Case # 278 Should lipoprotein cholesterol assays disappear?

Let's get into the case: I was contacted by a provider who states: "I have a 70 year old guy with absolutely no cardiac risk factors except for his age and some erectile dysfunction (which I believe this is a strong risk factor which is not a part of NCEP ATP-III). He has had lung cancer but his weight, BP, screening lipids and glucose (84 mg/dL) are all fine. His C2 small artery elasticity index is low."

With respect to lipid/lipoprotein testing:

Total Chol = 196 HDL-C = 47 TG = 124 non-HDL-C = 149 LDL-C = 125 (all in mg/dL)
TC/HDL-C = 4.1 TG/HDL-C = 2.6
Total LDL P is 2400 nmol/L (high risk is > 1600)
Total HDL P is 30 umol/L (low)
LP IR score is 63. (> 50 signifies IR) LP IR = Lipoprotein related insulin resistant score

The physician comments that, "Certainly based on the lipid concentration data, I would not treat him, but given the LDL-P, the erectile dysfunction, the decreased artery elasticity and possible insulin resistance, I am going to treat him with a statin. I hope this is the correct route even though he has only 1 cardiac risk factor and no family history. Surprisingly, his LDL-P is high despite having a normal sugar, normal TG, normal HDL-C (the black hole) and a normal non-HDL-C. I am not a lipid expert but ask if you agree with the above? Would your goal be to get him to a moderate level for LDL-P (under 1300)?"

DAYSPRING DISCUSSION

Of course using the existing NCEP ATP-III lipid guidelines (especially the 2004 update), if subjected to Framingham Risk Scoring (because of his age) this man is at moderately high risk (12% chance of having a hard event over the next decade), with virtually all of the risk related to his age. Therefore NCEP advises that lifestyle changes and if needed drug therapy is appropriate if his LDL-C is > 130 mg/dL with a goal of keeping the LDL-C < 130 mg/dL with an option to achieve an LDL-C < 100 mg/dL. However there is a double asterisk in this category which states: *"For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level < 100 mg/dL is a therapeutic option on the basis of available clinical trial results."* Because the TG are < 200 mg/dL the non-HDL-C value is not at play. So NCEP would advise this doc that they would be OK with the use of a drug in this man to lower the LDL-C to < 100 mg/dL.

Of course I think guidelines written in 2004 are of very little use in helping us manage patients in 2011. We certainly now know that non-HDL-C, regardless of TG levels are a better predictor of risk than is LDL-C (Am J Cardiol 2006;98:1363–1368).. And there is very little serious debate that if you have them, lipoprotein particle concentration measurements are much more predictive of clinical events than are any lipoprotein cholesterol concentration measurement (TC, LDL-C, HDL-C, non-HDL-C) including

lipoprotein subparticle cholesterol measurements (small LDL-C, large or small VLDL-C, large or small HDL-C). The only debate that exists is whether lipid concentration testing should be totally abandoned in favor of particle concentrations in all. We now have 7 statements from prestigious organizations advocating particle concentration testing: ADA/ACC, AACC, NLA (debuted at May meeting: now in press), EAS, ECS (European Atherosclerosis and Cardiology Societies), and of course Canada Lipid Guidelines.

So now let's pretend we are in 2011, not 2001 and let's look at this man from a particle perspective. An LDL-P of 2400 is the 99th population percentile cut-point (using MutliEthnic Study of Atherosclerosis or MESA data), similar to what an LDL-C of > 200 mg/dL cut-point would be. NCEP called such an LDL-C an extreme elevation which calls assignment into the high risk category for immediate drug therapy even if no other CV risk factors are present. In such cases where two markers (in this case LDL-P and LDL-C) that usually have a high correlation agree, the two parameters are said to not only be correlative but are also said to be concordant. A clinician can use either value with confidence. Yet in this man the LDL-C of 125 is at the 45th Framingham Offspring percentile cut-point and at the 60th cut-point. In this scenario where two lab assays that usually correlate, but for whatever reason, do not, they are said to be discordant. In virtually every study looked at when discordance between LDL-C and LDL-P occurred risk follows LDL-P.

There is no way a clinician who is only doing lipid profiles and looking at LDL-C or non-HDL-C or TG/HDL-C ratios can have any idea which patients have LDL-C/non-HDL-C and LDL-P discordance (trust me on that – I am pretty well schooled in lipids and lipoprotein pathophysiology and I cannot predict LDL-P from a lipid concentrations with any serious degree of accuracy). If you think the discordance can be predicted by looking at TG and HDL-C, or the TG/HDL-C ratio you will often be "dead" wrong (the patient above has a normal TG/HDL-C ratio, normal TG and normal HDL-C – yet grossly discordant LDL-C and LDL-P values. In both Framingham and MESA studies when LDL-C was unremarkable and LDL-P was elevated (i.e., the values were discordant) risk followed LDL-P: Journal of Clinical Lipidology 2007;1:583–592 and 2011;5:105-113. Finally for those who obtain subparticle cholesterol concentrations – i.e. large or small VLDL-C, LDL-C, HDL-C, it provides nothing beyond standard lipid cholesterol concentrations in predicting apoB or LDL-P. You must obtain apoB <u>using standard protein immunoassays</u> (as directed in the ADA/ACC position statement on Management of Lipoproteins) or LDL-P using NMR spectroscopy. It is that simple.

Can I also bury another myth: Because it is generally stated that the 20th percentile population cut-points for LDL-C is 100 and LDL-P is 1000 (which also are commonly used as the goals of therapy for high risk patients), I have heard people who should know better state that all one needs to do is simply multiply LDL-C by 10 and you will have your LDL-P. The reality is that there is **<u>no specific relation</u>** between the milligrams of cholesterol in all of the LDL particles per deciliter of plasma (i.e. LDL-C) and the number of nanomols (10 to the 9th power) of low density lipoproteins that exist in a liter of plasma. Using my analogy that lipoproteins are dump trucks that traffic both CE and TG, the question at hand is how many dump trucks are needed to carry X amount of CE.

It will depend on how big are the dump trucks and are they empty dump trucks or partially filled with something else (such as TG).

The number of LDL particles that are needed to traffic 100 mg of cholesterol is therefore a function of both the size (diameter) of the particles and the particle core ratio of TG and cholesteryl ester (CE) - that is how much TG and CE is the particle carrying. Even if a clinician measures LDL size, he has no idea of each LDL particle's core ratio of CE to TG (normally ~4:1 in favor of CE over TG). People's LDL CE/TG composition varies significantly and cannot be guessed based on serum TG levels: two people with the same sized LDL particles who have different LDL core compositions will have very different LDL-P values. The person with the high LDL-TG will have a low CE/TG ratio (<4.0) and will therefore have CE depleted particles and a higher LDL-P than the patient with a normal LDL-TG value. For those still using the "multiply LDL-C by ten" nonsense, I have some more bad news. Using MESA cut-points, the 20th percentile LDL-P is 1000 nmol/L but the 20th percentile LDL-C is 90, not100 mg/dL. The common belief that the LDL-C of 100 mg/dL is the 20th percentile cut-point comes from a very outdated Framingham Offspring Study (FOS) analysis not MESA. Adding to confusion on this issue, the 20th percentile cut-point for LDL-P in FOS is 1100 nmol/L not 1000 nmol/L. Thus a careful reading of the recommended LDL-P goal in the AACC guidelines (Clinical Chemistry 2009;55:3:407–419.) which uses FOS values, is 1100 nmol/L, not 1000 nmol/L (the MESA 20th % cut-point).

It is now therapeutic decision time. After lifestyle there is no doubt a statin is the first line med to get to goal. It would be very easy to achieve NCEP optional LDL-C goal of < 100 mg/dL in this man with a low to moderate dose statin, and if that is all I wanted to do, pitavastatin (Livalo 2-4 which would be a good choice especially in the elderly because of its very clean pharmacokinetics) or baby rosuvastatin (Crestor 5-10 mg) would also be fine. Emerging data also seems to indicate pitavastatin is very different that other statins including rosuvastatin with respect to glycemic issues and diabetes onset. However, there is almost no chance that any statin, even if one started 40 mg of rosuvastatin (Crestor) that LDL-P goal could be achieved (note that 40 mg of Crestor is an off label starting dose). Even in a statin hyper-responder dropping an LDL-P of 2400 to 1000 nmol/L is probably wishful thinking. Over synthesizers of cholesterol have excess HMGCoA-reductase activity), and can be diagnosed by ordering a lathosterol or desmosterol level (cholesterol synthesis precursor sterols). In the patient at hand, I suspect we are going to likely need pretty serious combo therapy to achieve LDL-P goal.

So what are the drugs that one can add to a statin to get additional LDL-P reduction? You have three: ezetimibe, niacin (of course extended-release or Niaspan is the preferred choice) or colesevelam (Welchol) which would make sense if there were any glycemic issues. Niacin and ezetimibe can add another 15-20% LDL-P lowering (interesting that the NMR data that is published shows immediate release niacin, which of course few can tolerate at the required doses, is more potent than extended-release niacin in lowering LDL-P). I loved the Fazio (Diabetes, Obesity and Metabolism 12: 983–993, 2010) study showing the great efficacy of statin/ezetimibe and extended-release niacin – that is where I think one may have to go to drop LDL-P to where it should be in this man.

Because the TG are < 200 mg and the HDL-C is normal, fibrates would be unlikely to be of benefit in this man. It is well proven that fibrate monotherapy increases LDL size and especially fenofibric acid, significantly reduces LDL-P but when added to statins fibrates do not cause any (zero) additional decrease in LDL-P. Please note that if one adds fenofibric acid or high dose Omega-3 FA to a statin there is a ~5% apoB drop – which due to a reduction in VLDL-P (remnants) not LDL-P (VLDLs contribute about 5% of the total ApoB particles).

The old theory that it is wise to shift LDL size as the statin-upregulated LDL receptors would more easily recognize, bind to and clear the larger LDLs no longer holds up to scientific scrutiny. Niacin shifts LDL size upward and when added to a statin significantly drops LDL-P beyond the statin induced drop. Fibrates and Omega 3 shift LDL size yet add no LDL-P efficacy to a statin. For the most part ezetimibe does nothing to LDL size but significantly reduces LDL-P beyond what a statin does. So I no longer think we should feel totally obligated to shift LDL size to enhance LDL-P lowering.

Fibrates do significantly increase total HDL-P (something almost no other lipid med except statins do) and this man has a low HDL-P. As discussed in the last two previous Lipidaholic Newsletters niacin does not typically raise HDL-P. Same with high dose omega 3s: there would be very little LDL-P reduction beyond a statin. Niacin increases HDL-C by increasing HDL size not HDL-P. Paradoxically niacin does increase apoA-I. Since HDLs can carry multiple copies of apoA-I, it is possible to increase apoA-I without increasing total HDL-P.

So this patient is at much higher risk than NCEP tools can ever discover. Therapeutically if one followed NCEP advice and achieved LDL-C goal – there would likely still be lots of residual risk due to the still high LDL-P. The LDL-C – LDL-P discordance at the heart of this case cannot be discovered without having ordered the NMR analysis.

Keys to the Case:

You will never be as good as you can be by betting lives on lipid concentrations. Atherosclerosis is a lipoprotein mediated disease and we must measure atherogenic particle number. Particle or subparticle cholesterol measurements have outlived their usefulness.

DO NOT EVER ASSUME that an at goal LDL-C and/or non-HDL-C means apoB or LDL-P is also at goal.

Master the concept of lipid and lipoprotein discordance: it is likely that a patient with cholesterol depleted LDL particles will have a high apoB and/or LDL-P. LDL size and core TG increase is what depletes LDLs of its cholesterol. A fantastic editorial on this is We Must Prevent Disease, Not Predict Events by Allan Sniderman J. Am. Coll. Cardiol. 2008;52;300-301

Therapeutically you do not have to increase LDL sizes. You have to reduce apoB and LDL-P.