-rich, CE poor LDLs and small CE-poor LDLs). It should be obvious that proper treatment in such patients is to direct therapy at the high apoB (total LDL-P) not HDL size per se. The HDL size should never ever be repeated once therapy is started because different drugs remodel HDL particle in very different ways and there is zero evidence that shifting HDL-C improves outcomes.

Cardioprotective drugs that increase HDL size: Niacin, statins

Noncardioprotective drugs that increase HDL size: estrogen, dilantin, torcetrapib

Drugs that lower apoB and do nothing to HDL size: ezetimibe, sequestrants

Cardioprotective Therapies that lower HDL-C, HDL size: very low fat diet (Ornish), probucol (CETP inducer).

Drugs that shrink HDL size increase HDL-P and slightly influence HDL-C: Fibrates. In the VA-HIT study gemfibrozil barely raised HDL-C, yet dramatically raised total (mostly small) HDL-P and reduced large HDL-P ((Circulation. 2006;113:1556-1563).

Thus in the case above, the major treatable risk factor is high LDL-P which is simply due to the elevated TG increasing both VLDL-P, primarily LDL-P and reducing HDL-P. Therapy with lifestyle is crucial and TG usually respond so well to that. Both niacin and fibrates are powerful TG lowering drugs. However because fibrates increase hepatic scavenger receptors B1 or SR-B1 (the hepatic HDL delipidation protein) and niacin does not, large CE-rich HDLs are delipidated in patients on fibrates, leading to a reduction of large HDL-P but an increase in small and total HDL-P. Niacin by inhibiting the hepatic holoparticle or catabolism receptor (beta-chain apoA-I synthase), slows hepatic internalization of large HDLs, increasing their half life and increasing their number. Because this patient had both a high TG and low HDL-C (exactly the type of patient that responds so well in the fibrate trials) a fibrate or fibric acid makes perfect sense: however one would further reduce large HDL-P but significantly increase total HDL-P, slightly increase HDL-C (who cares) and of course the fibrate would help further lower apoB and LDL-P. The niacin would increase dramatically HDL size, large HDL-P, total HDL-P (likely less than a fibrate), HDL-C (more than a fibrate) and would also help lower apoB (an underappreciated benefit of niacin). The doc does ask if there is much fibrate benefit if TG are less than 200 mg/dL and the answer is if you review most of the fibrate trials no there is not (exception: the benefit of gemfibrozil in the IR patients in VA-HIT had no relationship to baseline TG or HDL-C).

For those who have been getting the new LipoScience report form (when the blood is sent directly to Raleigh, not LabCorp) you get the LP-IR score: insulin resistance is based on a formula using LDL size, small LDL-P, large VLDL-P, VLDL size, large HDL-P and HDL size. This derived LP-IR is a predictor of T2DM onset and CV risk. However, because different drugs remodel lipoproteins very differently, the LP-IR has no meaning in patients on medication (especially fibrates and niacin). We all know niacin has the potential to increase IR, yet by increasing large HDL-P and HDL size, it would lower the LP-IR. On the other hand fibrates, which reduce HDL size and lower large HDL-P

would increase the IR score: yet there is some data that fibrates may actually improve insulin sensitivity.

So as always my suggestion in high risk patients is to blow away LDL-P and then increase total HDL-P using lifestyle and FDA approved therapies and hope you are also making the HDLs functional (which we cannot measure). In the above case you have to ask is he high risk? If so one could defend statin/ezetimibe, statin/Niaspan (Simcor) or statin/feno (new combo product using rosuvastatin and fenofibric acid called Certriad may appear soon). If I used statin/ezetimibe, on follow up if the total HDL-P was still low or the LDL-P still high I would then titrate in the Niaspan. If I used Simcor (or other statin/Niaspan combo) or statin/fibrate and the LDL-P was still high I'd simply add ezetimibe. Perhaps as we all try using the new liquid Welchol, it may become a more popular add on choice if patient compliance increases compared to oral Welchol. Remember this man had glucose of 115 mg/dL, which colesvelam would help. The clinician also worried Niaspan use might induce T2DM: that would be rare, but glycemic indices would have to be followed.

On our web site [www.lipidcenter.com](http://www.lipidcenter.com) under professionals there is a pdf describing in more detail HDL remodeling by drugs. Check it out