

LIPID CASE 263 Is it or is it not isolated low HDL-C?

I was just recently asked to help out with what else: low HDL-C. Can you answer this question? When is it proper to call a low HDL-C vale "isolated?" Pick an answer: I'll provide mine and then tell you what NCEP ATP-III states later.

- 1) HDL-C below 40 but TC, LDL-C and TG all normal
- 2) HDL-C below 40 with normal LDL-C - TG can be variable (normal or high)
- 3) HDL-C below 40 with variable lipids but normal apoB and/or LDL-P
- 4) HDL-C below 40 with normal LDL-C normal LDL-C, normal TG and normal apoB/LDL-P
- 5) Simply a low (< 25th percentile) apoA-I or HDL-P in the setting of normal apoB and LDL-P.

The case was sent by a Midwestern cardiologist asking advice on a 54 year old male, with an unremarkable past medical history. He has not had a checkup for a decade. He is normotensive, with a normal BMI (23), who exercises like a olympian. There is no premature CAD in his 1st degree relatives but a paternal grandfather died of MI- unknown age- (suspects it was young < 50 years). A maternal uncle died of MI in his early 40's; The patient presented with symptomatic paroxysmal atrial fibrillation.

Labs:

TC = 151 LDL-C 85 TG = 189 HDL-C = 28 Non-HDL-C = 123 VLDL-C = 37

NMR LipoProfile:

LDL-P 1437 nmol/L (optimal < 1000 nmol/L)
Small LDL-P 1376 (increased)
LDL Size 19.3 (pattern B)
HDL-P 26.5 umol/L (bottom 25th percentile population cutpoint)
Large HDL 0.9 umol/L (very low)
HDL Size < 8.3 (quite small)

The cardiologists states: "*Exercising as much as he does, why is his HDL-P, and HDL-C, and large HDL-P SO UGLY??? Is this Hypoalphalipoproteinemia? A non-lipidaholic provider of course would look at LDL-C only- 85 , see its below goal of 130 (Framingham risk is 4%) and perhaps think they were done. A cardiologist might look at his total LDL-P (but ignore other parameters in the NMR report), and conclude 1437 nmol/L is 10% away from goal of 1300 nmol/L and prescribe therapeutic lifestyle.*" The card concludes he is a Dayspring Padawan (he promised he would not ever refer to me as Yoda or Quigon) and when he looks at other NMR parameters he is very worried about the HDL-P and even more worried about his SKY HIGH Small LDL-P of 1376! Lastly he stated he was going to check a CIMT, but thinking ahead, he thought this guy would be a perfect Simcor candidate - get up that HDL and drive down the LDL-P?"

Man that is a lot of questions form a cardiologist but I am not usually at a shortage of words - so here goes:

DAYSFRING ANALYSIS:

It is important that the card looked at the patient using conventional standards like NCEP. Because of age and the low HDL-C (an independent risk factor for CHD) the patient qualifies for Framingham Risk Scoring (FRS) and his ten year risk for an event is quite low. Quick point: the patient was drug naive - had he been on meds FRS is not a validated tool and it is unfortunate so many clinicians utilize FRS with folks on lipid meds. It is even more important that the clinician realized the limitations of FRS and went to advanced lipoprotein testing. How many readers performed the following calculations: TC/HDL-C = 5.3 TG/HDL-C = 6.7. Both are quite abnormal. I would have looked at the markedly increased TG/HDL-C ratio, diagnosed a TG/HDL-C axis disorder (Am Heart J 2004;148:211–21) and rapidly concluded the patient has two of the three needed criteria for the metabolic syndrome. Insulin resistance thus enters the diagnostic possibilities. For those who think the patient's slimness rules out this diagnosis I caution you: Using NHANES data 20% of patients meeting Met Synd criteria have a BMI less than 26 - they are called metabolically obese (Diabetes Care 27:2222–2228, 2004). So if we believe this man has metabolic risk - what the heck could we offer to this exercise "fiend" with respect to lifestyle advice? I was not provided with the lipoprotein-related insulin resistance score now provided by LipoScience or labs providing NMR parameters like HDL in Richmond, VA (www.myhdl.com) or Cleveland Heart Lab (www.clevelandheartlab.com).

As far as the etiology: sure looks like insulin resistance with the high TG & low HDL-C. Using NHANES data 20% of folks with full blown metabolic syndrome have a BMI < 26. They are called "metabolically obese." Did you have an Lp-IR score? If CETP activity is increased even subtle hypertriglyceridemia (anything > 70) can cause exchange of TG for cholesteryl ester. The LDLs will be TG-rich and CE-poor and after exposure to hepatic lipase and other secretory lipases transform into smaller particles which are less effectively cleared by LDL receptors. This is why it is near impossible to predict LDL-P in IR patients. Same thing happens to the HDLs. They become TG-rich, undergo lipolysis with HL and endothelial lipase and get so small they are pissed away.

What is the lipoprotein pathology at play? Is it primarily an apoB disorder, an apoA-I disorder or both and if the latter are they related? Is this some genetic hypoalphalipoproteinemia? Clearly there are too many LDL particles, and almost all of them are small (Pattern B). The provider seems frightened by the fact the small LDL-P is > 1300 nmol/L and likely considers < 600 nmol/L as normal. The parameters that frightens me the most is the Total LDL-P of > 1400 nmol/L. I keep stating that what drives apoB-containing lipoproteins (chylol and VLDL remnants, IDLs, and LDLs) into the vessel wall is particle number and not particle cholesterol content or particle size. A person having too many LDLs has increased CV risk whether the LDLs are small or big. All of the previous data that suggested small LDLs were the most dangerous come from studies where no one ever adjusted for LDL-P. Whenever that adjustment is made, LDL size is no longer an independent predictor of risk (see Atherosclerosis 2007;192:211–217 and J Am Coll Cardiol 2007;49:547–53). Persons with familial hypercholesterolemia have the worse CV disease rate (far higher than T2DM patients) and they have primarily large LDL particles. I realize the small LDLs are more easily oxidizable, carry phospholipase A2, etc., but the evidence is that all LDLs, if present in increased numbers are atherogenic. I am sick and tired of reading in peer-reviewed journals about the highly dangerous, more atherogenic small LDL as if the fluffy buffy counterparts are not as deadly. Risk is related more to particle number than to size. That belief is no longer supported by evidence.

Before totally dismissing small LDLs, they do present a very difficult therapeutic challenge. When we use drugs that primarily upregulate LDL receptors (statins, ezetimibe, sequestrants like colesevelam) it is very difficult to normalize LDL-P or apoB if the LDL size is small. ApoB assumes a different conformation on small compared to big LDL particles and the apoB

conformation on the smaller (or indeed very large) LDLs is not as easily recognized by LDL receptors (LDLr) (J Lipid Res. 1991;32:1741-1753). It is believed but not proven that shifting LDL size from small to normal would facilitate LDLr uptake of LDLs. Normally significant TG reduction is required to cause an upward shift in LDL size. In the COMBOS trial where N-3 FA acids (Lovaza) were added to statin, LDL size did not increase much until a TG of 150 mg/dL was attained. So this patient's LDL phenotype suggests combination therapy may be needed to aggressively reduce LDL-P. Taking this point further: the goal of therapy is therefore total LDL-P or apoB. There is no evidence that once LDL-P and apoB are at goal that LDL size has any meaning.

How about the HDL situation. All parameters are quite low: HDL-C and total HDL-P and large HDL-P and although not reported if total and large HDL-P are significantly low, then small HDL-P is also likely low. NMR does not measure prebeta-HDLs, only alpha HDLs. A consensus group of top HDL experts met at the end of 2009 and a manuscript getting into some standardized HDL nomenclature should hopefully be published in the near future. Briefly: HDLs consist of unlipidated apoA-I, prebeta HDL species (1 and 2), more mature species called alpha (with 4 being the smallest and 1 being the largest). For a just published review of HDL dynamic remodeling see Schaefer et al. Current Opinion in Lipidology 2010, 21:289–297. Anyone with a significant reduction in HDL-C has to lack large HDLs. Just like LDLs, and despite a widely held belief, there is no HDL subspecies that is any more cardioprotective than the next. I can forward dozens of references showing that there is no particular cardioprotective HDL species. Prebeta's are quite crucial to initiate HDL lipidation. ATP binding cassette transporters A1 and G1 are crucial to lipidation and maturation (the enzyme LCAT also plays a role). Apart from the prebeta species, HDL functionality has nothing to do with HDL size and lots to do with HDL proteomics and HDL phospholipid content. The reason a lack of large HDL-P is an independent risk factor is that it is large HDL particles are usually missing in insulin resistant patients (who have increased CV risk). The large HDL is reduced in number because the increased TG and cholesteryl ester transfer protein (CETP) activity typical of IR patients makes the HDLs TG-rich and CE-poor. Such HDLs become substrates for the lipolytic actions of hepatic lipase and endothelial lipase and they are transformed into small HDLs, the smallest of which break up enabling renal excretion of apoA-I. Such patients have low HDL-P, low HDL-C, very few large HDLs, reduced small HDLs and most importantly high LDL-P and apoB. So my guess is this is not a genetic hypoalphalipoproteinemia but rather one induced by IR and elevated TG and increased CETP activity. HDL mapping at Boston Heart Lab can be used to clarify this.

Therefore the real danger in this patient (apart from the elevated LDL-P) is that the total HDL-P is in the bottom quartile of HDL-P concentration of < 27 umol/L (using MESA data). Combine that with the elevated LDL-P and there is a very high LDL-P/HDL-P ratio. In the VA-HIT trial this particular ratio was the most predictive ratio associated with CV risk (significantly more predictive comparing it to the TC/HDL-C and apoB/apoA-I ratios). The LDL-P/HDL-P calculation of 54.2 in this patient puts him into tertile 3 of 4 using VA HIT data (with higher tertiles associated with increasing risk): see Table 5 in Circulation. 2006;113:1556-1563.

So how did you respond to the question above about the definition of isolated low HDL? Here are some random NCEP ATP-III (final report published in 2002) statements about low HDL-C (all direct quotes - Circulation 2002;106:3145-3421).

- a) A categorical low HDL-C should be defined as a level of <40 mg/dL, in both men and women. If and only if a woman has the metabolic syndrome than an HDL-C < 50 is abnormal.
- b) Whether raising HDL per se will reduce risk for CHD has not been resolved. (still true in 2010)

c) Some persons with severe deficiency of HDL do not manifest premature CHD; this suggests that HDL is not uniquely involved in atherogenesis, as is LDL.

d) A specific HDL-C goal level to reach with HDL-raising therapy is not identified.

e) In some persons, low HDL-C levels can occur in the absence of other lipoprotein abnormalities. These persons are said to have isolated low HDL. **They are not common in the general population**, however; **MORE OFTEN**, low HDL-C occurs as a component of the lipid triad (elevated triglycerides, small LDL particles, and reduced HDL-C. But it gets more complicated: NCEP elucidates further: the term isolated low HDL can be reserved for HDL-cholesterol levels <40 mg/dL in the presence of serum triglycerides <150 mg/dL.

f) A low HDL-C can be a marker for the metabolic syndrome; many persons with isolated low HDL have the other risk factors characteristic of this syndrome.

g) Meta-analyses of statin trials showed no difference in benefit of LDL lowering between high HDL and low HDL strata. These studies taken together document that lowering LDL-C in persons with isolated low HDL significantly reduces risk for CHD.

So the correct answer to the question posed at the top of the discussion is # 4 (scroll up to review) and the proper therapy in patients with isolated low HDL-C is to normalize apoB - LDL-P (or their lipid surrogates LDL-C and non-HDL-C). Therefore this patient under discussion does not have isolated low HDL-C as his TG are high and his LDL-P is high (mostly because of too many small LDL particles).

PLEASE STOP USING THE TERM ISOLATED LOW HDL IF YOU HAVE NOT DONE APOB OR LDL-P. If apoB or LDL-P is high, the low HDL-C is not ISOLATED. My preferred definition (which keeps it simple and accurate) would be #5 (Low total HDL-P and apoA-I with normal apoB and LDL-P). In this scenario the low HDL-C is indeed isolated. The next take home point is that first line treatment for patients **at CV risk** with isolated HDL-C is to normalize apoB and LDL-P (or their lipid surrogates). This is exactly the therapeutic strategy recommended by the ADA/ACC consensus statement on managing CV risk in patients with cardiometabolic risk (Diabetes Care 2008;31:811-822). Should we raise HDL-P?? VA-HIT certainly showed that in insulin resistant patients, raising HDL-P with a fibrate reduced events.

In a second paper looking at HDL in VA-HIT patients: an altered baseline HDL subpopulation profile marked with low alpha-1 and alpha-2 levels and a high alpha-3 level in coronary heart disease patients indicated an elevated risk for new CVD events. Moreover, prebeta-1 and prebeta-2 levels were superior to HDL-C levels in risk assessment in patients with low HDL- (Arterioscler Thromb Vasc Biol. 2005;25:2185-2191). So in this analysis of IR patients in VA-HIT with high TG and low HDL-C, the lack of large HDL species was a risk factor. Of course the only place to get prebeta and alpha HDL concentrations are to order HDL Mapping at Boston Heart Lab (www.bostonheartlab.com). Amazingly even though the lack of large HDL was a predictor of risk: once gemfibrozil was used most of the event reduction was related to the increase of Total HDL-P, the vast majority of which were small HDL particles. Remember even though the fibrate only increased HDL-C by 6% (1.8 mg/dL) over all and 3% (0.9 mg/dL) in the IR patients, the total HDL-P increase was 10%. Increasing small HDL-P cannot be associated with much of a rise in HDL-C. Keep in mind how fibrates modulate HDL: they cause increased production of apoA-I and apoA-II, upregulate ABCA1 (which lipidate prebeta HDLs) and they upregulate hepatic scavenger receptors B1 (SR-B1) which shrinks the HDLs. Thus fibrates increase total HDL-P primarily by increasing small HDL-P. The rise of HDL-P is out of proportion to the rise (often trivial) in HDL-C.

As mentioned, this patient does qualify for the term hypoalphalipoproteinemia as his total HDL-P is in the bottom 25th population percentile cutpoint (using MESA data). He also qualifies for

NCEP's definition of isolated HDL-C but not the Dayspring definition as his LDL-P is still much too high. To me this supports IR, not a genetic cause of the low HDL. As mentioned above the primary goal is to improve the LDL-P and conjecture (need a trial to prove it) would say a secondary goal is to raise total HDL-P. I cannot disagree with the cardiologist's analysis and his suggested therapy (simvastatin plus extended release niacin or Simcor). Except: my goal for LDL-P (simply because of the genes and high LDL-P/HDL-P ratio) would be an LDL-P < 1000 not 1300 nmol/L. I'd also like to (it may not be possible) to raise HDL-P and I really do not care about HDL-C as a target (of course nor I do not sweat bullets over LDL-C as the definitive goal). However, should we say this man has a profile like that seen in VA-HIT or one quintile of ACCORD. The latter is a trial of T2DM, but this man is a likely a prediabetic and if he was not so religious with his exercise T2DM would perhaps have manifested by now (I'd carefully watch glucose and HgbA1c over time). Remember in ACCORD the fenofibrate worked well in those with a TG > 200 mg/dL and a low HDL-C. So maybe a statin plus fenofibrate would be a good choice -- is Certriad (fenofibric acid/rosuvastatin) available yet (just kidding)????? When will we hear from the FDA? So the ACCORD regimen (simvastatin/fenofibrate) or a more potent statin/feno combo could be used. Finally if per chance he is statin intolerant, a fibrate/niacin combo (without a statin) reduced events and CV mortality in the Stockholm Ischemic Trial (Acta Med Scan 1988;223:405-418).

If CIMT or perhaps coronary calcium is positive add ASA unless other anticoagulation is used for the atrial fibrillation. Lastly look for other causes of IR -- Lipodystrophy disorder? HIV? Psychotropic meds. And get an omega-3 index test (www.omegaquant.com). I'd for sure prescribe at least 1000 mg or more of N-3 FA daily depending on the result.