Case # 282 Low HDL-C & HDL-P: Lifestyle or Drugs?

A provider asked for my input on the following case, namely a 63 year old man who at age 21 had his right testicle removed (associated with hernia surgery). Although he had a descended left testicle and he was hypogonadal and has been on testosterone replacement therapy since age 21. He also has chronic hepatitis C and has elected not to be treated for this. His mother died in her late 70's of melanoma and his father at 83 of lung CA. Two sisters are living and well.

He has had persistent low HDL-C. In 2003 his lipid panel was:

Total cholesterol was 187, HDL-C 39, TG = 64, LDL-C 135.
Non-HDL-C = 148 T/HDL-C = 4.7

With improved diet and exercise in 2004 His TC decreased to 145, HDL-C to 37 with a TG of 106 and an LDL-C of 87. Non-HDL-C was 108 and the TG/HDL-C = 3.9

In 2009 a Berkeley profile was done on him.

TC = 139, HDL-C = 35, LDL-C = 94, TG = 48,
LDL III a+b 23.9 (high), LDL IV b 2.6 (N)
HDL 2b 10 (borderline),
Apo B 72 mg/dL
Lp(a) = 2
Homocysteine = 14.1. umol/L

He was treated with simvastatin 20 and titrated to 40 mg daily. The follow up lipid and NMR LipoProfile was:

TC = 100 mg/dL, HDL-C = 34, TG = 33 and LDL-C = 59.
Total LDL-P = 855 nmol/L
HDL P = 27.7 umol/L

Niaspan was added and titrated and the values now with 40 simvastatin plus 2000 Niaspan are:

TC= 92, TG= 34, HDL-C = 39 and LDL-C = 46.
Total LDL-P 804 nmol/L
Total HDL-P = 28.7 umol/L

The provider asks: “In light of the recent Niaspan study would you a) sit tight, b) stop Niaspan and try TriCor or something else?

DAYSPRING DISCUSSION

Basically we have an on-treatment eugonadal male who has also been aggressively treated with lipid-modulating therapy because of a low HDL-C. Was such treatment even indicated? One thing NCEP has always gotten right is that treatment as well as the goal of therapy depends solely on the risk of the patient. If we look at the history and initial lipid profile he qualifies for Framingham Risk scoring because he has two major risk factors, namely his age and a low HDL-C. His calculated ten year risk is 12% which places him in the moderate risk category. His goal of therapy would be an LDL-C < 130 mg/dL with an option for < 100 mg/dL. According to NCEP ATP-III non-HDL-C goals would not apply because his TG are < 200 mg/dL. However newer data now teaches us that non-HDL-C always predicts risk better than LDL-C irrespective of the TG level (Am J Cardiol 2006;98:1363–1368).

So looking at his initial lipid values his LDL-C and non-HDL-C (the poor man's LDL-P) were not at the optional goals of therapy. Looking beyond the guidelines the TG/HDL-C ratio was 4.7, which is associated with increased total and CV mortality in men and an 80% or greater that his LDL particles are small. The risk of small LDL is related to the fact that virtually all drug-naïve patients with small LDLs have a high total LDL-P (the number one risk factor for atherogenesis). Because the volume of a sphere is related to third power of the particle's radius it takes 40-70% more small than large LDLs to traffic a given mass of cholesterol. Have you ever thought about why some folks with small particles with have 40% more LDL particles and others will have 70% more particles—why is that?

It comes down the fact that LDL particle number is related to the number of cholesterol molecules per particle. The more molecules or the fewer molecules a given LDL particle can carry will ultimately determine how many total LDL particles are needed to carry the mass of cholesterol molecules that exist per deciliter or liter of plasma. So if one compares LDL particles carrying 2500 molecules of cholesterol to those carrying 1800 molecules, it should be obvious that less particles capable of carrying 2500 molecules (cholesterol-enriched) will be needed to traffic a given cholesterol mass than particles capable of only carrying 1800 molecules (cholesterol-depleted). Thus what actually determines the total LDL particle count (LDL-P) are those metabolic or drug-induced situations where LDL particles are cholesterol depleted.

1) Small LDLs are more cholesterol-depleted than large (volume of a sphere is $4/3\text{pi}(\text{radius}^3)$
2) LDLs carrying TG at the expense of cholesterol will be cholesterol-depleted. Thus anyone with an elevated LDL-TG will have a cholesterol-depleted LDL particle. These LDLs may be large or small—the more TG they pack, the less cholesterol they can carry. A normally composed LDL has a $\geq$ 4:1 ratio of cholesterol to TG.
3) Statins reduce LDL particle cholesterol more than they do LDL particle number and thus can make LDL particles cholesterol depleted. Thus many folks on statins achieve LDL-C goal without achieving LDL-P goals.

If you wonder how LDL particles acquire TG, there are two possibilities. A larger, TG-rich VLDL upon the lipolytic action (hydrolysis of TG) of lipoprotein lipase becomes a TG-rich IDL which after further lipolysis creates an LDL particle where the CE/TG ratio is < 4.0 (CE = cholesteryl ester). More common is TG-rich VLDLs, chylomicrons and IDLs swap their TG for the CE within an LDL particle using the lipid transfer protein called cholesteryl ester transfer protein (CETP, also called apolipoprotein D. When apoB-containing lipoproteins (chylos, VLDLs, IDLs and LDLs) exchange TG for CE, this process is called homotypic transfer which contrasts with the process of apoB swapping TG or CE with apoA-I containing HDLs which is called heterotypic exchange. Bottom line: if a small or large LDL acquires TG from other LDL particles that LDL will become CE-depleted and more will be required to traffic a given cholesterol mass. As LDL-P rises, the particles will enter the artery.

Is non-HDL-C really the poor man's LDL-P? The tragedy is that it is not and is unfortunately being used as such by way too many people. Let me explain. Non-HDL-C is actually apoB-C, or the cholesterol mass trafficked by all of the apoB-containing particles almost all of which are VLDLs and LDLs. Yet the half-life of a VLDL particle is 2-6 hours and that of an LDL 1.5 to 3 days. Small LDLs which are not as efficaciously cleared compared to large LDLs have a half-life of up to 5 days. Thus 90-95% of apoB particles are LDLs. Thus apoB is simply another assay that provides the clinician the LDL particle concentration. VLDL-P contributes very little to apoB (~ 5%). Non-HDL-C is apoB cholesterol and most of the apoB particles are LDLs. So most believe if non-HDL-C is an apoB surrogate, lowering non-HDL-C would be an excellent indicator that the therapy is reducing LDL-P. Indeed is not that why NCEP ATP-III gave us non-HDL-C goals.

So if I add ezetimibe (Zetia) or niacin (Niaspan) or colesevelam (Welchol) to a statin I get additional LDL-C, non-HDL-C, apoB or LDL-P reductions than I would get with the statin itself. No one can argue with that. Indeed back in 2001 when NCEP ATP-III was published, they stated that when on statin therapy non-HDL-C was not at goal in patients with TG > 200 mg/dL one could increase lifestyle or add a fibrate or add niacin: Zetia was not yet available in 2001.

Non-HDL-C = TC – HDL-C or
Non-HDL-C = LDL-C + VLDL-C where VLDL-C = TG/5

Zetia lowers LDL-C and TG (VLDL-C) a bit and helps lower non-HDL-C
Niaspan lowers LDL-C, significantly lowers TG (VLDL-C), and nicely raises HDL-C and thus help further reduce non-HDL-C
Fibrates do little to LDL-C, raise HDL-C a small amount and very significantly lower TG and hence VLDL-C. Thus fibrates added to statin significantly further reduce non-HDL-C

So if the above three drugs can help a statin-treated patient achieve non-HDL-C goal you would presume statin/ezetimibe, statin/Niaspan and statin fenofibrate would all further

reduce apoB or LDL-P beyond what a statin can do. If that is not true then no one should be using non-HDL-C as a goal of therapy. Well here is the reality:

Statin + Zetia or statin plus Niaspan cause significant additional LDL-P lowering than statin monotherapy. Neither Zetia nor Niaspan increases HDL-P beyond what a statin does.

Statin + fenofibric acid does not lower LDL-P beyond what a low or moderate dose statin does. Yet statin/FFA significantly lowers non-HDL-C beyond what a statin does. What is feno doing? By drastically lowering TG by inhibiting VLDL synthesis and increasing VLDL catabolism (reducing VLDL half-life) does lower VLDL-C and VLDL-P. If one looks at apoB, adding FFA to a statin understandably does give an additional 5% apoB reduction. There is also a very significant HDL-P increase (beyond the ~5% provided by a statin).

We certainly have no comparative outcome data with statin/Zetia, Statin/Niaspan or Statin/fibrate. We do have outcome data in patient with high TG and low HDL-C with statin + feno (FIELD metabolic syndrome group and ACCORD). So even though statin/feno does not give one additional LDL-P beyond a statin, the combo seems to work if TG are high. Is it the rise in HDL-P, or an increase in HDL functionality, or a decrease in remnants, or other pleiotropic effects? Who knows? But for sure non-HDL-C is not an apoB or LDL-P surrogate in patients on statin/feno.

Statin + Zetia = significant apoB and LDL-P lowering: no HDL-P effect beyond the statin. No outcome evidence exists

Statin + Niaspan = significant apoB and LDL-P lowering: no HDL-P effect beyond the statin. No outcome evidence exists

Statin + feno = no LDL-P benefit beyond the statin, a 5% apoB reduction (due to VLDL-P reduction) and a very significant 10% increase in HDL-P beyond what a statin causes. Level 2 outcome evidence exists

Back to the case at hand: Once LDL-P is at goal you are theoretically done because at this time there is no HDL-P (and certainly no specific HDL-C) goal of therapy. However in insulin resistant men there is data that raising HDL-P can be associated with better outcomes (VA HIT trial: Circulation. 2006;113:1556-1563). This patient is presumably insulin resistant based on the original high TG/HDL-C ratio but patient was at lipid (LDL-C and non-HDL-C) as well as LDL-P goal after therapeutic lifestyle. So following all guidelines that currently exist, there was probably no need to start drug therapy with a statin and absolutely no indication to add Niaspan to it.

No doubt because of the low HDL-C the provider assumed residual risk was present and he added a statin. Prior to that, a Berkeley profile showed a perfect apoB of 72 and a normal Lp(a) mass. Homocysteine was high. I do not think there is a lot of data showing that if apoB or LDL-P is fine (at goal), that a low HDL-C is predictive of residual risk. In the Dean Ornish study (Lifestyle Heart Trial – Lancet 1990;336:129-133), the very low

fat diet drastically reduced TC (as in this case and lowered HDL-C but there was significant improvement in plaque on angiograms. In this man statin/Niaspan therapy lowered TC to 102 and LDL-C to 46 and LDL-P to 854, but the HDL-P was still low. Note that the 2000 mg of Niaspan did not raise the HDL-P to any significant extent.

It might be nice to raise total HDL-P, but other than use of statin and lifestyle there is no way to do it. Niacin has no effect on HDL-P (as you can see in this case). Fibrates can raise HDL-P, but only in IR persons with high TG. The niacin did further lower LDL-P a bit. The only reason niacin raises HDL-C is that it makes HDL particles larger and they carry more cholesterol per particle (not very important) but I does not raise total HDL-P (J Clin Lipidol 2011;5:368-370). We all must come to the realization Niaspan is an apoB (LDL-P) lowering drug (and a superb one at that) and one should not think its effect on HDL-C is relevant to any of its benefit. If you do want to raise total HDL-P you need a statin or a statin/feno combination. Because of TG being superb in this man, and his moderate (not high or very high CV risk) I would not add fenofibrate or fenofibric acid in such a case. If he was on say his second stent (very high risk) I might.

We will get the publication of AIM High a week from Tuesday when it will be presented at the AHA Scientific Sessions in Orlando. I sure hope they release the NMR data. Of course we now know there may be no event reduction with niacin in such patients (I believe because the statin or statin/ezetimibe had apoB, LDL-C and non-HDL-C at goal at baseline, that this trial was doomed from the start as one would not expect an apoB lowering drug like niacin to help those with normal apoB levels). So you can hold the status quo with the current regimen or use Zetia/statin instead of Niaspan