

LIPID CASE 264 Revisiting Lipoprotein Little a

Let's get right to the case at hand. The patient is a 33 year old health care provider, with a height of 5'7", and weight of 150 lbs. He has no dietary restrictions, and because his LDL-C was 161 mg/dL in 2007, he has been taking Vytorin 10/40 mg for 3 years. Vytorin was chosen because he assumed he would respond to Zetia. There is no "early" CAD in his family, but his grandfather had a CABG at age 60 and died of CHF at age 70. His father has high cholesterol and his mother also has high cholesterol and type 2 DM (and is overweight).

Current numbers are:

TC = 131 HDL-C = 51 LDL-C = 64 TG = 93 (all in mg/dL)

Lipoprotein Testing: LDL-P = 987 nmol/L ApoB = 57 mg/dL sdLDL = 16 mg/dL

HDL-P: 31.6 umol/L which is low (50th MESA population percentile cut point)

Lp(a) mass = 93 mg/dL (high risk >30) Lp(a)-C = 15 mg/dL (high risk is >6)

Inflammatory markers were not elevated (hs-CRP, Lp-PLA2, fibrinogen)

The clinician states: "I am inclined to think that since my LDL-P is perfectly at goal, I should not worry about the abnormal values (which is what I would tell a patient of mine should they have these exact values). What do I make of the elevated Lp(a)? Do I do anything in addition (other than better lifestyle)?"

DAYSRING DISCUSSION:

Certainly using NCEP ATP-III (a now 9 going on 10 year old guideline) criteria, risk scoring this young provider shows him to be low risk. How many of you are driving around in 9-10 year old cars? Indeed this man does even qualify for Framingham Risk Scoring and even if you did it his ten years risk of an event is very low. It is not listed as a risk factor in any guideline but if I were him I'd be a bit concerned that Grandpa had an event (CABG) at 60. Clearly Grandpa had been developing atherosclerosis for decades. - might the same be going on with this patient? Both of his parents have lipid disorders and mom is a diabetic. For those of you stuck in lipid yesteryear who still pay a lot of attention to NCEP ATP-III, you would advise this man that he has an LDL-C that is abnormal and he should approach it with more aggressive lifestyle. Being low risk he would not at this time qualify for drug therapy.

So, what about the elevated Lp(a) mass? Do we have to worry. Lipoprotein little small case or little a has been confusing lipidologists for a long, long time since it was first discovered in 1963. It seems to be a risk factor in some people and not in others and race is involved. Overt time the data associating apo(a) with CV risk has gotten stronger and stronger.

The following discussion utilizes facts and concepts from four nice reviews: Atherosclerosis 211 (2010) 15–23, Journal of Clinical Lipidology (2010) 4, 240–247, JAAC 2008;52:132-134 and JAAC 2010;55:2168-70. Lipoprotein (a) is an LDL particle (a collection of core cholesteryl ester and TG in a 4:1 ratio) with a phospholipid and free cholesterol surface enwrapped with a single molecule of apolipoprotein B 100 that has attached to it another protein called apoprotein (a) which is a plasminogen-like glycoprotein. This differentiates it from apoprotein A (upper case A) which is a family of very different apoproteins (apoA-I through apoA-V). Without trying to confuse you, apo(a) can also be on VLDL and other apoB particles (most would be LDLs). Apoprotein (a) is made up of multiple repeated amino acid loops or motifs resembling a German pretzel called kringles (K). These "kringles" (K) on apo(a) resemble kringles IV and V that are present on the plasminogen molecule. Plasma levels of lipoprotein(a) vary greatly among individuals and are determined by the KIV polymorphisms that are present. Kringle IV consists of distinct kringle types from 1 to 10 (KIV-1 through KIV-10). The most important of the polymorphisms is the KIV-2 (kringle IV type 2) size polymorphism, which can exist from 2 to > 40 copies of 5.6 kb repeats which results in the large number of different sized isoforms of apolipoprotein(a). In other words, some folks have 2 copies of the KIV-2 and the next patient might have 50. Other kringle types (KIV1-3 and 4-10) are also present on apo(a) but they only exist in one copy - not repeats or multiples like KIV-2 and thus no inter-individual differences exist. Thus the KIV-2 size (how many repeats) polymorphism determines the copy number variability explaining why there are different apo(a) or Lp(a) isoforms (small and large). Patients with the smaller isoforms have less KIV-2 repeats (< 22) than the larger isoforms (> 22). The number of KIV-2 repeats correlates inversely with levels of lipoprotein(a); small apolipoprotein(a) isoforms associate with high lipoprotein(a) plasma concentrations, and vice versa. Why is that? It seems the liver is much better at secreting the smaller apo(a) isoforms than the larger ones. The molecular weight of the apolipoprotein (a) molecule depends on how many kringle repeats are present. The less KIV-2 repeats, the lower the MW. So paradoxically, even though small isoforms have a lower molecular weight than the larger isoforms, serum levels of apo(a) mass of Lp(a) will usually be higher patients with the smaller, lower molecular weight isoforms compared to the larger and higher molecular weight isoforms. The small, low molecular weight isoforms of apo(a) or Lp(a) are considered more atherogenic than the larger high molecular weight isoforms. If a patient does secrete too many larger higher MW isoforms, Lp(a) mass will be high but CV risk may be lower than that suggested by the apo(a) mass measurement. That is the shortcoming of Lp(a) mass concentration testing.

The literature until recently has been quite conflicting in large part because there has been no standard assay and every study used something different. In 2003 the NHLBI issued a recommendation that Lp(a) concentrations be reported not in mg/dL but in molar concentrations, yet there are no real world labs who have such an assay. Any lab now reporting Lp(a) in molar units is simply takes mg/dL value and uses a molecular weight (MW) formula to convert it. Unfortunately because the apoprotein (a) isoforms can vary significantly in MW one cannot use such conversion formulas without knowing what

isoform is present (isoform testing is not available to real world clinicians). If one uses apo (a) mass measurements (readily available) errors can be made (as discussed above) depending if the patient has the more atherogenic isoforms (small) vs. the less atherogenic larger isoforms. More on this later. Unfortunately isoform testing is not available to real world clinicians. New data looking at apo(a) SNPs (single nucleotide polymorphisms) might help us better understand the all of these relationships.

One can now order a reliable Lp(a) -C which is the amount of cholesterol carried by all of the Lp(a) particles that exist per deciliter of plasma (mg/dL). As discussed below, neither Lp(a) mass levels or Lp(a)-C by themselves can help us discern risk, but when used together we have a real world tool on more accurately guessing isoform size. Health diagnostic labs in Richmond VA (www.myhdl.com) offers Lp(a) mass and Lp(a)-C testing (developed by Joe McConnell at the Mayo clinic). Lp(a)-C is simply the amount of cholesterol trafficked within all of the Lp(a) particles that exist in a dL of plasma. Let's look at two patients with high Lp(a) mass levels, but one has the large isoform and is thus likely not at CV risk and one has the smaller isoform and likely is at risk. Because there are so many more Lp(a) particles in the person with the small isoforms (due to its high hepatic secretion rate) compared to the patient with larger isoforms, the former will have a high Lp(a)-C and the latter will not. So when I now order Lp(a) mass I always get Lp(a)-C. In the above instance two patients both have high Lp(a) mass but only the higher risk person with the smaller isoform will have the higher Lp(a)-C. So the easiest way for me to understand risk related to high Lp(a) mass is to always look at both Lp(a) mass and Lp(a)-C: if both are up the isoform is small and risk is present. If mass is up and Lp(a)-C is normal, the isoform is large and no risk exists. The 75th percentile population cut point (high risk) for Lp(a) is 30 mg/dL or 70 nmol/L. But here is where one gets into trouble. If one has large isoform apo(a) and level of 30 mg/dL is only the 50th percentile and not at a high risk. I hope you see how Lp(a)-C can help us very much in these scenarios. Conclusion: Lp(a) mass or Lp(a)-C by themselves are not really that helpful in adjudicating CV risk. It is hoped that one day soon we will have Lp(a)-B measurements. Remember apo(a) traffics on an apoB lipoprotein: LDL is a apoB containing particle. Would not it be nice to simply count Lp(a) particles. Maybe that is all we will need. Or else we can use it with in addition to Lp(a) mass and Lp(a)-C. That day is not that far away.

ATP-III gave little impact or discussion to elevated Lp(a) levels in the final report published in 2002. They stated it may be a major risk factor but the studies were inconclusive. They did note African American's can have high levels without risk and they pointed out the lab assays were far from properly developed. They state: "*the quantitative contribution of elevated Lp(a) to CHD risk beyond the major risk factors is uncertain.*" They correctly pointed out back then (and it remains true today) that there is no outcome evidence related to lowering Lp(a) with drugs. They concluded "*some authorities believe that Lp(a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk than revealed by those factors. According to advocates for Lp(a), the option of measurement is best reserved for persons with a strong family history of premature CHD or those with genetic causes of hypercholesterolemia, such as familial hypercholesterolemia. An elevated Lp(a) thus presents the option to*

raise a person's risk to a higher level. ATP III did not find strong evidence to support this approach, but accepts it as an option for selected persons." Thus using NCEP ATP-III recommendations the patient under discussion should never have had his Lp(a) tested. NCEP did not discuss Lp(a)-C in 2001.

More information was forthcoming in the Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: Recent Advances and Future Directions authored by Santica M. Marcovina et al. Clinical Chemistry 49:11 1785–1796 (2003). The authors stated: "*Because Lp(a) and LDL are metabolically distinct, it is evident that the special characteristics of Lp(a), including its size and density heterogeneity, are almost entirely attributable to apo(a). apo(a) is a carbohydrate-rich, highly hydrophilic protein characterized by a marked size heterogeneity that is primarily attributable to a genetic size polymorphism of the polypeptide chain.*" They go on to state: "*assay standardization can be achieved only if each assay is properly optimized in addition to being evaluated for its sensitivity to apo(a) size polymorphism.*" The committee had several recommendations including: "*The expression of Lp(a) values in terms of total Lp(a) mass should be abandoned because what is measured is the protein component of Lp(a) and not its lipid and carbohydrate content. In addition, to correctly reflect the number of Lp(a) particles and to compare data from different studies, the values should be expressed in terms of nmol/L of Lp(a) protein. Screening for increases in Lp(a) in the general population is not recommended at this time. However, measurement of Lp(a) is recommended in individuals with an increased risk of CVD, particularly in those with borderline LDL-cholesterol or high apo B.*" So using the Marcovina recommendations, the patient at hand because of his originally high LDL-P (apoB) should have had his Lp(a) measured.

However just this year (7 years after the above article) Marcovina in the J Clin Lip reference cited above states: "*The conversion factor from mg/dL to nmol/L varies from 2.85 for a small Lp(a) size to 1.85 for a large one. Therefore, a factor of 3.5 is too high, and we suggest a mean conversion factor of 2.4, even though the conversion can be more or less imprecise depending on the apo(a) size. However, **the major problem of Lp(a) values** is not the units used to report the results but is related to the inaccuracy of the methods that are affected by apo(a) size heterogeneity. These methods overestimate the levels of Lp(a) in individuals with large Lp(a) molecules and consequently underestimate the levels in individuals with small Lp(a) molecules.*"

Exactly, why Lp(a) may be a risk factor is still debated but the evidence is now pointing to not only the acting as a faulty plasminogen (inhibiting fibrinolysis) but to the fact it is an inflammatory marker and that the apo(a) (especially the small isoforms) traffics oxidized phospholipids, many generated as a result of lipoprotein phospholipase A2 (Lp-PLA2). Of course ox-PL are very good at causing endothelial dysfunction and aggravating the maladaptive inflammatory process that occurs when apoB particles enter the arterial wall and get ingested by macrophages. No randomized clinical trial of the effect of lowering lipoprotein(a) levels on CHD prevention has ever been conducted. The well illustrated editorial in JACC cited above 2010;55:2168-2170 entitled The Mysteries of Lipoprotein(a) and Cardiovascular Disease Revisited by Kiechl and Willeit concludes

"the puzzling pieces of knowledge are being assembled to a promising whole. - We are on the verge of understanding the physiologic role and pathologic properties of Lp(a) particles and await the development of specific Lp(a)-lowering therapies. - But alas for those requiring level 1 evidence: we are not close." Are there any official guideline treatment recommendations regarding treating at risk patients with high small isoform Lp(a)? No other than to lower LDL-C. However expert opinion (see the J Clin Lip reference cited above) suggests lowering LDL-C and apoB (LDL-P) with a statin and then adding Napa for multiple lipoprotein benefits (including additional LDL-P and HDL-P benefits) and whatever apo(a) lowering one might get. This will never be solved without trial data - maybe AIM-HIGH will offer some data. So back to the patient at hand: if because the patient has high Lp(a) and high Lp(a)-C we consider him high risk, then we need to further lower LDL-P (maybe to < 750 nmol/L) and that can be done by adding Niaspan to the Vytorin 40. There would also be some Lp(a) and Lp(a)-C lowering (if indeed that is important) and there would be HDL-P improvements (his level is low). If needed the ultimate (most powerful) therapy would be Crestor/Niaspan/Zetia. Please note there is a warning in Chinese patients not to exceed Niaspan dose of 1000 mg when a statin is used.