Case # 279 Treatment Dilemma: Horrific CV risk vs. Hepatic Safety

This 65 year old asymptomatic woman is one of my cases and was referred by her primary care physician. As many of you know, my practice is referral only and is limited to severe lipid and lipoprotein abnormalities, treatment refractory lipid disorders and those with recurrent CHD events.

She has a very strong paternal history of premature CHD and was found in 2005 to have elevated cholesterol. She has osteopenia and well treated hypothyroidism. Her mother is still alive at 90 with severe osteoporosis but no CHD. Her father died at 55 after his third MI; 5 of her father's siblings had premature CHD. Her younger brother has had a CABG. Her 2 adult daughters in their 30s have never tested for lipids. Back in 2005 she was started on Vytorin (simvastatin and ezetimibe) and within 2 weeks' time developed dark urine, jaundice, anorexia and was found to have jaundice with severe hepatic abnormalities requiring hospitalization for 5 days: no biopsy was done. The Vytorin was discontinued by the patient when she started to feel severely ill prior to admission. No other etiology of the liver dysfunction was found (standard Hep A, B & C tests negative) and the condition resolved spontaneously. The patient was never challenged with any other type of statin or lipid medication except niacin which because of flushing was not tolerated. In reality the lipids have been ignored but she has had two negative stress tests (last one in 2010). She has never had a coronary calcium test or CIMT. Current medication includes weekly Fosamax with D, calcium and Levoxyl 50 mcg. Because of a very low Vitamin D the patient had just been started on Replesta 50,000 units weekly a few weeks before my testing. The patient has become increasingly concerned with her untreated risk and asked he provider to perhaps try a different statin, but he steadfastly refused saying he did not want to destroy her liver. Finally he referred to a lipidologist. (me).

Height: 60 Weight: 143 BP: 130/70 BMI: 28

All of my new patients get significant lab screening two weeks prior to seeing me: this way I have all the data I need to assess risk and outline a treatment regimen on the day I see the patient. My testing is NMR based (www.lipoprotfile.com) and greatly enhanced by Health Diagnostic Labs in Richmond, VA (www.myhdl.com). Here are the results:

LIPIDS:

TC =268 LDL-C = 153 HDL-C = 79 TG = 129 Non-HDL-C = 189 (all in mg/dL)
The LDL-C is at the 75th percentile population cut point
The non-HDL-C is at the 81st percentile

Synthesis markers: Lathosterol 4.4 Desmosterol = 3 (Normal)
Absorption markers: Sitosterol = 4.4 Campesterol = 6 (Normal)

LIPOPROTEIN ANALYSIS:

ApoE3/E3 genotype
ApoB = 127 mg/dL (FOS 88th percentile)
ApoA-I = 215 mg/dL (high)

ApoB/ApoA-I ratio = 0.59 (normal)

Total LDL-P = 2026 nmol/L MESA (98th percentile) – very high risk
Small LDL-P = 608 nmol/L (unremarkable)
LDL size = 21.3 nm fairly large particles (Pattern A)
Total HDL-P = 41 umol/L (excellent)
LDL-P/HDL-P = 49 (2nd quartile)
Large VLDL-P < 0.7 nmol/L (normal)
LP-IR score = 15 (low)
Lp(a) = 110 mg/dL Lp(a)-C = 19 mg/dL (both high and indicative of high Lp(a)-P)

INFLAMMATORY MARKERS:
Myeloperoxidase (MPO) = 500 pmol/L
Lp-PLA2 = 190 ng/ml
hs-CRP = 7.9 mg/L
NT-proBNP elevated at 146 pg/ml
High-sensitivity Troponin I normal

OTHER MARKERS:
HgbA1c 5.3 Insulin level normal at 4
Vitamin D 27 ng/mL (low)
Omega 3 Index 5.7 (low)
Homocysteine: 11 umol/L
MTHFR Genotype T/T (abnormal)

DISCUSSION: This woman presents with a real challenge because based on her age, family history, significant lipoprotein and inflammation abnormalities her risk for a CV event is high and she easily qualifies for lipid modulating medication. Her biggest risk factor and the first therapeutic mission is to try and reduce the excess of atherogenic apoB-containing lipoproteins almost all of which are LDL particles. There is no better apoB lowering monotherapy than statins. Yet all lipidologists know that as good as statins are at achieving LDL-C goals, they are far less efficacious at attaining non-HDL-C goals and not very good at all in achieving apoB or LDL-P goals (see Sniderman Journal of Clinical Lipidology (2008) 2, 36–42). But we have to start with something. Of course the dilemma is her previous hepatic episode. But let's examine that closely. Seemingly on Vytorin (simvastatin plus ezetimibe) she had severe hepatitis within two weeks of use: the rapid onset of hepatic disease in itself is extremely unusual with a statin and to my knowledge unheard of with ezetimibe. The Vytorin package lists hepatic aminase abnormalities as a warning but makes no mention of fulminant hepatic disease. The NLA statin safety report in the hepatology manuscript (Am J Cardiol 2006;97[suppl]:77C–81C) states *"there have been rare case reports of liver failure in patients receiving statin therapy with an evidence level of 2D* (meaning the evidence is confident but is undocumented and not definitive). *After an extensive review of the literature, the Liver Expert Panel could find no direct evidence of death due to liver failure caused by statin*

therapy." Is it possible the patient was coming down with some viral hepatitis and the statin had little to do with the reaction or perhaps aggravated it? We can only guess.

Before we decide on therapy, let's look closely at what is going on. Clearly there are way too many apoB particles present. As the American Association of Clinical Chemistry (AACC) Guidelines state, apoB is simply another methodology other than NMR spectroscopy to determine LDL-P. ApoB is not a measure of VLDL particles and unfortunately too many look at apoB as if it is providing information on VLDL: it is not! Why are there so many LDL particles in this woman? The markers of cholesterol synthesis and absorption are normal, which thus would suggest there is a problem clearing the LDL particles – an LDL receptor defect, defective apoB or a PCSK9 gain of function mutation or who knows what.

Since it is atherogenic particle number, not particle size that forces LDLs into the artery, our best measurement of lipid and lipoprotein risk is not cholesterol measurements within the particles (such as LDL-C) or subparticle cholesterol measurements but rather particle numbers measured as LDL-P or apoB. LDL particles that are small, or that carry more TG than cholesterol are "cholesterol depleted" particles. Such patients usually have very high apoB or LDL-P levels even though the cholesterol within the particles (LDL-C) is normal. This explains how one can have atherosclerosis with normal particle cholesterol measurements. Normally LDL particles carry very little TG, but when they do, the LDLs may be both large but yet very cholesterol-depleted and therefore it will take a lot of LDL particles to traffic whatever cholesterol is present. Because she has large LDLs with a bit of discordance between LDL-P and LDL-C I suspected elevated LDL-TG might be at play in this patient, but I actually had that test (LDL-TG) done and it was not elevated.

What is also worrisome in this woman is the elevation of both Lp(a) and Lp(a)-C both of which together indicate a high Lp(a)-P. We now know that apart from aggravating coagulants, apo(a) traffics oxidized lipids and the elevation of MPO makes me worry that Lp(a) is creating arterial wall havoc. The normal Lp-PLA2 provides some comfort. The low vitamin D and Omega 3 index levels are serious risk factors, but at least both are easily treated. Over the last few years little has been more confusing than trying to understand homocysteine as a risk factor for CHD and Alzheimer's disease and deciding whether to treat high levels or not. Although most think it has been ineffective, in reality we are still awaiting a properly designed trial using folic acid therapy to lower homocysteine in those with high levels to answer the question will it reduce clinical events. One problem is that folic acid is metabolized differently in different patients as the gene methylenetetrahydrofolate reductase (which converts folic acid to its active form, 5-methyltetrahydrofolate or MTF) has mutations (normal genotype is C/C, heterozygotes have C/T and homozygotes T/T). The appearance of the T allele is associated with less MTHFR activity. Without proper methylation homocysteine is not converted to methionine and it accumulates. Folic acid supplementation may overcome the MTHFR abnormalities but not always. Some advise recommending methylfolate (OTC FolaPro by Metagenics or prescription Metanx by Pamlab). Since the patient's homocysteine is only 11, at this time, despite the TT genotype specific homocysteine-lowering therapy (apart from lifestyle) is not indicated. When it comes time to consider

drug therapy in patients with homocysteine issues especially if an MTHFR mutation is present, caution (meaning close monitoring) if fibrates or niacin are used. Use those drugs of needed but monitor the homocysteine. Fibrate induced elevations of homocysteine are readily treatable (Nutrition 2001;17:721-723).

OK, it is decision time: what are we going to do – I see little prayer of getting close to goal without statin therapy. I sort of doubt her previous liver issue had anything to do with the statin, but I will proceed with significant caution. Here is what the hepatologists who wrote the NLA statin safety report state: "W*hen a healthcare professional is concerned about the possible occurrence of a hepatotoxic reaction due to statin therapy (eg, because the patient reports jaundice, malaise, fatigue, lethargy, or related symptoms during treatment), the Liver Expert Panel believes that an assessment of fractionated bilirubin level is advisable. In the absence of biliary obstruction, bilirubin is a more reliable prognosticator of liver injury in the setting of drug toxicity. If the direct fraction of bilirubin is found to be increased in association with elevated aminotransferases, it is reasonable to assume that there is ongoing liver injury and further appropriate testing should be undertaken to ascertain the etiology."*

The patient was advised that she has very high LDL-P, very high Lp(a), elevated inflammatory markers, borderline homocysteinemia, hypovitaminosis D, a low Omega 3 Index in the setting of a horrific family history of premature CHD. All of these puts her at very high risk for an atherothrombotic event. Aggressive therapy will be needed (albeit complicated with her previous experience with a statin). Performing imaging like a coronary calcium test in an asymptomatic woman is unlikely to change any therapeutic decisions.

Of course, statins inhibit the synthesis of cholesterol in the liver and other tissues. To replenish that needed cholesterol the liver forms a protein called LDL receptors which bind to and internalize apoB particles. Lipidologists understand the low cellular cholesterol causes LXR down regulation, leading to activity of the nuclear transcription factor called sterol regulatory element binding protein 1 and 2 (SREBP) which leads to increased production of hepatic LDL receptors (LDLr). (Thus statins are quite good at lowering apoB and LDL-P). Most of that LDLr upregulation comes with the lower doses of the statin.

Of all of the statins now available, Livalo (pitavastatin) has a very clean pharmacodynamic profile and is the least likely statin to have a drug-drug interaction. It also gets in and out of hepatocytes with the membrane solute transporter proteins called organic ion transporters (OAT), specifically 1B1, without much interference from other meds (indeed only cyclosporine and to a much lesser extent erythromycin and rifampin can influence it. These membrane transporters may also explain why pitavastatin may not enter myocytes so easily, but that remains to be proven. There is certainly a belief in the lipidology community that pitavastatin is associated with significantly less myalgia (a belief that is not in the drug's FDA package insert) and is the go-to statin when myalgia occurs.

Once in the hepatocyte pitavastatin (the active drug) is rapidly converted via glucuronidation enzymes not used by other drugs, to its inactive lactone form and both pitava and pitava-lactone transform back and forth in a happy equilibrium and recycle in the hepatobiliary system. There is almost no CYP oxidative metabolism (and certainly no clinically significant interactions). Because of its unique structure that includes a cyclopropyl group (something no other statin has). This three carbon triangle shaped molecule looks like a martini glass if you glance at the structure of the pitava molecule.

We will try one mg tablet, to be taken twice week starting today: it has a tremendous binding affinity for HMG CoA reductase (much more so than HMGCoA itself. The pitavastatin cyclopropyl group affinity for the enzyme is why pitavastatin is at least 8 times more potent at inhibiting the enzyme than other statins and why it only takes 1, 2 or 4 mg to do what the other statins need doses of 10, 20 and 40 mg to do. Indeed pitava has non-inferiority data against simva 20 and 40 mg and atorva 10 and 20 mg and in just published study non-inferiority against atorva 40 mg. Of even greater interest is that in that study pitavastatin was much better on glycemic parameters than atorva (see Diabetes, Obesity & Metabolism doi: 10.1111/j.1463-1326.2011.01477.x). If one reviews the multiple studies it seems pitava is as good or superior to other statins on increasing apoA-I, HDL-C, upregulation of ABCA1, inhibiting apoC-III, reducing adiponectin and inducing LPL (all of these are PPAR-alpha effects). The best all-encompassing review of pitavastatin is Clin. Lipidol. (2010) 5(3), 309–323 (not to be confused with the Journal of Clinical Lipidology).

So after a discussion with the patient, in view of her severe CV we decided to start Livalo at 1 mg twice a week and to monitor LFTs on a weekly basis for the foreseeable future until we arrive at an effective dose. At least 2 to 4 mg will be needed and ultimately Zetia may also have to be revisited. For the next month every 7 days, hepatic functions will be done. The patient was instructed to report any adverse symptoms whatsoever including muscle aches or weakness or fever or malaise and to hold the drug should any of those occur. After week one, the LFTS are normal.

Take home points: After age, elevated LDL-P is the number one risk factor for CHD. Clinical decisions ultimately come down to the provider, with counsel from the patient, who makes therapeutic choices based on experience, solid understanding of the pharmacology of the drug, guidelines. With respect to using statins pitavastatin (Livalo) is fairly new to the US and as more and more providers begin to understand its pharmacokinetics and dynamics, is becoming a major tool of lipidologists in others in their complex polypharmacy and lipid-drug intolerant patients. I hope you all read the review cited above.