## LIPID CASE 258 LDL-C & LDL-P at goal Now what?

I was consulted by a Midwest cardiologist re the following two patients: both patients are at lipid/lipoprotein goal - raising the question what else if anything needs to be done.

1) 73 year old male, non-diabetic with a 20 year history of hypertension who presented with unstable angina in 1989, had POBA (plain old balloon angioplasty) to LAD. He is now asymptomatic, exercises like a fiend and watches his diet like a hawk. Current BMI is 24. A "surveillance" stress MPI was done last year - 10 METs' (+ ). There were ST/ECG changes and Reversible anterior ischemia An angiogram 2 years ago revealed a 50% proximal left anterior descending artery (LAD) lesion; 100% mid LAD that fills via left to left collaterals. His LDL-C has been < 100 mg/dl since he's been under care of the current provider over the past 8-9 years. The most recent NMR last month while on 10 mg Lipitor:

TC =125 mg/dL LDL-C 62 mg/dL HDL-C 55 mg/dL TG 41 mg/dL

LDL-P 515 nmol/L (well below the 5th percentile population cutpoint)
Other NMR data not provided

But, his Lipoprotein Associated Phospholipase A2 or Lp-PLA2 (PLAC Test) is 335 ng/ml (>235 ng/ml listed as "HIGH"). 235 is the 50th percentile population cutpoint. In reality the risk threshold for this biomarker is equal to or slightly above 200 ng/mL.

The provider asks am I done, or do I titrate his statin to lower his Lp-PLA2?

Case 2) 51 year old white male - former smoker, non-diabetic; normal Lp(a); S/P LAD STEMI 2009- receives rescue percutaneous transluminal coronary angioplasty (PTCA) to LAD then 4 vessel coronary artery bypass graft (CABG) 3 months later: Saphenous vein graft (SVG) to right posterior descending artery (PDA), SVG to D2; Radial to D1 and LAD; baseline stress MPI last week within 6 minutes was markedly positive: ECG (2.5 mm downsloping in 5 leads). Nuclear images show entire anterior wall and apex reversible defect. No chest pain and there was normal LV function.

Catheterization today (4.5 months since CABG): 70 distal SVG to PDA; long diffuse 90% lesion in SVG to D2; closed radial to D1 and LAD; 90% LAD bifurcating lesion with a 70 % ostial D1. Now deciding on repeat CABG vs. fancy PCI (rotoblator TEK catheter).

The patient is on Crestor 20 mg and 1 gm of Omega 3 FA: BP 110's/70's on Ramirpril 10 mg daily and Carvedilol 6.25 mg bid.

Last LDL-P 919; with an LDL-C 67; and HDL-C of 53;

The cardiologists asks: any thoughts on what I can do for this guy- He is thinking he needs to check his Lp-PLA2 level and drive down LDL-P to < 700???

**DAYSPRING ANALYSIS**

Case 1: This is a case of a very high risk individual who is at lipid goal and well, well below LDL-P goal. Technically the only guideline currently offering an official LDL-P goal is the American Association of Clinical Chemistry statement: Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices John H. Contois et al (Clinical Chemistry 2009;55:3:407–419. For high risk patients they suggest the 20th percentile population cutpoint (using Framingham data collected in the late 1980s) or a value of 1100 nmol/L (note LipoScience uses the more contemporary Multiethnic Study of Atherosclerosis or MESA data and the 20th percentile LDL-P

is 1000 nmol/L). At this time did the panel did not suggest a lower LDL-P for very high risk patients. Canadian guidelines for some time and ADA/ACC (2008) have issued apolipoprotein B goals. Never forget apolipoprotein B is simply a measure of LDL particle count (LDL-P) and many do not realize VLDLs (VLDL-P) and IDLs (IDL-P) contribute very little to an apoB level. The 20th percentile population cutpoint for LDL-P is 1000 nmol/L, for VLDL-P is ~40 nmol/L and for IDL-P is zero. Even when TG are extremely high the VLDL-P might be 150-250 nmol/L - well below the number of LDL particles (which would, then be much higher than 1000) in circulation.

The dilemma for the treating cardiologist is does the still elevated Lp-PLA2 suggest a need for additional therapy. So what is a clinician to do when an "atheroma-specific" inflammatory marker is elevated. Should we even care? Current data suggest that Lp-PLA2 which mostly traffics with LDL particles (especially small ones is an actual player in atherogenesis. Inflammatory markers at this time should be used to help determine risk. There is no high level evidence at this time that any inflammatory marker should be a goal of therapy. The strongest data suggesting outcomes would be better if an inflammatory marker comes from PROVE-IT and JUPITER trials where patients did best if both the inflammatory marker hs-CRP and lipids and in the case of JUPITER (lipids were at goal at baseline) lipoproteins measured using apoB (not at goal at baseline) were at goal" i.e. the patients who did best on statin therapy were those who had both lipids/lipoproteins and CRP lowered to normal. We also have Lp-PLA2 data from PROVE-IT and it showed Lp-PLA2 cannot be used as a predictor soon after ACS. However after 30 days it is a better predictor than hs-CRP and was lowered by statins (Circulation. 2006;113:1745-1752).

Yet, current expert consensus is that inflammatory markers should be used as ways of helping do better CV risk assessment but not as a goal of therapy. A consensus panel recently advised that *"Lp-PLA2 is recommended as a diagnostic test for vascular inflammation to better identify patients at high or very high risk who will benefit from intensification of lipid-modifying therapies. However, at this time Lp-PLA2 cannot be recommended as a target of therapy"* (Am J Cardiol 2008;101[suppl]:51F–57F). Therefore in patients with high Lp-PLA2, we might strive for a more aggressive lipid/lipoprotein goal of therapy -- but this man is well below lipid and LDL-P goals. So in reality using the best evidence, Lp-PLA2 should not even have been measured in this extremely high risk patient who was at lipid/lipoprotein goal. But real world docs sometimes have to practice the art of medicine (outside of the box) in such patients and sometimes go beyond expert opinion. Remember there are no trials that show that lowering Lp-PLA2 would not provide additional help and CRP data from PROVE IT and JUPITER make it plausible. Also of importance is unlike LDL parameters the Lp-PLA2 is an excellent predictor of stroke which would be a catastrophe in this patient.

What else might help? The total HDL-P was forwarded to me. Studies, staring with VA-HIT suggest after reducing atherogenic LDL-P that increasing HDL-P may be important (very interestingly in VA-HIT apoB had no predictive value but LDL-P did). This patients HDL-C seems fine but if his HDLs are quite large, the HDL-P may not be high. We know from the IDEAL study, that patients getting events with elevated HDL-C had low apoA-I (estimate of HDL-P). Few know of the amazing data from the THROMBO Study where the people who had the highest number of CV events, the best indicator of the risk was abnormal inflammation and the presence of large HDL particles (clearly dysfunctional): The authors conclusion was *"that in non-diabetic postinfarction patients, elevated HDL is predictive of risk of recurrent coronary events within a subgroup of patients characterized by simultaneous elevations in serum CRP and total cholesterol"* (Atherosclerosis 187 (2006) 191–197). In THROMBO, those people with the highest numbers of events all had very large HDLs, which certainly shoots down the theory that clinicians must make HDLs large. In another study it was shown that inflammation impairs RCT at multiple steps in the RCT pathway, particularly cholesterol flux through liver to bile and feces (Circulation. 2009;119:1135-1145). Of course all of this data suggest HDL functionality is at play. We await the development of HDL function tests but there is some evidence that another inflammatory marker, myeloperoxidase (MPO) might indicate HDL dysfunction and it would be interesting to see if it is also abnormal in this case (available at www.clevelandheartlab.com).

So one "outside of the box" suggestion is to measure total HDL-P. If it is low in a person with that much risk and CAD I would add and titrate Niaspan to 2000 mg (the effective dose in almost all of its trials). It is also very effective at helping a statin lower Lp-PLA2 (fibrates and omega-3 fatty acids can also help lower Lp-PLA2 beyond that seen with statin) if indeed that is necessary. A new study showed that niacin inhibits vascular inflammation and protects against endothelial dysfunction independent of these changes in plasma lipid levels (Arterioscler Thromb Vasc Biol. 2010;30:968-975). Niaspan of course will also raise HDL-P by delaying its catabolism and perhaps increasing apoA-I production (Arterioscler Thromb Vasc Biol. 2008;28). I do not see what increasing the statin would do in the face of an LDL-P of ~ 500, so unless you believe there are pleiotropic effects of statins at the higher does that are not present at lower doses (a theory yet to be proven) increasing statin may not help. Many would point to ASTEROID that Crestor 40 was associated with regression (although there was no comparator arm): but they did not study with patients with LDL-P of 500. I'd also make sure the patient is also on 1-2 grams of Omega-3 FA (preferably Lovaza: an off-label use) and I'd follow his Onega-3 index (www.omegaquant.com) to judge that therapy.

Case 2: As mentioned above, neither the ADA/ACC Consensus statement on Lipoprotein Management or the AACC Statement on apoB advised dropping apoB (LDL-P) below the 20th percentile population cutpoints (80 mg/dL, 1100 nmol/L LDL-P) due to lack of clinical trials supporting those therapeutic goals. Nonetheless in this case we are dealing with a 51 year old total nightmare in this case. I and my coauthors (see our Lipoprotein Pocket guide at www.lipidcenter.com) would agree with the 20th percentile cutpoint of high risk patients but believe using clinical judgment the provider has the option in such a case to reduce the LDL-P to less than the 5th percentile cutpoint or < 700 nmol/L (apoB to < 60). Based on emerging data, I'd also suggest that the HDL-P should be raised to > 35 umol/L. Thus in this case, I'd likely go to Crestor 40 mg daily in this man (the dose used in ASTEROID to induce regression) and I tend to favor using Niaspan for additional apoB or LDL-P lowering and many of the reasons listed above (titrated to 2000 mg daily) in all patients with significant CAD if they can tolerate it. Based on its several angiographic trials one can make the case if a patient has significant CAD, why is the patient (after statin use) not on niacin? Based on some of the discussion in case 1, I am not sure that measuring Lp-PLA2 will help very much.