LIPID CASE 266 Lipids perfect: does Lp(a) matter?

I was asked about what the provider calls an interesting patient. He's 41 year old male with a BMI of 23,who takes 81 mg ASA/day and fish oil supplements. He has no other health conditions, uses no other meds, exercises regularly and reports a healthy diet. His father died of an MI at age 54 but was a heavy smoker. His CIMT which showed a 95th percentile value for his age/gender: a raw measurement 0.856 mm, no discrete carotid plaque seen. He reported that in his 20s and early 30s his diet was terrible (he's a police officer who worked nights at the time so he ate fast food constantly) and he had his first lipid screen at age 35 and was told his cholesterol was "through the roof." He changed his diet dramatically and had it rechecked two years later, was told it was great. His PCP ordered further testing (VAP autoprofile) in 2009 which, according to the patient, had no abnormalities but in looking at it the Lp(a)-C of 8 was reported as 'normal' on their report but I always thought Lp(a)-C greater than 6 was abnormal.

He had a profile done last month at Celera and it showed the following:

TC = 145 LDL-C =73 HDL-C =58 TGs =71
Apolipoprotein B of 50 mg/dL
Lp(a) mass of 45 mg/dL
Pattern A LDL
Lp-PLA2 = 196
apoE: 2/2
KIF6: trp/arg
glucose =99 insulin =6

The provider states: "His apoB is perfect but his Lp(a) mass is elevated and his CIMT was abnormal. His glucose is borderline. The patient wants to wait and repeat the CIMT after 18 months to see if it is stable or progressing. We discussed Niaspan as well and the patient wants to wait...I don't want to increase his glucose further either. I know you don't put much stock in KIF6 but given his family history, Lp(a) mass elevation, abnormal CIMT--statin therapy comes to mind, but with an apoB of 50....
what am I to do?

DAYSPRING DISCUSSION:

First let's get rid of the KIF six testing issue. It is now recognized as totally useless (not my words although I agree): I hope all of you read the just published study and scathing editorial in JACC. 1) Lack of Association Between the Trp719Arg Polymorphism in Kinesin-Like Protein-6 and Coronary Artery Disease in 19 Case-Control Studies. Conclusion: Looking at a total of 17,000 cases and 39,369 controls, the KIF6 Trp719Arg polymorphism was not associated with the risk of clinical CAD in this large replication study. The findings question not only the usefulness of the KIF6 test in identifying subjects at increased risk of incident or recurrent CAD but also its usefulness in identifying subjects most likely to benefit from statins(J Am Coll Cardiol 2010;56:1552–63). The editorial entitled The KIF6 Collapse by Eric J. Topol, and

Samir B. Damani where they ask "Why have 150,000 KIF6 genotypes been ordered in the past 2 years for a test that now seems to be useless? and then state "Although several cardiovascular-related genomic and pharmacogenomic biomarkers have clearly surpassed this important evidence threshold including the aforementioned apolipoprotein E, LPA, and the recently identified CYP2C19 variants involved in clopidogrel metabolism, the KIF6 association has lacked such data from the time of its initial reports. Going forward, the KIF6 story should serve as a valuable reminder of the potential pitfalls present in prematurely adopting a genomic test without sufficient evidence. --- The previous KIF 6 data was from antiquated candidate gene-based methodologies and not genome-wide association studies (GWASs) for the purpose of identifying, in an unbiased manner, genetic markers of complex trait susceptibility that reach stringent statistical significance thresholds." (J Am Coll Cardiol 2010;56:1564-1566).

Now back to the real issues the case brings to light:

Theoretically if it was properly done (and in many cases that is a big if), the very abnormal CIMT establishes the presence of high risk. Yet using any existing guideline all lipid parameters and apoB are at goal even if you think this is a very high risk patient (and he does not meet NCEP's criteria for that classification). The Lp-PLA2 is normal and nothing else reported above points to CV risk. A glucose of 99 and a normal insulin level carries little weight. Despite the E2/E2 genotype the current lipids are not currently a type III lipid phenotype at this time. 95% of E2/E2 do not ever manifest the Type III lipid phenotype and thus patients with E2/E2 have lower CV risk than other apoE genotypes [Conclusions There are approximately linear relationships of apoE genotypes with both LDL-C levels and coronary risk. Compared with individuals with the ε3/ε3 genotype, ε2 carriers have a 20% lower risk of coronary heart disease and ε4 carriers have a slightly higher risk (JAMA. 2007;298(11):1300-1311)]. Some other metabolic assault (typically T2DM) is what converts E2/E2 patients to a Type III lipid phenotype. However the patient remarked that his cholesterol was sky high -- one might speculate if his TG were also sky high in which case he at one time may have manifested the Type III phenotype. His lifestyle could have made the Type III phenotype disappear.

- The elevated Lp(a) mass and Lp(a)-C [although they should be done on the same specimen (which is not the case here)] suggest that the Lp(a) particle count or Lp(a)-P is abnormally high and that the apo(a) isoform is the smaller, lower molecular weight molecule associated with the high risk. The liver cannot readily secrete the large apo(a), high molecular weight isoform due to its size. Thus although folks with the large isoform can have a high Lp(a) mass, but they do not have a high Lp(a)-P and thus less risk. Since Lp(a)-P or Lp(a) mass in molar concentration is not available, Lp(a)-C serves as the Lp(a)-P test at present. Note: companies like LipoScience that do report Lp(a) in molar units simply use a conversion to change apo(a) mass in mg/dL to mols/L. That conversion factor is not always accurate as the molecular weight of apo(a) isoforms varies considerably between patients. The best current way to know if Lp(a)-P is high is: high Lp(a) mass + high Lp(a)-C means high Lp(a)-P and risk where high Lp(a) mass but normal or absent Lp(a)-C means low Lp(a)-P and less risk. Be sure you lab provides both Lp(a) mass and Lp(a)-C. So in the patient at

hand the Lp(a) situation adds to his risk as both Lp(a) mass and Lp(a)-C are high. He has the small apo(a) isoform.

Ideally, you need to do Lp(a) mass and Lp(a)-C on the same specimen. The problem is the CV risk depends atherogenic particle count or LDL-P. ApoB cannot be used to count particles in persons with elevated Lp(a) as the apo(a) molecule binds to the LDL particle apoB in a way that can conceivably interfere with the apoB test. Apo(a) binds to apoB and covers the LDL receptor binding site which is why it is difficult for the liver to clear Lp(a)-P. Could not the apo(a) also block (camouflage) the apoB epitopes the apoB assay antibodies are seeking, creating false negative apoB. Apo(a) does not hinder NMR measurement of LDL-P.

So you can only judge risk by looking at LDL-C, non-HDL-C or better yet LDL-P or best of all Lp(a)-P (not yet commercially available). For a very thorough discussion of understanding Lp(a) I will be posting a new "Lipid Short" on understanding Lp(a) complexities at www.lipidcenter.com - Click on professionals and go to lipid study materials.

Until very recently no guideline advocated reducing Lp(a) mass per se, but very recently in the European Heart Journal (doi:10.1093/eurheartj/ehq386) the European Atherosclerosis Society Consensus Panel issued their statement entitled Lipoprotein(a) as a cardiovascular risk factor: current status. The concluded: We recommend screening for elevated Lp(a) in those at intermediate or high CVD/CHD risk, a desirable level < 50 mg/dL as a function of global cardiovascular risk, and use of niacin (1-3 grams daily) for Lp(a) and CVD/CHD risk reduction. They readily admit there is no data showing lowering Lp(a) with niacin is related to event reduction. Also recently in the Journal of Clinical Lipidology a roundtable of experts advocated statins plus niacin (2010;4:240-247)

So in this case the LDL-C is perfect; so is the apoB but could it be a false negative? The lipid concentrations are quite good. Could apo(a) block apoB epitopes that the assay antibody paratopes are seeking? I'd do an LDL-P, which is not affected by apo(a) attaching to the LDL particle) and perhaps would know with more confidence what to do. My concern in this case is the LDL-P might still be high despite the normal LDL-C, non-HDL-C and apoB. Who knows?

In the real world, where not everyone takes advantage of more sophisticated lab testing, my guess or inclination based on the terrible CIMT is his LDL-P is still high and Niaspan would likely be a good choice to add to a statin. In Europe they might tell you to go with niacin alone, but with the high LDL-P, I would want a statin on board. Simcor is probably the ideal choice for this man. If the patient is still reluctant to accept therapy, perhaps doing a coronary calcium - if it is positive will scare him more than a CIMT and he might then agree to therapy.

Lastly since persons with Lp(a) issues have thrombotic tendencies aspirin is indicated. I now do routine Aspirinworks (urine 11-dehydro thromboxane B2) testing to make sure he is an aspirin responder.