

LIPID CASE 261 LDL-C ultra-perfect - reduce the statin?

I was contacted by a practitioner working in a CV clinic who stated "we have a diabetic patient with bad vascular disease who is on insulin, Lipitor 40 mg and Zetia 10 mg among other meds. He has had coronary stents in 2007 and 2008, has a pacemaker and ICD.

His lipid and lipoprotein NMR results are as follows:

TC = 101 HDL-C = 35 TG = 92 LDL-C = 48 Non-HDL-C = 66 TC/HDL-C = 2.8

Total LDL-P= 980 nmol/L, Small LDL-P = 726, LDL size= 20.3, large HDL-P= 6.4 umol/L, large VLDL-P= <0.7 nmol/L and his Lipoprotein Insulin Resistance Score (LP-IR) = 22.

The patient's cardiologist is suggesting that he decrease his Lipitor to 20 mg because his last standard lipid panel done by the VA (not an NMR) showed

TC= 81, LDL-C of 39 mg/dL TG= 43 and HDL-C = 34.

The provider disagreed with Cardiology and stated "with his NMR results and the fact that his small LDL-P = 726, we wanted him to continue his current regime." My advice was sought.

DAYSRING DISCUSSION: This is easy and the answer is supported by lots of studies and expert opinion. The provider is correct and the cardiologist is wrong. If anything makes the case for lipoprotein, in addition to lipid testing, this case does. No one would disagree this is a very high risk patient which deserves aggressive lifestyle and pharmacologic support.

Where do our lipid and lipoprotein goals of therapy come from? The answer is clinical trials relating lipid concentrations to outcome reduction. Of course in all of the trials, LDL-C was the goal used. Thus from trial data NCEP suggests an LDL-C of < 70 mg/dL for very high risk, < 100 mg/dL for high risk and < 130 for lower risk folks. To determine what apoB or LDL-P or non-HDL-C goal of therapy is appropriate, experts use values from population studies using percentile equivalencies. That is, if one desires an LDL-C of < 100 how many folks in a large population would actually have such an LDL-C - how many would have higher or lower values. Thus if an LDL-C of 100 mg/dL is the 20th percentile population cutpoints then we could simply see what are the 20th percentile cutpoints for apoB and LDL-P and make those values the apoB and LDL-P goals.

The lipid and lipoprotein goals of therapy in this very high risk patient would be to reduce atherogenic lipoproteins (LDL-C, non-HDL-C or better yet apoB and LDL-P) to below the 5th population percentile cutpoint. If the patient were simply high risk, we would shoot for 20th percentile cutpoints. The populations that have been conventionally used to determine these cutpoints are Framingham Offspring or FOS (see <http://www.lipidcenter.com/pdf/Framingham.pdf>) and the MultiEthnic Study of Atherosclerosis (MESA). The latter is a more contemporary and compared to Framingham includes a wider array of ethnicities. Here are the values:

80th percentile cutpoint (puts patient at high risk): FOS/MESA LDL-C 160/143 Non-HDL-C 187/? ApoB 118/P LDL-P 1820/1610 For reasons unknown to me MESA has never published its apoB data cutpoints. Why not????

20th percentile cutpoint (high risk patient goal): FOS/MESA LDL-C 100/93 Non-HDL-C 119/? ApoB 78/? LDL-P 1100/1000

5th percentile cutpoint (very high risk patient goal): FOS/MESA LDL-C 78/70 Non-HDL-C 94/? ApoB 78/? LDL-P 1100/770 PS: The NCEP ATP-III suggested LDL-C goal for very high risk patient is 70 mg/dL which is actually the second % cutpoint. Using MESA the 2nd percentile LDL-C cutpoint would be < 70 mg/dL.

What have those of you with sharp eyes noted? NCEP uses LDL-C values at the 2nd and 20th percentiles as recommended goals for very high risk and high risk respectively, but uses 100 and 130 mg/dL as non-HDL-C goals of therapy when those numbers actually represent the not the 2nd and 20th but rather the 10th and 30th percentile cutpoints. As you know we now have organizations that give us apoB or apoB and LDL-P as well as LDL-C and non-HDL-C goals of therapy: namely ADA/ACC Consensus Statement (Diabetes Care 2008;31:811-822) and AACC statement (Clinical Chemistry 55:3:407-419 (2009). Try not to become confused when you follow the experts!

| risk/high risk) | LDL-C | Non-HDL-C | ApoB | LDL-P goals of therapy | (very high risk) |
|-----------------|--------------|---------------|-------------|---------------------------|------------------|
| NCEP ATP-III | 70/100 mg/dL | 100/130 mg/dL | no apoB or | LDL-P goals given in 2001 | |
| ADA/ACC | 70/100 mg/dL | 100/130 mg/dL | 80/90 mg/dL | No LDL-P numbers provided | |
| AACC | 70/100 mg/dL | 80/120 | ?/80 mg/dL | ?/1100 nmol/L | |

WOW: Some subtle disagreements there: Bill Cromwell, Michael Richman and I have made it easy for you in our Lipid/Lipoprotein PocketGuide http://www.guidelinecentral.com/product_41419/Lipid_and_Lipoprotein_Disorders_PocketGuide

LDL-C 70/100 Non-HDL-C 100/130 apoB 60/80 LDL-P */1000 nmol/L The * means use clinical judgment if you want in a very high risk person to drop LDL-P < 700-800 nmol/L. Note since publication of our manual if I did not have apoB or LDL-P, I would agree with the AACC non-HDL-C goals of therapy, not NCEP ATP-III or ADA/ACC

So in the patient at hand: He is certainly at (indeed well below) LDL-C and non-HDL-C goals (technical point: when first issued in 2001, NCEP ATPIII made non-HDL-C a secondary goal of therapy in those at LDL-C goal who still had elevated TG (> 200 mg/dL) or high TG and low HDL-C. Subsequent data has shown that non-HDL-C is as good or out predicts LDL-C no matter whether the TG is elevated or not. Thus the cardiologist seems a little nervous with the LDL-C of 48 or 39 mg/dL and wants to reduce the Lipitor. He likely knows, but wants to disregard the fact that clinical trials show that Lipitor 80 mg is better at lowering events than Lipitor 40 mg (TNT study) and that Lipitor 40 mg (REVERSAL) and JAPAN-ACS stopped or regressed atherosclerotic progression respectively in IVUS trials. Granted there is always more potential for statin side effects at the highest rather than lower doses, but we are dealing with a very high risk patient here who was tolerating the Lipitor 80 mg very well.

Like many I believe the cardiologist thinks there is danger in lowering LDL-C very low, even though that has been totally refuted in the following statin trials where several patients achieved extremely low LDL-C values (even lower than the patient at hand) PROVE-IT, TNT, IDEAL and JUPITER. Indeed in PROVE-IT the authors concluded: *"Compared with patients treated with an accepted LDL-C goal (80 to 100 mg/dl), there was no adverse effect on safety with lower achieved LDL-C levels, and apparent improved clinical efficacy. These data identify no intrinsic safety concern of achieving low LDL-C and, therefore, a strategy of intensive treatment need not be altered in patients achieving very low LDL-C levels"* (J Am Coll Cardiol 2005;46:1411- 6). The best example to show low LDL-C is of little concern is to look at patients with

hypobetalipoproteinemia. They produce little apoB or because of a loss of function of proprotein convertase subtilisin kexin type 9 (PCSK9) (a protease that catabolizes LDL receptors and go through life with extremely low LDL-C values (as low as 5 mg/20 mg in complex cases) and of course have longevity because they do not get atherosclerosis and suffer no symptoms related to any cholesterol deficiency. In reality virtually every cell in our bodies makes all of the cholesterol it needs for its function - mostly use in cell membranes. Specialized cells that make steroids from cholesterol get their cholesterol from de novo synthesis and delivery by HDL particles. The physiologic purpose of an LDL (which is simply the waste product of a VLDL or IDL that has lost most of its TG and surface phospholipids) is to return the cholesterol to the liver: i.e. indirect reverse cholesterol transport.

If one looks at the LDL-C distribution of the 136,000 patients all requiring hospital admission for coronary atherosclerosis in the Get with The Guidelines Study (Am Heart J 2009;157:111-7.e2.), ~ 55% had an LDL-C < 100 mg/dL and ~ 18% had an LDL-C < 70 mg/dL. Indeed some has LDL-C values in the 20s and 30s. Could the patient above be one of those with perfect LDL-C levels about to have an event?? I would say yes if the LDL-P is still high. There is support in the literature from survival curves in FOS. (Cromwell et al. Journal of Clinical Lipidology (2000;1:583-592). The data shows: In multivariable models adjusting for nonlipid CVD risk factors, LDL-P was related more strongly to future CVD in both genders than LDL-C or non-HDL-C. Subjects with a low level of LDL-P (25th percentile) had a lower CVD event rate (59 events per 1000 person-years) than those with an equivalently low level of LDL-C or non-HDL-C (81 and 74 events per 1000 person-years, respectively).

The paradox is how can someone with an LDL-C in the 30-40 mg/dL range still have a high LDL-P. I discussed this at length in the last Lipidaholics (please see a pdf on my web site based on the last Lipidaholics tutorial which relates LDL-P and LDL-C disconnects to several factors including particle size and TG content. (Case #260)

http://www.lipidcenter.com/pdf/Lipoprotein_Composition_and_LDL-P.pdf

I want to get into it in a little more depth as I get lots of e-mails from confused providers who see very high apoB or LDL-P in the face of perfect, physiologic LDL-C values. They like the cardiologist in this case get a little nervous to introduce additional therapies. It has become very apparent that statins low LDL-C significantly more than LDL-P or apoB. So for those who want to take it to the next level read on!

Cholesteryl ester transfer protein (one of the family of lipid transfer proteins) or CETP traffics neutral lipids, namely cholesteryl ester (CE) and TG between lipoproteins. CETP's function is to help lipoproteins properly traffic lipids, maintain normal lipoprotein composition and particle size. It is important that LDLs maintain a normal size because if they become too small or too large the apoB conformation changes and it may become no longer as recognizable to hepatic LDL receptors. LDL clearance can thus be impaired or hindered creating a pathologic state where LDL-P and apoB will be high. There are two ways to keep lipoproteins at normal size: make sure they have a full lipid core (i.e. enough CE and TG to keep the size normal) and of course make sure they have physiologic function of the lipases that hydrolyze lipids.

A normal LDL particle has a 4 to one ratio of CE to TG. A VLDL as a 5:1 ratio of TG to CE. In any given individual there is no set TG level at which CETP activates or exchanges neutral lipids (one molecule for one molecule). Although classically TG seemed to drive CETP activity we now are seeing that abnormal core lipoprotein CE/TG compositions (high TG or low cholesterol) even in the face of normal TG levels can drive CETP activity

So statins of course deplete LDL particles of their core CE content - but in general statins do not reduce LDL size. Why not? To maintain normal LDL size CETP goes to work. It needs to fill the LDL with something. So the VLDLs which have lots of TG are happy to allow CETP to take their TG and bring it over to LDLs to maintain LDL size: The LDL gives up its CE to acquire TG. TG

molecules are larger than CE molecules and TG thus takes up more space in the LDL core. So to maintain its size the statin CE-depleted LDL exchanges CE for TG. It will always take more CE-depleted LDLs than CE-rich LDLs to traffic a given level of LDL-C and LDL-P does not go down as much as LDL-C. Normally TG-rich LDLs would be a substrate hepatic lipase (HL) to lipolysis (hydrolysis of core TG and surface phospholipids) but statins can inhibit HL. Thus much to our surprise CETP activity can occur at any TG level and result in further LDL particle CE depletion.

Here is the explanation from Cromwell's Framingham paper (reference provided above):
"Surprisingly, our data also indicate that LDL particles become progressively cholesterol-depleted as LDL concentrations decrease. This relationship, which we are unaware of having been noted previously, is independent of triglyceride level and is not associated with any change in LDL size. We speculate that the cause of this particle size-independent cholesterol compositional change is the lipid exchange reaction mediated by cholesterol ester transfer protein, in which a cholesterol ester molecule in the core of LDL is replaced by a triglyceride molecule from VLDL. Elevated triglycerides (VLDL) have generally been considered necessary to drive this reaction in the direction of making LDL more triglyceride-rich and cholesterol-poor. However, what is relevant is not the absolute VLDL concentration, but the relative difference between VLDL and LDL concentrations. Even with serum triglyceride (VLDL) levels that are not elevated, LDL particles can become cholesterol-depleted and triglyceride-enriched if LDL concentrations are low."

"It suggests that LDL-lowering treatment alone (with statins or other agents) can induce a disconnect between LDL-C and LDL-P numbers. Our data suggest that the magnitude of this disconnect would increase in proportion with the magnitude of LDL reduction, irrespective of triglyceride level (although the greatest disconnect would be seen in those with the highest triglyceride levels because LDL-P would be both small and compositionally cholesterol-depleted and triglyceride-enriched). Direct evidence has been obtained that statin treatment changes the cholesterol and triglyceride content of LDL particles. After atorvastatin treatment, with no change in LDL particle size, isolated LDL particles contained a lower ratio of cholesteryl ester to triglycerides. If LDL-lowering does give rise to cholesterol-depleted LDL-P, one would predict that the percentage decrease in LDL-C produced by statin treatment would exceed the percentage decrease in LDL-P number. Such differences ranging from 4% to 15% have been noted in NMR studies of LDL-P reduction by three different statins and in studies using ApoB to estimate LDL-P number decreases."

Finally Alan Sniderman in a review of over 17,000 patients taking statins and having lipid panels, apoB and LDL-P measurements has commented on this phenomenon in the Journal of Clinical Lipidology 2008;2:36–42 and he states "Many patients who achieve LDL-C and non-HDL-C target levels will not have achieved correspondingly low population-equivalent ApoB or LDL-P targets. Reliance on LDL-C and non-HDL-C can create a treatment gap in which the opportunity to give maximal LDL-lowering therapy is lost." ----- "To argue that cholesterol indices are the only acceptable markers of adequacy of LDL-lowering means either doubting the evidence that ApoB and LDL-P are accurate indices of atherogenic particle number, or that lowering atherogenic particle number is associated with clinical benefit (or perhaps both). It would demand doubting that LDL particles are atherogenic. We submit that such doubts are unreasonable in the face of available evidence."

I beg and implore all of, you who manage lipids who have not both Bill Cromwell's MESA data and Sniderman's statin analysis to do so before you see you next patients.

So in this patient I would leave the Lipitor alone but I would immediately, measure markers of sterol absorption namely sitosterol and campesterol, available at Boston Heart Lab (www.bostonheartlab.com). The report will also come with a lathosterol level which is a marker of cholesterol synthesis. Based on data from STELLAR we know that Lipitor 80 mg is the statin most likely to induce over absorption of all sterols including the potentially atherogenic

phytosterols. Please see Himbergen et al. *J. Lipid Res.* 2009;50:730–739. If sitosterol is elevated, rosuvastatin or Crestor (less likely to induce over absorption of sterols) would make better sense or adding ezetimibe to the Lipitor.