Case # 277 Niacin, statin or both or neitherin a high risk woman?

THE CASE: The case is a 49 year old woman who has a family history of early CAD in her father. She does not have hypertension or diabetes nor does she smoke. Her BMI is 31, but otherwise her vitals are normal. A recent CIMT revealed increased risk of CAD. Her labs done at Health Diagnostic Labs in Richmond VA are as follows:

TC = 116, LDL-C = 56, HDL-C = 40, TG = 58, Non-HDL-C = 55 (all in mg/dL)
TC/HDL-C = 2.9 TG/HDL-C = 1.45
ApoB = 44 mg/dL, ApoA-I = 124 mg/dL
Total LDL-P = 707 nmol/L Total HDL-P = 25.1 umol/L
HDL2 = 11 mg/dL

The provider notes: I am concerned about her CVD risk, and have started her on simvastatin/Niaspan. I recognize her LDL–C is low, but I am uncomfortable with using Niaspan alone, especially in view of the recent AIM-HIGH study. The doc then asks if he should discontinue the simvastatin or continue both medications. He notes that the results of the ARBITER studies were a major influence on his choice of treatment. He was seeking my comments.

Dayspring Comments: All cases come down to (1) proper risk assessment, (2) determining the proper goal of therapy, and (3) then trying to achieve that goal using lifestyle and if needed pharmacotherapy. Issues one and two have been done conventionally using lipid concentrations but a more contemporary (cutting edge) approach involves using lipoprotein concentrations.

Despite the doc's concern that she needs more aggressive treatment she is actually at both lipid and lipoprotein goals. If one considers her a high risk patient because of the abnormal CIMT (subclinical disease), one should realize that she has an LDL-C and non-HDL-C level that are below all lipid guideline goals and indeed her LDL-P and apoB are below lipoprotein goals. All my readers certainly know, due to a lack of level one evidence there is no specific NCEP ATP-III HDL-C goal and none of the lipoprotein management statements (ADA/ACCF, AAAC, Canada) have issued an HDL-P or apoA-I goal. Therefore despite being on no lipid meds, since she is at LDL-C, non-HDL-C, apoB and LDL-P goal no drug treatment (other than continued lifestyle to improve the BMI) is called for.

There are plenty of studies indicating there is usually significant residual risk when one is at LDL-C goal but HDL-C is still abnormally low but there is also a lot of data suggesting that such residual risk is in large part related to persistently high apoB/LDL-P so typical in patients with low HDL-C levels. But are there any published studies showing that if apoB or LDL-P is at goal, that treatable residual risk exists or does not exist? I am not aware of such data.

The answer might be in data from the recently stopped AIM HIGH trial. Patients with stable CAD (with a very high incidence of T2DM and/or metabolic syndrome) were enrolled, 92% of whom had their well lipids treated (with statins or other meds). At

baseline prior to randomization with simvastatin (with or without ezetimibe) or simvastatin (with or without ezetimibe) plus extended release niacin (Niaspan). The lipid/lipoprotein values were: mean LDL-C was 71, HDL-C was 34 and non-HDL-C was 106. The median TG was 160 and the mean apoB of 81 (all values in mg/dL). Please see Am Heart J 2011;161:538-43. An apoB of 81 is at the 20th percentile population cut point (normal for a high risk patient). In other words almost all (92%) patients in AIM HIGH had normal apoB (LDL-P data will ultimately be available) with a concomitant low HDL-C and elevated TG/HDL-C ratio. In the face of the normal apoB with low HDL-C the addition of niacin provided no additional clinical benefit (even though niacin raised HDL-C). But I ask why would niacin add benefit if apoB is normal? Despite the widespread belief that niacin's primary benefit is raising HDL-C in reality it is apoB lowering. So applying this to the case at hand, why would one add Niaspan to a statin in a woman with a perfect apoB and LDL-P? One should not. But please note if the apoB was high niacin monotherapy works. There is outcome data and angiographic benefit when niacin is used as a monotherapy. My guess is that if in AIM HIGH the baseline apoB was still high despite statin or statin/ezetimibe niacin would have brought additional clinical benefit due to its apoB lowering capabilities. Adding niacin to further reduce an already normal apoB does not make a lot of sense and it now appears that is exactly what happened in AIM HIGH.

So if the residual risk related to low HDL-C is mostly related to elevated apoB/LDL-P then there is no reason to start any lipid/lipoprotein-modulating medication. Based on VA HIT and other data, perhaps total HDL-P should be increased (if it is low) but that is a formidable clinical challenge. Please go back and read my detailed discussion of Aim HIGH in the last issue this newsletter where I listed all of the data showing that even though niacin raises HDL-C, it does not raise HDL-P: the HDL-C rise see with niacin administration is due to an upward shift in HDL size. Increasing HDL size per se has no known therapeutic relationship to event reduction. At this time with respect to current medications and outcome reduction it is speculative at best correlating event reduction to what a drug does to HDL-C. For this very reason there is certainly no specific HDL-C goal in NCEP.

Because of potential discordance, normally I do not consider low LDL-C (by itself) as being very informative. I am more impressed by low LDL-C in the face of a very low TC. However once we see that the low LDL-C is concordant with the low LDL-P, we should all be reassured. Her risk has been much reduced from what it was when her LDL-P was likely high. As mentioned above, in AIM HIGH the baseline apoB was normal at 81 mg/dL, (not as good as this patient) and in AIM HIGH adding niacin to a statin, despite the low HDL-C did nothing. If this patient has a low total HDL-P – should it be raised? There is some data that raising HDL-P matters (VA-HIT). Statins have the ability to raise HDL-P a bit. The only other drug that can significantly raise HDL-P further is a fibrate but current data suggests they are not really associated with event reduction in patients with TG < 200 mg/dL.

Henceforth, pending future data, niacin at this time can be used by itself, added to a statin or a fibrate for improvements in LDL-P and apoB (the lipid surrogates of which are LDL-

C and non-HDL-C) but for not for any HDL-modulating reasons. With respect to the other question asked by the provider regarding the ARBITER studies, I have no idea what those studies proved that has use in the real world: There is no data that what a drug does to IMT measurements (or any other imaging modality) has any statistically significant relationship to outcome benefit. Certainly AIM HIGH did not support the conclusion of ARBITER that adding niacin to an LDL-C lowering therapy (a statin) would reduce events. ARBITER did not prove that adding ezetimibe to a statin would not reduce events. If the ARBITER results had any translational meaning, then AIM HIGH would have been a positive trial. Tragically no lipoprotein concentrations were done or reported from ARBITER. This may be the only lipid trial in the new millennium where lipoproteins were not measured. How is that possible?

Bottom Line: Evidence based medicine supports getting apoB and LDL-P (or their lipid surrogates to goal. Statins are the best apoB lowering meds: additional LDL-P lowering can occur by adding in alphabetical order: colesevelam, ezetimibe or niacin. Adding a fibrate or omega-3 FA to a statin does not further lower LDL-P. The fibrates and omega-3 would lower apoB by 5% (remnant lowering – with no effect on LDL-P). Adding a fibrate would raise total HDL-P.

Lipid Vignette: I was asked about a patient who has a very elevated Lp(a) concentration of 349 nmol/L (normal being < 75 nmol/L). The clinician asked: Why is it that even though this is a markedly elevated level of Lp(a) that total cholesterol is not much higher? He noted that in my previous writings I have many times referenced the following equation

TC = HDL-C + LDL-C + VLDL-C + IDL-C + Chylomicron-C + Lp(a)-C + Remnant-C

The Lipid Profile is

TC = 217 mg/dL TG = 141 mg/dL HDL-C = 43 mg/dL LDL-C = 146 mg/dL

Let's plug these numbers into the above equation

TC = 217 represents the concentration of cholesterol molecules trafficked within all of the lipoproteins that circulate in a deciliter (dL) of plasma. VLDL-C is the amount of cholesterol within the VLDLs – right? Nope: Theoretically it is the cholesterol molecule concentration that is carried within **all** of the chylomicrons (not usually present when fasting), VLDLs, chylomicron remnants and VLDL remnants (the latter two lipoproteins also not present in fasting plasma in normal patients). VLDL-C is usually calculated using the Friedewald formula or TG/5 (this assumes all of the TG are within the VLDLs and the VLDL has a normal core composition of five times more TG than cholesterol and cholesteryl ester). That assumption is incorrect in almost everyone with elevated TG levels.

What is the exact meaning of LDL-C? One would guess that it represents the concentration of cholesterol molecules within all of the LDLs that exist in a dL of plasma. That guess would be erroneous. In actuality:

LDL-C = IDL-C + LDL-C + Lp(a)-C

Most labs calculate LDL-C using Dr. Friedewald's formula of :

LDL-C = TC – [HDL-C + VLDL-C] where VLDL-C = TG/5 (fasting required)

Other labs use totally nonstandardized direct LDL-C measurements (I hope you all sought out the paper I cited in the last newsletter (Reliability of LDL-Cholesterol, NonHDL-Cholesterol, and Apolipoprotein B Measurement" by John H. Contois, G. Russell Warnick, Allan D. Sniderman doi:10.1016/j.jacl.2011.05.004). **Regardless of whether the LDL-C is calculated or measured, the value represents the cholesterol trafficked within all of the IDL, LDL and Lp(a) particles that exist in a dL of plasma.**

Other than specialized lipoprotein laboratories, no lab separates IDLs, from LDLs from Lp(a) particles and then assays (measures) the cholesterol content of each. If the lipid profile is done in a fasting state most people have very few IDL particles in their plasma (it is a postprandial protein – a catabolic derivative of a VLDL that has lost much of its core TG and surface phospholipids. Thus under such circumstances IDL-C contributes very little to an LDL-C. With respect to correlating LDL-C to lipoprotein concentrations, specifically IDL-P, there is no relationship. LDL-C is a surrogate of LDL-P (although the two measures correlate they are often discordant). Note: IDL-C drives LDL-C in patients with Fredrickson's Type III dysbetalipoproteinemia.

With respect to this paragraph I urge all of you to seek out the latest (Spring 2011 edition) Lipid Spin (one of the NLA Journals) in which I authored an article entitled: "Demystifying Lp(a) Measurements." The Lp(a) value (in this case 349 nmol/L) refers to the mass of the apo(a) protein in a given amount of plasma (mg/dL or nmol/L). Most labs report Lp(a) mass in mg/dL. There is no assay that measures apo(a) in molar units as the assay does not exist. When you see Lp(a) reported in molar units (as in this case) a lab has simply multiplied the mg value by the molecular weight of apo(a) and comes up with molar units. The problem with that is no one can possibly know what the MW of apo(a) is in a given patient as two isoforms exist, a high and a low molecular weight. Apo(a) has a very variable number of amino acids (and thus differing MW) in its protein chain. What the labs who report in molar units do is take what is presumed to be an average MW of apo(a) and use that in the conversion. Clearly using a MW guess cannot be accurate in every patient since they have very variable #s of amino acids. Thus Lp(a) values represent the concentration of apo(a) and it has nothing to do with how many Lp(a) particles there are [Lp(a)-P] or how much cholesterol is trafficked by Lp(a) particles in a dL of plasma. Lp(a)-C is the measurement that refers to the cholesterol molecule concentration trafficked or carried within all of the Lp(a) particles that exist in a dL of plasma. That test is available at Health Diagnostic Labs in Richmond VA or by

Atherotech (via very different methodologies). Right now Lp(a)-C is the best surrogate we in the clinical world have of what is the Lp(a) particle count [LP(a)-P]. Of course, most patients do not have abnormal concentrations of Lp(a) particles and thus Lp(a)-C in such patients would be extremely low or zero and have no effect on the LDL-C value.

Now with respect to the patient at hand and the very high Lp(a) mass. Does this patient have a very high Lp(a)-P or does he not. If he has the high MW isoform he may have very few Lp(a)-P despite the high apo(a) mass and vice versa if he has the low MW variant [he will have a very high of Lp(a)-P]. Since we have no way of assaying his apo(a) isoform or MW, it would be very useful to have an Lp(a)-C: we would assume if that level were high (> 3.0 mg/dL) he has the low MW isoform and a high Lp(a)-P. As with all LDL particles risk with Lp(a) follows Lp(a)-P better than Lp(a)-C.

Let's assume this man has the low MW isoform: Not only would his Lp(a) be very high as it takes a lot of low MW proteins to raise apo(a) mass (in this case 349 nmol/L) but because his Lp(a)-P would be high (lots of low MW proteins attach to a lot of LDL particles) the Lp(a)-C would also be high. But how high: might range from 10-30 mg/dL. For a more detailed discussion of this (lipidologists only: see my treatise at http://www.lipidcenter.com/pdf/Entire_Lpa_Complexities.pdf

So if that was the case: this patient's LDL-C of 146 is likely:

LDL-C = IDL-C + LDL-C + Lp(a)-C
Let's assume the Lp(a)-C is 20 mg/dL
Let's assume the IDL-C = 2 mg/dL
Then the LDL-C of 146 = 2 + LDL-C real + 20
146 = 2 + 124 or IDL-C = 2 Lp(a)-C = 20 LDL-C real = 124
Thus even when folks have high Lp(a) mass and the low MW isoform, Lp(a)-C is not a super major contributor to the LDL-C value.

Bottom line: Lp(a) mass is not a measure of Lp(a)-C or Lp(a)-P. In the real world at the present time the only surrogate we have of Lp(a)-P is Lp(a)-C. The molar assay is not available to clinicians. When LipoScience reports Lp(a) in molar concentrations it is a calculated value. Note: NMR methodology cannot detect apo(a).