LIPID CASE 265 Lipid treatment frustrates a lipidologist

"I am 36, do not smoke, drink only wine, and rarely. My wife and I eat mostly vegetarian, and are mostly healthy. I now exercise 30 minutes 5 days a week. I am 5'8" 180 lbs, for a BMI of 27.4. My father is 66 and has T2DM, not on insulin. My mother is 65 and at age 61 had 1 vessel CABG at the time of her mitral valve repair (she had been asymptomatic, but on the routine pre-op cath they found an LAD lesion)."

TD: ***Sure sound healthy and the parental CAD is not premature and thus not a major risk factor. However there is T2DM or insulin resistance in the genes.***

"I had a history of having a high LDL-C (~160s), so I started taking Lipitor (atorvastatin) 20 mg when I was ~30-32 years old. Just before the NLA annual conference in Miami in May 2009, I went off the med, as LFTs went up minimally and I wanted to make sure it was only the statin and not something else. I had my NMR done there and the results, are off all meds and before I was exercising: (TD note: LP IR stands for lipoprotein insulin resistance score (0-100) with above 50 indicative of IR)."

May 2009

HDL-C	41	Normal for male
TG	155	(abnormal)
VLDL-C	31	(borderline using NCEP - abnormal using AACC statement)
TG/HDL-C	3.7	(abnormal)
LDL-C	~160	(abnormal)
TC	~230	(abnormal)
TC/HDL-C	5.6	(abnormal)

TD: So the LDL-C (the amount of cholesterol reported in mg that exists in all of the LDL particles that exist in a deciliter (100 ml) of plasma. It is likely calculated using the Friedewald Formula of LDL-C = TC minus [HDL-C + VLDL/C] where the VLDL-C is calculated as TG/5 (on the premise that in a fasting state all TG are in VLDLs and each VLDL particle core have 5 times more TG then cholesteryl ester (CE). How about a little biochemistry? The hydrophobic CE in the core is different than the free or unesterified cholesterol (FC or UC) that sits on the lipoprotein surface in between phospholipid molecules. FC has a hydroxy (-OH) group at the #3 position of the first ring. CE is a hydrophobic molecule where an acyl group (fatty acid) has replaced the -OH moiety. In most folks it is linoleic or palmitic acid (cholesterol linolate or cholesteryl palmitate). Because it is so hydrophobic (lipophilic) the CE moves deep into the core of the lipoprotein - which is why lipoproteins are spherical. The -OH moiety on FC (which makes cholesterol an alcohol) makes FC an amphipathic molecule: one side is hydrophilic (the -OH side) and the other end of the molecule with ethyl groups is hydrophobic (hates water --- i.e. plasma). Thus on the surface of the particle (and in cell membranes) the -OH moiety sticks out on the surface and the other side points inward towards the lipid core. This special biochemical characteristic helps make lipoproteins (lipid carriers)

soluble in water - i.e. plasma). Often the terms polar (water soluble) and nonpolar (water insoluble) are used for hydrophilic and hydrophobic).

The LDL-C is ~160. Well using NCEP ATP-III he is a low risk person and his LDL-C goal is 160 mg/dL with an option for 130 mg/dL. To the unknowing the TG of 155 and HDL-C of 41 seem unremarkable (but my readers in view of the FH of T2DM should be a little suspicious). The non-HDL-C is approaching 200 and according to NCEP (2001), Non-HDL-C in this man is not a goal of therapy since the T are not > 200 mg/dL. We now know non-HDL-C is a better predictor of risk than LDL-C no matter what the TG are. So those in the know should be suspecting there is an atherogenic particle number problem in this doc. What are the other clues? The TC/HDL-C is 5.6 (the poor man's apoB/apoA-I ratio) and that often is associated with high apoB. The TG/HDL-C ratio is 3.7 - which is associated with CAD mortality in men and women and with the presence of too many small LDLs. So what is your guess on what the lipoprotein analysis will show.

LDL-P	2448	extremely high (> 95th percentile)
Small LDL-P	2162	extremely high (in essence all LDLs are small)
LDL particle size	19.6	Pattern B quite small
Large HDL-P	3.3	Low
Large VLDL-P	0.1	Normal

So you must realize that if one has and

TD: Pretty amazing. An extremely high total LDL-P, almost all of which are small. The particle size is really small at 19.5 nanometers (nm). LDL size using NMR testing is: a particle with a diameter < 20.6 nm is small or pattern B. There is a 0.9 nm downward shift in LDL size from 20.6 (normal size) which is a very large change. The particle's volume [which determines how many lipid molecules can be in the particle core is calculated as (4/3) pi times the radius cubed]. Thus particle volume is related to a third power of the radius. Even a change of a few nm can translate into very significant volume changes (smaller particles carry less core lipids). In the patient, there is some discordance in that the LDL-C is the 90th percentile population cut point and the LDL-P of 2448 is the 99th percentile cutpoint - but both are clearly way too high and indicative of risk not predicted by history or lifestyle. Note that the large HDL-P is also quite low? Almost all of the LDLs are also small. Is there a commonality here? Yes - it is the insulin resistance (IR) and especially the TG of 155 in the face of IR. What supports IR in this man? Family history, the TG/HDL-C ratio, the small LDL-P, the lack of large HDL, the small HDL size, and the very small LDL size are all markers of IR.

If we did additional advanced CV testing (beyond particle analysis) as I now do (see www.myhdl.com) we might see elevated free fatty acids or elevated insulin level. What usually causes really small LDLs, and HDLs? The answer is TG in the face of abnormal particle catabolism (lipolysis) typical of IR. Overproduction of VLDL-P (even though the large VLDL-P seems OK, I'll bet small and medium VLDL-P are

very high) and increased CETP activity that facilitates a swap of CE for TG between VLDLs and LDLs and HDLs. The HDLs and LDLs become TG-rich and CE poor and after exposure to hepatic lipase in the hepatic sinusoids, they become small LDLs and HDLs. the latter are vulnerable to catabolism and renal excretion of apoA-I and the former cannot be readily cleared by LDL receptors, resulting in very high LDL particle counts (high apoB). This man has really small LDLs and thus it takes a heck of a lot of them to traffic his 160 mg of cholesterol.
Keep in mind the LDL core should be a 4:1 ratio of CE to TG. If a person has an LDL core of less than 4:1 the LDL will be even more CE depleted, which means even more LDL particles will be needed to carry his 160 mg of cholesterol. So when trying to figure out what contributes to LDL-P, it is not only LDL size but LDL core composition (meaning its ratio of CE to TG). The more TG that are inside of LDLs (or HDLs), the less CE the particle will be capable of carrying. What causes the influx of LDL and HDL TG and exodus of CE? It is CETP activity which of course is TG-driven A physiologic TG level is 10-70 with a mean of 30, So in this IR man with a TG of 155 - it should be no shock he has a malignant LDL-P and his CV risk is substantial - way more than that predicted by his lipid profile. Simply following NCEP guidelines in this man might not be so wise. Fortunately it is not a felony to think outside the box and deviate from guidelines. I hope one day soon we will be able to measure

A side note: Can we all get rid of the idiotic, no longer useful term small, dense when we speak of LDL. That is like calling an obese person as that fat, plump man. Lipoproteins can be buoyant or dense and that is how they separate in the centrifuge. If you measure diameters what are the sizes of the buoyant vs. the dense particles. The buoyant particles (lots of lipids) are always larger. It is lipid content that makes a lipoprotein buoyant and it is the surface protein content that determines density. Proteins have much higher molecular weights than do lipids. The most dense particles will have little lipids and lots of proteins. The more lipids a particle has, the more buoyant and the larger it will be - it takes a lot of volume (related to size) to carry a lot of lipids. Thus it is the lipid content relative to the protein content that really determines density. All buoyant particles have way more lipids relative to their protein mass (THEY ARE LARGE due to their lipid content). Particles with less lipids and therefore will have higher density. All small particles are denser than their larger relatives. So let's just call the obese man fat and let's just call the small, dense LDL small. The word density adds nothing to the discussion and is a total redundancy. What are the smallest particles as well as the densest? The HDLs- very little lipids - lots of proteins. Everyone says small dense LDL and no one uses the term large, buoyant LDL. So please: henceforth - it is small LDL. Get rid of the redundant adjective dense. EVERY small LDL is dense.

Clinician: "So, I "saw the light" and started exercising and started Crestor 20 (rosuvastatin) mg daily"

September 2009

HDL-C	37	now low (was 41)
TG	200	higher (was 155)

VLDL--C	40	higher
TG/HDL-C	5.4	Much higher (was 3.7)

TD: Wow looking at that you start to wonder how did those parameters worsen on a powerful statin like Crestor. LDL-C was not reported. But of course lipidologists know for many if not most IR patients lipid concentrations (how much lipids are inside of various lipoproteins) have great potential to cloud the issue and confuse the provider. So here is the follow up NMR LipoProfile:

Total LDL-P	1216	Much better: now at 30th percentile cutpoint
Small LDL-P	1120	improving - still high
LDL particle size	19.5	slightly smaller
Large HDL-P	8.0	higher than previous and now normal
Large VLDL-P	2.3	now slightly abnormal

TD: So who cares what Crestor did to the lipid concentrations: It dramatically reduced the number of atherogenic lipoproteins (LDLs). Is Crestor really that good? When statins work way beyond what is expected we should suspect hypoabsorption of sterols, meaning the high LDL-C is the result of cholesterol over production, which is of course is related to HMGCoA reductase activity. Clearly statins would work better in persons with increased HMGCoA reductase activity than in those with less activity. An easy way to diagnose over production of cholesterol is to measure the cholesterol precursor sterol called lathosterol (www.bostonheartlab.com).

Why would HDL-C drop if large HDL-P went up. If the HDL particles were apoE enriched, the statin upregulated LDL receptors could clear them - that would be inducing indirect reverse cholesterol transport (HDLs returning cholesterol to the liver), which is likely beneficial. Why the increase in TG and large VLDL-P? We do not know what happened to total VLDL-P, but I am sure it was lowered drastically. So I am not sure the VLDL size shift has a lot of clinical meaning, other than it reminds us the patient is insulin resistant. The statin did little to the LDL size, but no one expected it to and this shows you again one does not have to shift LDL size to get CV benefit. Reducing the LDL-P by over 1000 nmol/L will reduce risk, no matter what the LDL size is. .

Clinician: "I Added Zetia 10 mg and Fish Oil 4g (of EPA/DHA) and here are the follow up labs:"

May 2010

HDL-C	42	now normal (back where it was originally)
TG	84	much better almost physiologic
VLDL-C	16	
HbA1c	5.7	

TD: Again LDL-C not reported. Notice how the HDL-C is jumping all over the place. Is this real or is this just lab assay variation: remember HDL-C can vary by up 5-10% depending on lab quality and variance. The TG have really dropped which should be no surprise with 4000 mg of N-3 FA in the regimen. So obviously TG do not have to be > 500 mg/dL for N-3 FA to be efficacious. And if his previous HDL particles were TG-rich, then removing TG would mean the HDL could go back to trafficking CE and HDL-C would go up. A normal HDL particle has 90% core TG and 10% TG. In an IR patient with high TG and increased CETP activity the HDL would be exchanging CE for TG with VLDLs, making it TG-rich and CE-poor. Why do I even discuss lipids: let's look at the lipoprotein analysis: (LPIR stands for Lipoprotein Insulin Resistance score (0-100 with a value > 50 indicating insulin resistance).

Total LDL-P	1060	Further improvement: now at the 20th percentile
Small LDL-P	854	improved - still above 50th percentile
LDL particle size	19.8	small but slightly larger
Large HDL-P	0.9	very low
HDL size	8.3	small
Large VLDL-P	<0.7	now normal
LPIR	45	This score is not validated on persons using medication (ignore)

TD: Adding the Zetia and N-3 FA improved the profile above what Crestor did. There was an additional drop in LDL-P which would be expected: the N-3 FA shifted the LDL size up a tad and the Zetia upregulated additional LDL receptors beyond what the stain did. When one does shift LDL size, the apoB conformation on the LDL changes in a way that better exposes the LDL receptor binding segment of apoB. The better exposure makes it easier for the LDL receptor to bind to it. Caution with using the LPIR in patients on medication: its validation was done in drug naive patients. Different drugs remodel lipoproteins in very different ways and thus caution is at play assuming what a drug does to lipoproteins correlates with improving or worsening IR. Best example: niacin would improve the LPIR score but can in fact aggravate IR. Bottom line is this patient is at LDL-P goal and nothing more need be done. However sometimes physicians start over-thinking

Clinician: "Thinking that my primary problem was insulin resistance, I stopped Zetia, and started Actos 15 mg (still taking Crestor 20, 4g fish oil)"

July 2010

HDL-C	50	highest yet
TG	87	near physiologic
TG/HDL-C	1.7	
HbA1c	5.7	
LPIR	61	Again: Lp IR is not validated in patients taking lipid meds

TD: HDL-C up a bit. TG remain near perfect on the N-3 FA. Over time the N-3 FA seem to be inhibiting CETP (but Crestor is also known to do this) - by lessening CE depletion of HDL reduced CETP activity is associated with rising HDL-C. Of course the dose was low, but Actos inhibits hepatic lipase which would increase HDL-C and raise HDL-C. But what happened to the particles?

Total LDL-P	1431	up again
Small LDL-P	932	up again
LDL particle size	20.6	Pattern A (normal size)
Large HDL-P	1.7	Low again
HDL size	8.4	Small
Large VLDL-P	1.4	normal but rising

Clearly stopping Zetia was not the thing to do. There would be less LDL receptor upregulation and less clearing of LDL particles and surprise - LDL-P went up. Lesson learned I hope! By the way the above stated Actos inhibits HL and can increase large HDL-P - that did not happen as the Actos dose is too small. That gets me into the real issue is why anyone would even consider Actos use in this patient with no glycemic issues? The clinician chose it as he had a desire to increase LDL size - a fictional goal of therapy supported by no trial data. His LDL-P was at goal - who cares if they were small particles. What drives LDLs or any apoB particle into the artery is particle number not particle size. Small LDL because it is the preferential carrier of lipoprotein associated Lp-PLA2 - the enzyme that hydrolyzes LDL surface phospholipids to oxidized fatty acids and lysophosphatidyl choline (an endothelial irritant). That makes small LDLs, once they enter the arterial wall prone to oxidation and arterial wall macrophages love to ingest oxidized LDLs. So looking at Lp-PLA2 and a neutrophil secreted enzyme myeloperoxidase might be very insightful in this patient.

A better reason to use Actos is to delay the onset of T2DM - but the absolute best way to do that is lifestyle which is already being well done. If a drug is desired, most would pick metformin (not only because of cost) but because of safety. TZDs (all of them) cause osteopenia, osteoporosis and increase fracture risk. That is way too much a price to pay in a young man who was at LDL-P goal who has an HgbA1c of 5.7.

Clinician: "Frustrated that particles went up that much, and kicking myself for stopping Zetia, I restarted Zetia 10 mg (still taking Crestor 20, 4g fish oil, Actos 15 mg)"

September 2010

HDL-C	43	down from previous
TG	46	physiologic
TG/HDL-C	1	normal
HbA1c	5.6	
LPIR	44	Whatever

TD: Not much help here with the above lipids - all look fine. Back to the particles:

Total LDL-P	1215	dropped a bit was 1431 1215 is 50th percentile cutpoint
Small LDL-P	807	down a bit but still higher than would be seen in a non IR pt
LDL particle size	20.3	Pattern B again
Large HDL-P	1.3	dropping a bit
HDL size	8.4	no change still small
Large VLDL-P	<0.7	normal

TD: Well Zetia did reduce LDL-P again, but not to < 1000 where we might ideally like it to be.
Clinician: "And this is where I stand. Currently taking Crestor 20/ Zetia 10/ Actos 15/ Fish Oil 4g. Should I switch Actos to metformin for the IR/small particle problem? Increase the dose of Actos? Start Niaspan (but TGs/VLDL don't seem to be a big issue now)? Welchol to lower LDL-P? Lengthen workouts, cut caloric intake and lose 10lbs? (I know I should do this...)"

In a young man I am not sure there is any evidence we should get more aggressive at this very moment. With continued and even a little more aggressive lifestyle (as he suggests) he can be followed with a close eye on the lipoprotein parameters. I suspect they will improve further. If not, then we can consider additional therapy (like increasing Crestor dose to 40 mg which is the dose used in METEOR and it more than halted CIMT progression). Is there anything that would make me get more aggressive at this moment: surely- I would be following his Lp-PLA2, myeloperoxidase or MPO, insulin level, with an occasional check of NT-proBNP. If he has never had them I'd also check a few other things that might clue me into a higher risk than I suspect: Lp(a) mass with Lp(a)-C and homocysteine.