

LIPID CASE 226 Low TC and Low HDL-C Treat?

Our first case of 2009 deals with a not uncommon clinical condition on which my opinion is solicited several times a year. It revolves around the ingrained assumption that low HDL-C is always a cardiac nightmare and any human being is doomed unless they have a perfect HDL-C level (whatever that is). A provider contacted me and stated: "I have a simple question. How low can HDL-C be if total cholesterol is less than 150? For example I have a patient with history of CABG with the following lipid profile:

TC = 111 HDL-C = 31 TG = 69 LDL-C = 62.

Is there a *general rule*: if total cholesterol is low, how low can HDL-C be before you treat it? I have heard mixed reviews on this and would like it answered by you."

DAYSRING ADVICE:

First I am presuming the lipid concentrations reported above are on-treatment lipid levels: likely the patient is on a statin, statin/ezetimibe or statin/niacin combination.

We have to be careful with semantics here: A careful reading of the NCEP ATP-III guidelines would reveal the only lipid parameter that guides treatment is LDL-C and the only goals of therapy are LDL-C and non-HDL-C if the TG are elevated > 200 mg/dL. There is no HDL-C or TG level (under 500 mg/dL), per se that mandates treatment and there are no specific HDL-C or TG goals of therapy once treatment begins. NCEP defined several risk categories and stated within each category at what LDL-C level lifestyle and pharmacological therapy is triggered. Once treatment is initiated there are specific LDL-C and non-HDL-C goals of therapy levels, with more aggressive goals in the high and very high risk categories. NCEP states the best way to reduce risk in at risk patients with high TG or low HDL-C is to normalize LDL-C and then non-HDL-C if the TG are high. NCEP mentions that patients with isolated low HDL-C (normal LDL-C, normal TG) who are in **A HIGH RISK CATEGORY** might be treated with a fibrate or niacin but again offered no specific HDL-C level triggers for such therapy or a specific HDL-C goal of therapy to attain. If you see a person in a lower risk category with low isolated HDL-C, it was not discussed in NCEP.

Let's review some of the pathophysiology: In our insulin resistant world, the most common scenario where patients have low HDL-C is in patients with TG/HDL-C disorders (T2DM and metabolic syndromes: full or partial).

Yes there is a general rule in Lipidology: As TC drops all cholesterol levels drop. Remember that TC is simply the sum of one's LDL-C, VLDL-C and HDL-C and if cholesterol is leaving the serum those numbers will reduce. The last phase in an HDL's journey in reverse cholesterol transport is to give up its cholesterol: i.e. the HDL particles delipidates (at the liver or intestine or via CETP) or is endocytosed by the liver

Technically speaking, you never ever treat low HDL-C per se, but rather the risk that may be associated with it. In essence you treat any and all of the associated risk factors which are amenable to therapy, presuming they are identified. In untreated insulin resistant patients with low HDL-C, such other treatable risk factors almost always do exist (remnant lipoproteins, cholesterol-poor LDLs). There is no guideline anywhere that tells you to start therapy depending on what the specific HDL-C is. The majority of patients with CAD who have low HDL-C prior to therapy have very high apoB or LDL-P (due to TG induced overproduction of VLDL). Yet, there are genetic conditions where low HDL-C is not associated with CV risk and one would not want to treat those folks unnecessarily (interestingly these people with low HDL-C usually have low apoB levels).

As you dramatically lower TC, all cholesterol levels, including HDL-C, will drop. NCEP provides two and only two goals of therapy, both of which are lipid concentration surrogates of apoB (atherogenic particles): LDL-C and non-HDL-C. In the very high risk patient under discussion both have been normalized or in other words that patient has reached his NCEP goals of therapy. This suggests that atherogenic particles no longer exist, so why treat further? You are done with therapy according to guidelines. Also note the TC/HDL-C ratio is perfect despite the low HDL-C and this suggests whatever risk used to be present has disappeared. You might think you want to raise HDL-C to promote reverse cholesterol transport, but readers of my newsletter know a serum HDL-C level has no relationship to the RCT process (see Duffy & Rader. *Circulation*2006;113:1140-1150).

The cholesterol that causes atherosclerosis is trafficked into the artery wall as a component within an apolipoprotein B containing particle: smaller chylomicron and smaller VLDL remnants, IDLs and of course LDL particles (of any size). These particles are driven in by concentration gradients. Once the apo B particle concentrations have been minimized (returned to physiologic levels), they no longer enter the arterial wall. We are still learning what functions HDL particles perform, and believe me we are still in our infancy on this subject. Certainly HDLs can traffic cholesterol from a source of lipidation (usually the liver and small intestine) to its destination for delipidation (steroidogenic tissues, adipose tissue or back to liver or intestine), but many fail to realize that the major component that contributes to the high density of HDLs are the numerous surface proteins (over 50) they traffic. Until we learn the function of each and every one of those proteins we will never truly understand HDLs. Until clinicians can assay the beneficial CV proteins that may or not be present on an HDL we will never totally and accurately predict are we helping a given patient by modulating some laboratory parameter such as how much cholesterol is within all of the HDLs in a deciliter of plasma (HDL-C). The amount of cholesterol within the HDLs has little correlation with the presence or absence of beneficial surface or unbeneficial HDL proteins. The presence or absence of these proteins determines an HDL's functionality: an HDL lacking critical proteins would be "non or dys" functional. I urge you all to read a very recent article entitled HDLs: Fall from grace? in *Annals of Medicine* 2008; 40: 584-593. The author's state: the progressive insight that HDL may actually be predominantly a carrier molecule of a wide array of proteins rather than merely a cholesterol-transporter has resulted in the interest to look beyond HDL-C levels alone.

Another developing story with HDLs is that it may be more important to know how many HDLs are present (HDL-P) rather than how much cholesterol is inside of the particles (HDL-C). Certainly if one has functional HDLs, it makes sense that having a lot of them would be beneficial and any reduction would be problematic. However even those measurements would not tell us are the HDLs lipidating and delipidating in proper fashion, are they delipidating arterial wall macrophages (macrophage reverse cholesterol transport) and are they carrying the critical proteins. *J Am Coll Cardiol* 2008;51:634-42. See my writings and slides on the web site www.lipidcenter.com click on professionals and scroll down to PP files and go through the slides on the program called "HDLs Do we have a clue?"

It is amazing how many folks try to raise HDL-C when there is no need to do so and where raising it (as in the case at hand) would likely be impossible. In such cases the only way to raise HDL-C would be to raise TC and clearly that would be asinine. Patients who used the Dean Ornish very low fat diet significantly dropped HDL-C yet plaque regressed on angiograms (*Lancet*. 1990;336:129-133). Of course that same diet significantly dropped apoB. I however would check LDL-P before assuming there are no remaining increases in atherogenic particles (see below).

In the patient being discussed:

TC = 111 HDL-C = 31 VLDL-C = 53 LDL-C = 62 TG = 69 Non HDL-C = 80

For cholesterol induced atherosclerosis to occur the patient has to have too many apoB particles (which traffic the sterols into the artery). The surrogates in the lipid profile that have some

correlations with apoB are TC (if > 200), LDL-C (if > 70 in a very high risk patient) and Non HDL-C (if > 100 in a very high risk patient). Thus all of the apoB-related lipid measurements in this patient are perfect. One could order apoB or LDL-P to be sure and that makes sense to do in a very high risk individual. Bill Cromwell did report in last year's analysis of the Framingham Offspring Study (Journal of Clinical Lipidology 2007;1:83–592) that there are some people with normal LDL-C, normal LDL size and normal TG who still have high LDL-P, because their particles are very cholesterol depleted. If one has cholesterol-depleted LDLs it will take more LDLs to traffic a given level of cholesterol. So if an LDL-P was performed on this man and it was high, further treatment would be indicated to normalize LDL-P. So again if we assume, based on perfect apoB-cholesterol parameters (LDL-C, non-HDL-C) that perfect LDL-P (or apoB) concentrations exist, then why would one want to raise HDL-C? What trial would support that?

Why does the Dean Ornish extreme low fat diet so effectively reduce all cholesterol levels? Well the initial substrate from which cholesterol is synthesized is acylCoA (acetoCoA, acetylacetyl CoA) which is derived from fatty acid breakdown (oxidation). So eliminating fat from the diet will drastically reduce endogenous cholesterol synthesis and all cellular cholesterol levels will lessen. As cellular cholesterol synthesis reduces, less is effluxed via ABC family transporters into HDL particles: HDL-C will lessen. Also in people significantly restricting fat intake, the liver will have less cholesterol (less chylomicron delivery of fat, less production, less being brought back to the liver in HDLs: the results is when the liver makes VLDLs and IDLs, they carry a lot less cholesterol (less VLDL-C, less IDL-C and this will ultimately result in less LDL-C. Of course Ornish showed that by drastically reducing TC levels (as well as LDL-C) via fat restriction angiographic improvement occurs in persons with CHD. It mattered little that because of reduced cellular cholesterol, HDLs were no longer being fully lipidated (thus reducing HDL-C).

If the patient is not already on it, would niacin raise this man's HDL-C ---- Probably not! Niacin with a PPAR effect on liver X receptors (LXR) upregulates hepatic ABCA1 transporters facilitating hepatic lipidation of HDL particles. In a patient like the one under discussion, the liver would not have a lot of excess cholesterol to export and thus HDL lipidation would not be facilitated by niacin in this type of patient. Niacin also inhibits hepatic lipase which would prevent HDL particle lipolysis and tend to keep large HDLs large. However because of the very low HDL-C, this patient would not have very many large HDLs (patients with HDL-C < 40 mg/dL have predominantly smaller HDL species (see Cromwell and Otvos's Chapter in Therapeutic Lipidology) and inhibiting HL would not do much. HDL-C would not change much. Niacin (nor any other currently available drug) is unlikely to raise HDL-C in a patient with a TC of 111 and normal TG levels.

In conclusion, the patient is at goal, it is unlikely he has a high LDL-P (although I would certainly check it) and I do not believe further lipid/lipoprotein treatment is needed. Forget the HDL-C. Move on!

LIPID CASE 227 Fibrates

Let's use the following case to try and understand fibrate therapy: a 50 year old male physician with no family history of premature CHD and with a coronary calcium score of zero and a negative CTA is obese with an abdominal circumference of 41 inches. His BP is 120/65. He has the following lipid profile:

TC = 214 mg/dL, HDL-C = 30, TG = 277 LDL-C = 129 Non-HDL-C = 184
FBS is normal as are aminases hs-CRP = 0.8 mg/L

The patient was advised to follow a diet, exercise, lose those abdominal inches, and take a reliable fish oil, 4 g/day. The provider asked me on whether to use a statin or not with the negative imaging studies.

DAYSRING ADVICE:

In the face of definite lipid and lipoprotein abnormalities, the negative imaging studies have little meaning to me with respect to lifetime risk of disease, thus I am not sure what the negative CAC means as far as saying he has no worries. Recent presented data showed there still can be considerable atherosclerosis despite a negative CAC: Earls J. #SSK02-03. Presented at: Radiological Society of North America 94th Scientific Assembly and Annual Meeting; Nov. 30-Dec 5, 2008; Chicago. About 14% of those with a calcium score of zero showed noncalcified plaque in the angiograms. After a rereading by two blinded reviewers, the percentage of patients with a calcium score of zero rose to 26%. Sixty-eight percent of the patient had plaque <25% luminal narrowing, 31% had <50% narrowing and four patients had stenosis >50%.

For sure there are significant lipoprotein abnormalities in this patient and I believe based on age and the presence of the metabolic syndrome (note the high TG, low HDL-C and obesity) he is a high risk patient. Without apoB or NMR particle quantification numbers available, advanced students of the lipid profile should have immediately ignored the LDL-C and look for further evidence of atherogenic lipoproteins. Never forget lipids are trafficked as passengers within lipoproteins and any lipoprotein carrying sterols that is capable of penetrating the endothelium, becoming oxidized and are considered atherogenic. Of course they are the beta-lipoproteins diagnosed as apoB-containing particles (VLDLs, IDLs, and LDLs). If too many are present they enter the intimal layer. It is particle number that best correlates with atherogenesis. Elevated TC and LDL-C suggest high apoB, but there is great discordance with these lab tests in patients with cardiometabolic risk (insulin resistance).

When TG are high, the liver over produces and over secretes too many large VLDL (very TG-rich) particles. NMR data has shown large VLDL-P to be a good predictor of CV risk as well as a predictor of the metabolic syndrome. In IR patients the half life of these gigantic "fat balls" is markedly increased due to decreased activity of several catabolic lipolytic forces (high apoC-III, decreased lipoprotein lipase activity). Letting these TG fat balls float around increases blood viscosity, downregulates endothelial nitric oxide production and increases coagulation via PAI-1 and fibrinogen. With increased residence time in plasma, these large VLDL have plenty of time using cholesteryl ester transfer protein (CETP) to swap their TG for cholesteryl ester (CE) from HDLs and LDLs. Think about this carefully: The large apoB-enwrapped VLDL steals CE from HDLs where it was not atherogenic and from LDLs. The LDLs and HDLs are now carrying TG rather than CE. If one looks at the lipid profile: nothing has happened to total cholesterol or TG levels, but VLDL-C has gone up, LDL-C and HDL-C has gone down. Even though LDL-C goes down, the VLDL-C has risen and HDL-C has reduced, resulting in a now a higher non-HDL-C (the best lipid concentration surrogate of apoB). The unchanged TC divided by the now reduced HDL-C would now reveal a high level of the TC/HDL-C ratio: this correlates with RISK! The grossly high TG/HDL-C ratio ($277/30 = 9.2$) is well above 3.5 and extremely suggestive of small LDL particles. Small LDLs have very high LDL-P (apoB). The large VLDLs that have become CE-rich when exposed to lipoprotein lipase lose some of their TG and become smaller, CE-laden VLDL or IDL particles (considerably larger than LDLs): these are called remnant lipoproteins and are considered very atherogenic. Because of their much longer half life, there are many, many more LDLs than VLDLs. VLDL-P although atherogenic, do not really contribute much to total apoB levels. One can reduce apoB and still have too many atherogenic VLDL particles present. This is another reason I prefer the NMR profile rather than apoB: it is tough to diagnose remnants using apoB, but easy to diagnose then using various VLDL-P species reported on the NMR LipoProfile (www.lipoprofile.com). Of course NCEP ATP-III states elevated VLDL-C (determined by using the Friedewald Formula where one divides TG by 5) is diagnostic of remnant lipoproteins: "which convey substantial CV risk above that predicted by LDL-C." So if you do not do NMRs or do not pay attention to VLDL-C (which is usually no longer reported by labs) you have never diagnosed a remnant particle in your clinical career. Think about this: if LDL-C is perfect but VDL-C is high, the non-HDL-C (the poor man's apoB and NCEPs secondary goal of therapy) will be high: NCEP advises that remnant lipoproteins has to be treated and of course the best way of doing that lifestyle and drugs that inhibit TG synthesis: fibric acids, high dose N-3 FA or high dose niacin

(Niaspan). However as long as the TG is < 500 mg/dL, statins ARE ALWAYS THE FIRST LINE THERAPY to treat patients with cardiometabolic risk. If a statin is tolerated there is no compelling rationale to prescribe N-3 FA, fibric acids or Niacin as a first line monotherapy: however there is plenty of rationale to start combination therapy on day one if the lipoproteins are significantly abnormal. Why: In patients with TG/HDL-C axis disorders statins fail to normalize non-HDL-C or apoB in anywhere from 30-70% of patients.

I am often asked when should you treat TG if the level is < 500 mg/dL. The answer is you do not treat TG. You are treating the atherogenic cholesterol that is carried in the TG-rich, associated apoB particles: remnants, IDLs and LDLs (either large TG-rich or TG-induced small LDLs). What are the lipoproteins know to kill insulin resistant folks with metabolic syndrome and T2DM: remnants and LDLs - all TG driven. Likewise how do you treat low HDL-C? I do not: I treat the associated atherogenic apoB particles that are almost always present in IR patients with low HDL-C: namely remnants, and too many LDLs (usually small, dense). Why is the HDL-C low to begin with ????? TG came from VLDLs and displaced the CE that the HDL should have been carrying. The TG-rich, CE-poor HDL loses its TG via hepatic lipase in the liver and becomes so small it is vulnerable to renal excretion. Thus, the real driving force of the remnants, small LDL, increased LDL-P, low HDL-C, low HDL-P, high blood viscosity, poor endothelial dysfunction, and hypercoaguability is tubby TG.

In summary with a high VLDL-C (diagnostic of remnant lipoproteins), an abnormal TG/HDL-C ratio (>3.5) diagnostic of small LDL particles, a TC/HDL-C ratio of 7.1 and a non-HDL-C of 184 (desirable < 130) suggestive of high apo B levels or LDL-P, I believe this patient has considerable CV risk. I would never ignore such risk because of a normal appearing imaging study.

Lifestyle management is essential: Because he is a high risk patient, pharmacological therapy is indicated. The provider suggested using 4000 mg of a reliable N-3 FA, and the only one the FDA considers reliable is Lovaza. Yet, Lovaza by itself is an inappropriate initial monotherapy in a patient with TG < 500. There is no prayer that Lovaza monotherapy will normalize his apoB or LDL-P. If you wanted to use Lovaza (the FDA approved, pollutant-free, properly dosed tablet), it would be off-label use combined with a statin (see Lovaza package insert or the COMBOS trial (Clinical Therapeutics 2007;29:1354-1367). In such high risk patients, with TG between 200 and 500, Lovaza should never be written without a statin or statin/ezetimibe combination. Of course there are other good therapies to handle patients with cardiometabolic risk and high TG: Statin monotherapy or statin/ezetimibe would upregulate LDL receptors but do not inhibit TG synthesis which I believe is critical. In addition to N-3 FA (high dose), fibric acids and extended release niacin (Niaspan) at 1500-2000 mg dose effectively inhibit TG synthesis and should be combined with a statin or statin/ezetimibe. Because of the recent release of the newest fibric acid, Trilipix I thought it would be important to use this case to discuss statin and fibric acid therapy and explain the differences among the fibric acids. For further info on niacin or N-3 FA therapy check out my web site www.lipidcenter.com professionals menu.

Why use fibric acids and a statin in this case? Clinical outcome trial data supports fibric acid efficacy when insulin resistant patients have the metabolic syndrome and the TG are > 200 and the HDL-C is < 50 in women and < 40 in men. How do fibrates work? They decrease fatty acid synthesis, increase beta-oxidation of FA, inhibit DGAT (the enzyme that attaches FA to diacylglycerol), reduce VLDL-P synthesis, secretion and TG content (size), decrease CETP activity (keeps HDLs and LDLs larger), increases VLDL and other TG-rich lipoprotein lipolysis, increase apoA-I and apoA-II production, increase hepatic lipidation of HDL-C, increase macrophage RCT, increase hepatic delipidation of HDLs (creating small HDLs that can return to the artery for more sterols), increase biliary excretion of cholesterol, reduce intestinal absorption of cholesterol (one of the reasons fenofibric acid works so well with ezetimibe - and is FDA approved for such use), improve HDL functionality (via paraoxonase), and multiple pleiotropic effects. For two great papers on this topic see:

1) Dayspring T & Pokrywka G. Fibrate Therapy in Patients with Metabolic Syndrome and Diabetes Mellitus. *Current Atherosclerosis Reports* 2006;8:356-364

2) Toth, P, Dayspring T, & Pokrywka G. Drug Therapy for Hypertriglyceridemia: Fibrates and Omega-3 Fatty Acids. *Current Atherosclerosis Reports* 2009;11:71-79

In this patient the statin/fibrate would reduce LDL-C and raise HDL-C, but more importantly would reduce non-HDL-C, apoB, VLDL-P, LDL-P, TG-rich remnants (VLDL-C).

In the above paragraphs I have intentionally use the correct chemical term fibric acids rather than fibrates. Fibrates, more precisely fibric acids, are amphipathic (one end is hydrophobic and one end hydrophilic) carboxylic acids characterized by the presence of a terminal carboxyl group (COOH). Many use the words polar and nonpolar to describe hydrophilicity where a polar substance is soluble in water whereas a nonpolar substance is not. In actuality the terms hydrophilic and phobic refer to the ability of a molecule to pass through a lipid membrane not its water solubility. Thus amphipathic molecules have one end that is polar and one end that is nonpolar. Cholesterol is an amphipathic molecule as the end with the -OH group at the #3 position is polar and the other end of the molecule with methyl groups is nonpolar. All but one fibrate are manufactured and swallowed not as carboxylic acids but as esters: an ester is an organic acid in which the hydroxyl (-OH) group is replaced by an -O alkyl group which are single chain arrangements of carbon and hydrogen atoms (CH): i.e. methyl, ethyl, etc. A carboxylic acid ester is -COH-OR where R is the specific alkyl group. A fibrate ester is F-COH-OR where F is the fibrate molecule and the R is the ester attached to the carboxylic moiety.

Esters are formed in a process called esterification when an alcohol reacts with an acid. Free or unesterified cholesterol is an alcohol with an -OH group at the # 3 position. When it combines with a fatty acid, it is esterified and becomes cholesteryl ester. When glycerol (an alcohol) combines with one, two or three fatty acids (acyl groups) you create, monoacylglycerol, diacylglycerol or triacylglycerol (better known as triglycerides). Triglycerides are thus esters of glycerol.

PPAR-alpha is a nuclear transcription factor or NTF (a protein that enters the nucleus and attaches to DNA causing transcription and creation of messenger RNA ultimately leading to protein synthesis as it is translated at ribosomes in the endoplasmic reticulum). PPAR-alpha potentially regulates hundreds of genes involved with energy expenditure: lipid and lipoprotein synthesis and catabolism, fatty acid regulation and vascular wall biology. Natural ligands for PPAR-alpha are various fatty acids including eicosanoids (oxygenated 20 carbon fatty acids). Certain carboxylic acids have the ability to stimulate PPARs (alpha, gamma and delta). Anything that stimulates a nuclear transcription factor is called an agonist and anything that blocks an NTF is an antagonist. Thus PPAR-alpha stimulators like fibrates are called PPAR-alpha agonists. Interestingly fibrates can also influence other nuclear transcription factors such as liver X receptors (LXR) and ANGPTL which also play key roles in lipid biology. NTG agonism seems simple but in reality the process is extremely complex and very tissue specific as it depends on the presence or absence of multiple other proteins which serve as NTF coactivators or corepressors. For example in the liver, but not in macrophages, fenofibrate (the ester) is an LXR antagonist (important in inhibiting TG synthesis) whereas fenofibric acid (not an ester) has no hepatic LXR antagonist ability on TG synthesis but does have hepatic LXR agonist activity to upregulate ATP binding cassette transporters (ABCA1).

The fibrates that have been most tested in clinical trials and most prescribed are clofibrate (Atromid S), gemfibrozil (Lopid), bezafibrate (not available in US) and fenofibrate (Antara, TriCor and several other names). The newest fibric acid to come on the scene (accompanied by a considerable efficacy and safety data base) is fenofibric acid (Trilipix). All of these fibrates, except fenofibric acid are administered as esters and have to be converted by hepatic esterases (esterolases) to the carboxylic acid form. The vast majority of fibrate use in the USA is currently fenofibrate as the gemfibrozil is considered to have too many dangerous drug/drug interactions to

use safely in combination therapy (severe package warnings). For all practical purposes in the US, one will have to choose between fenofibrate and fenofibric acid.

Clofibrate (Atromid S) ----- Active PPAR- α form is clofibric acid
Gemfibrozil (Lopid) --- Active PPAR- α form is gemfibric acid
Fenofibrate (TriCor, Antara, etc) --- Active PPAR- α form is fenofibric acid
Bezafibrate ---- Active PPAR- α form is bezafibric acid
Fenofibric acid (Trilipix) – is the active PPAR- α form

Chemically Trilipix is the choline salt of fenofibric acid. Fenofibric acid is a carboxylic acid which has the ability (without undergoing any further modification) to agonize (stimulate) the nuclear transcription factor PPAR-alpha. Fenofibric acid is an amphipathic molecule with the carboxylic acid (COOH) moiety being the polar end. When the choline salt of fenofibric acids enters the intestine it dissociates into choline and fenofibric acid (Trilipix is manufactured as a delayed release tablet of fenofibric acid). Once the choline disassociates, the COOH (polar moiety) is exposed. The fenofibric acid is immediately absorbed and starts working (as a PPAR-alpha agonist) inside the enterocyte cell as a ligand recognized by PPAR-alpha. Enterocytes express PPAR-alpha which are involved with production of proteins involved with the regulation of sterol absorption (Niemann Pick C1 Like 1 or NPC1L1). After passing through the enterocyte, fenofibric acid then enters the blood stream, attaches to albumin and travels to and enters other tissues where PPAR-alpha is expressed (liver, vascular wall, adipocytes, muscles, etc.).

Unlike fenofibric acid, Fenofibrate is packaged and swallowed as a methyl-ethyl ester of fenofibric acid (-CO-CH₂(CH₃)). All other fibrates are also esters than require hepatic activation (de-esterification). Once absorbed it has to travel via plasma (bound to albumin) to the liver where it undergoes de-esterification (via an hepatic esterase). Once fenofibrate ester loses the ester (is hydrolyzed or de-esterified), via enzymatic cleavage, it becomes fenofibric acid which enters the blood stream, attaches to albumin and travels to tissues where PPAR-alpha is expressed. Fenofibrate (a methyl-ethyl ester of fenofibric acid) is not an active PPAR-alpha agonist, because it has two nonpolar ends, whereas fenofibric acid (an amphipathic carboxylic acid) is. As mentioned above fenofibrate ester can act as an hepatic LXR antagonist. Unlike fenofibrate, no hepatic (liver) metabolism is needed to modify the fenofibric acid molecule to render it able to agonize PPAR-alpha.

The chemical structures of all fibrates and these processes are on the web site www.lipidcenter.com on the Professionals menu, Power Point slide library. A picture of chemical structure can be very enlightening. In its simplest explanation: Antara, TriCor or other branded fenofibrates are prodrugs and Trilipix (fenofibric acid) is the actual active drug (PPAR-alpha-agonist). Fenofibrate requires active hepatic metabolism to change into its active amphipathic metabolite, namely fenofibric acid. Trilipix (fenofibric acid) needs no (first pass) hepatic catabolism to become active (amphipathic), it simply needs to lose its choline salt which it does in the intestinal juices. To be eliminated from the body via the kidney, fenofibric acid returns to the liver and undergoes glucuronidation (made water soluble). Glucuronidated fenofibric acid returned to plasma and is then excreted by the kidney. Fortunately the glucuronidation enzymes fenofibric acid uses are not those used by statins or other drugs (gemfibrozil, ezetimibe) and thus there are no interactions with those drugs. Since fenofibrate becomes fenofibric acid, it (TriCor and others) like fenofibric acid (Trilipix) have no drug-drug interactions other than with Coumadin (warfarin) which because of their protein binding avidity, they displace from albumin. All fibrates: NO EXCEPTIONS - are excreted in the urine, as are hydrophilic statins like rosuvastatin and pravastatin. Thus when renal impairment is present the dose must be reduced. That is why both fenofibrate and fenofibric acid come in the standard and the lower dose for those with reduced renal function. That is why one must use lower doses of rosuvastatin and pravastatin when renal function is impaired. The National Lipid Association Nonstatin Safety task force states emphatically: the recommendation is that the dosages of **ALL FIBRATES**

be minimized in patients who have renal impairment, especially when the GFR is < 60 mL/min, and that fibrates be avoided altogether when the GFR is <15 mL/min. (Am J Cardiol 2007;99[suppl]:3C–18C).

Theoretically fenofibric acid or Trilipix (the active drug) would be safer than fenofibrate as it requires no liver activation. However we have used fenofibrate for years without experiencing major difficulties. So whether the lack of hepatic activation has any clinical reality is unknown at this time. As we all know fenofibrate has been a very safe drug with no known serious statin interactions. In the FIELD trial there were three rhabdos with fenofibrate monotherapy used by 5000 folks over 5 years. In trials evaluating 2000 patients for a year there were zero rhabdos with Trilipix. However, Trilipix has significantly more published statin combo safety data than any other fibrate including fenofibrate, so its FDA label for combination with a statin is very positive, compared other fibrates including fenofibrate. This may have more medicolegal importance than clinical importance. Certainly no pharmacists should be calling up providers warning them not to use fenofibric acid (Trilipix) with a statin. Also keep in mind the package insert makes that clear. fibrate/statin use, like niacin/statin, use is to be reserved for high or very high risk patients (like T2DM or metabolic syndrome patients) not at goal on statin monotherapy. Academically, drawing conclusions from trial data (which is what the FDA does) one would have to say Trilipix is safer when used in combo with a statin as extensive published efficacy and safety data evidence exists whereas it does not for fenofibrate. The FDA label clearly assumes Trilipix is safer when combined with a statin and have stated such in the package insert. As a monotherapy several trials (including a very large one) are testament that fenofibrate monotherapy is quite safe: however except for treating TG > 500 no one should be prescribing fibrate monotherapy if the patient can tolerate a statin. In FIELD there was significant fenofibrate/statin use and it certainly seemed safe and there were no rhabdos in that cohort.

What about lipid/lipoprotein changes with Trilipix:

Briefly put: As monotherapy Trilipix, and statins, as well as the combination therapy all lower LDL-C, TG, VLDL-C, non-HDL-C, apoB and raise HDL-C for up to a year. As early as 12 weeks, the low dose statin/Trilipix combo therapy is better than feno monotherapy is on LDL-C and better than the statin is on HDL-C, TG, non-HDL-C, VLDL-C, VLDL-P, hs-CRP, increasing LDL size and apoB. The moderate dose statin/Trilipix is better than feno monotherapy is on LDL-C and better than the moderate dose statin monotherapy on HDL-C, TG, VLDL-C, hs-CRP, increasing LDL size and VLDL-P. Although there is no additional non-HDL-C or apoB benefit at 12 weeks between moderate dose statin vs. moderate dose statin/Trilipix combo there is benefit at one year. There is additional benefit at 12 weeks on VLDL-P, and VLDL-C: i.e. you will get rid of more remnants with the combo therapy and as discussed above remnants are a part of the atherogenesis in IR patients. Why no additional apoB lowering at 12 weeks if remnants are being removed. The in many patients reducing the elevated VLDL-P may not seriously impact apoB quickly. If you are following patients on fibrates with lipid profiles rather than the NMR VLDL-P, never fail to follow what happens to VLDL-C (a key component of non-HDL-C).

References on the Trilipix Data:

- Am Heart J 2009;157:195-203. (fenofibric acid/simvastatin)
- Atherosclerosis (2008), doi:10.1016/j.atherosclerosis.2008.09.027 (FFA & Rosuvastatin)
- Journal of Clinical Lipidology 2008;2:426–435 (FFA acid statin safety data)
- Journal of Clinical Lipidology 2008;2:219-220 FFA Particle size data (I am one of the authors)

I hope you all learned something about fibrates with this newsletter: What am I doing in my NJ practice where a fibrate is indicated (rules and formulary's may be different for others)? All new fibrate starts will be Trilipix. My patients controlled on TriCor (fenofibrate), including myself: most with next renewal likely switched over. I see no reasons why not to do so. At least my electronic prescribing software will stop warning me about the warning when writing a fibrate with a statin.

LIPID CASE 228 Phytosterols Seek and Ye Shall Find

I was asked about a 50 year old male, with a history of MI 8 years ago with very difficult to control cholesterol. He has been on Vytorin 10/40 (simvastatin plus ezetimibe) for a few years with never coming close to goal. I believe the best I have seen his LDL-C is about 170. I changed him to Crestor 20, and his LDL-C shot up to 250 mg/dL and his ApoB was extremely high at 180 mg/dL. I changed him back to Vytorin 10/80 and I have provided his most recent lab results below:

Total Cholesterol -- 260 mg/dL The cholesterol in all of the lipoproteins per deciliter (100 cc) of plasma

Triglycerides -- 211 mg/dL The TG in all of the lipoproteins per dL (most should be in chylous and VLDLs)

HDL-C -- 35 mg/dL The cholesterol content within all of the HDLs in a dL (80% of it in the larger HDLs)

LDL-C -- 183 mg/dL The cholesterol content within all of the IDLs and LDLs (of all sizes) per dL
Follow up APO B missing

LDL/HDL ratio 5.23 Chol/HDL ratio 7.43 These are surrogates of the ApoB/ApoA-I ratio which in the INTERHEART and AFCAPS and TexCAPS studies proved to be the best predictors of risk

The other test I ordered was Plasma sterols to determine if he was an over producer or over absorber. My problem is all 5 categories of sterols they gave me are through the roof and I am not sure how to interpret it. They are as follows:

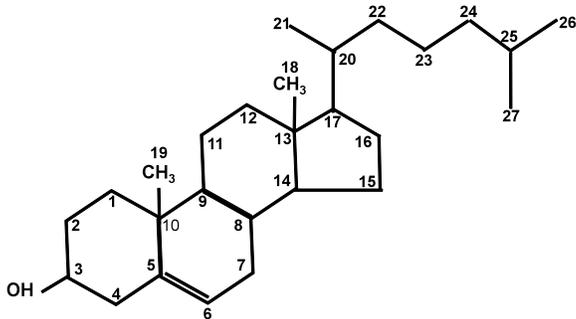
Desmosterol	18	normal range	(0-5)
Lathosterol	19	"	(0-7)
Campesterol	20	"	(0-7)
Sitosterol	21	"	(0-5)

To order sophisticated lipid testing including sterols please visit: www.bostonheartlab.com

DAYSRING DISCUSSION

Atherosclerosis is caused by the deposition of sterols into the arterial intima where they are subject to ingestion by macrophages. Many are unaware that there are numerous atherogenic sterols other than cholesterol. Here is the basic biochemistry:

Sterols are insoluble substances or lipids synthesized from acetyl coenzyme A (CoA). They are steroid-based alcohols having an aliphatic hydrocarbon (i.e. carbon hydrogen chains without aromatic ring) side chain of 8–10 carbons at the 17 beta position and a hydroxyl group (-OH) at the 3 beta position of the A ring (making it an alcohol). Because of the hydrophilicity at the -OH end and hydrophilicity at the hydrocarbon side chain, sterols are amphipathic and can thus be incorporated into the lipid bilayers of the cytoplasmic membrane (hydrophilic end protruding outwards and lipophilic end inwards). Cholesterol is a 27 carbon chain sterol with the hydrophilic 3-OH (alcohol) group and the aliphatic at the -17 position.



Free (unesterified) cholesterol depicted above can be converted into bile acids or steroid hormones like progesterone, estrogen, vitamin D). Free cholesterol is the only form of cholesterol that can be absorbed or excreted through cell membranes (intestine, hepatic). The storage or traffic form of cholesterol is cholesteryl ester where a long chain fatty acid (most often oleic acid) replaces the 3-OH group (thereby turning an alcohol into an ester. The cellular enzyme that enhances esterification of cholesterol is ACAT (1 and 2) and the lipoprotein enzyme that esterifies cholesterol is LCAT. Unesterified cholesterol because of the presence of the -OH group is subject to reactive oxygen species which changes it into an oxysterol (the cause of atherosclerosis) capable of inducing macrophage ingestion and the creation of foam cells. If cholesteryl ester is ingested it must undergo intestinal lumen de-esterification: this is accomplished by some of the lipases and amylases that more typically deesterify intestinal triglycerides.

Healthcare providers are often amazed to learn that humans eat as many noncholesterol sterols (a sterol that is not cholesterol) as they are ubiquitous in plants, shellfish, fungi, yeasts. There are also several intermediary sterols in the endogenous cholesterol synthesis pathway. Plants cannot synthesize cholesterol but instead make sitosterol and campesterol among many others. Fungi manufacture ergosterol, algae make fucosterol (and it is subsequently found in shellfish). Plant sterols are structurally related to cholesterol and differ in their chemical structure only due to the presence of an additional methyl (campesterol) or ethyl (sitosterol) group at the C-24 position of the side chain. Stanols differ from the corresponding sterols due to saturation of the delta 5 double bond to the 5 alpha position (cholestanol, campestanol, sitostanol). Apparently, the structural differences of these sterols-stanols seem to be only of minor extent. Nevertheless, previous studies in animals and humans revealed that the efficacy of their intestinal absorption differs markedly from cholesterol (J. Lipid Res.2003.44:533–538).

Be careful what you take from that last sentence on the absorption difference between cholesterol and non cholesterol sterols. In the jejunal lumen, all of the sterols along with fatty acids and phospholipids are entrapped among bile acid molecules in structures termed mixed biliary micelles. The lipids are then trafficked to the brush border (microvilli) of enterocytes. The sterols are internalized into the enterocyte via the Niemann Pick C1 Like 1 protein (NPC1L1) in a complicated process involving several other proteins including clathrin and AP2. Once in the enterocyte, cholesterol has the following options:

- 1) be esterified by ACAT and along with TG enter apoB48 enwrapped chylomicrons
- 2) be exported via ATP binding cassette transporter A1 (ABCA1) into apoA-I and prebeta HDLs
- 3) be exported back to the intestinal lumen via ABCG5 and ABCG8 half transporters (these join or heterodimerize to form a functional pair)

Once inside the enterocyte, all noncholesterol sterols and any stanols (a saturated sterol) are also immediately returned to the intestinal lumen via the ABCG5,G8 transporters. Homozygous absence of G5,G8 results in the disease formerly called sitosterolemia and now referred to as phytosterolemia (see my chapter 14 in Therapeutic Lipidology). This disease may be associated with tendon xanthomas and premature atherosclerosis where noncholesterol sterols, not cholesterol are the cause. Phytosterolemia is a very, very rare disease. Heterozygotes would be more common and subtle polymorphisms, all of which would have some inability to export noncholesterol sterols (and thus they will be absorbed) are likely common. There are also drugs that will affect ABCG5, G8 and NPC1L1 protein expression and thus effect sterol absorption.

Note that technically sterol absorption is only complete when a sterol enters the lymphatics or plasma in a chylomicron or HDL particle! A sterol that enters the enterocyte but is returned to the jejunal lumen has not been absorbed.

Paragraphs (in blue) for lipidologists only: NPC1L1 expression is regulated by nuclear transcription factors including PPAR-alpha (down-regulation) and LXR or Liver X Receptors (down-regulation). Remember that the LXR is the sterol toxicity gene which helps cells reduce cholesterol and noncholesterol sterol concentrations. If a cell like the enterocyte has too much cholesterol, PPAR-alpha will activate and NPC1L1 synthesis will be reduced: Less NPC1L1 will translocate (move) to the enterocyte surface to facilitate sterol absorption. Without proper NPC1L1, sterols will not enter the enterocyte but rather be excreted in the stool. Likewise, excess sterols in the enterocyte will activate LXR and there will also be down-regulation of NPC1L1 but also an upregulation of the intestinal sterol exporter (ABCG5,G8) causing secretion of sterols to the gut lumen: in effect LXRs cause less enterocyte sterol absorption, increased sterol exportation and ultimately increased stool sterol excretion.

Fenofibrate and its active PPAR-alpha agonist form fenofibric acid will downregulate NPC1L1 and reduce intestinal absorption and increase stool excretion of cholesterol (J. Lipid Res. 2007. 48: 2725–2735). This no doubt is one reason why fenofibrate/ezetimibe work so well together (and their combo use is FDA indicated). Feno down-regulates NPC1L1 and ezetimibe binds to and inhibits those that still remain. Of equal interest is that statins by depleting intracellular cholesterol levels (via synthesis inhibition) down-regulate LXR expression. A cell with depleted cholesterol will seek via genetic homeostatic mechanisms to acquire cholesterol. Less LXR expression in the enterocyte is associated with increased synthesis of NPC1L1 and decreased synthesis of ABCG5 and G8 (enterocytes will retain any sterols that are absorbed). Thus although statins inhibit cholesterol synthesis they paradoxically increase intestinal absorption and decrease intestinal excretion of both cholesterol and noncholesterol sterols.

Pearls: Ezetimibe will negate the statin-induced over-absorption of cholesterol and it is likely so will fenofibrate/fenofibric acid. Since N-3 FA also act through PPAR-alpha agonism they also reduce sterol absorption by inhibiting NPC1L1 and perhaps they also will negate statin induced sterol over-absorption (J. Lipid Res.2007. 48: 395–404).

Back to the basic case discussion: There is a reason why humans absorb cholesterol but not noncholesterol sterols. The former are required for human life and the latter serve no physiologic functions and when present in excess (especially skin and arteries) are toxic. Interestingly, the phytosterols seem to be more atherogenic than the animal produced sterol (cholesterol). This is probably due to the fact that noncholesterol sterols are poor substrates for ACAT or LCAT and cannot be readily esterified. Any nonesterified sterol that enters an artery wall is far more susceptible to reactive oxygen species and be converted to an oxysterol.

A key intermediary noncholesterol sterol in the conversion of mevalonic acid to cholesterol is lathosterol; another is desmosterol. If one has increased cellular cholesterol synthesis, they will have increased lathosterol and desmosterol levels in their plasma. If one is an over-absorber of cholesterol, there will be increased plasma levels of noncholesterol sterols or stanols. If a patient had high lathosterol levels, they are overproducing cholesterol. They would have high HMGCoA reductase levels (the enzyme that changes HMGCoA to mevalonic acid: this is the rate limiting step in the complex cholesterol synthesis pathway (for understanding the whole pathways see my book chapter or go to www.lipidcenter.com - Professionals and then scroll down to the PP slides on cholesterol synthesis). As one might guess, persons with high lathosterol levels have high HMGCoA reductase levels, and very powerful responses to statins. Au contraire, persons with low lathosterol levels would have little HMGCoA reductase and thus be very poor responders to a statin. The most common circumstance causing low lathosterol is over-absorption of cholesterol. The increased chylomicron delivery of cholesterol fulfills the hepatic need for cholesterol and thus there is little need for the liver (via Sterol Regulatory Element Binding Protein or SREBP) to upregulate HMGCoA reductase synthesis.

For Lipidologists: The hepatic cholesterol pool is regulated by a nuclear transcription factor located on the endoplasmic reticulum called sterol regulatory element binding proteins or SREBP. A lack of cholesterol releases SCAP (SREBP Cleavage Activator Protein) which carries SREBP to the Golgi where it is activated - it then attaches to specific response elements on the genes. In turn this leads to HMGCoA synthesis as well as production of the LDL receptor. Both will help the cell acquire cholesterol. This is how statins, ezetimibe and sequestrants work: all of those drugs deplete hepatic cholesterol stores, upregulate SREBP and increase production of LDLr.

In the 4S trial simvastatin had no effect on reducing events in the quintile of cholesterol over-absorbers (as measured by cholestanol assay) whereas it was very effective in reducing events in the cholesterol over-producers (BMJ 1998;316:1127-1130). One of course could speculate the folks with cholesterol over-absorption, would have had good benefit from ezetimibe (Zetia). In patients with cholesterol over-absorption, Zetia can reduce LDL-C by 40-70%.

So with all of the physiology and biochemistry as a background let's analyze the case at hand. We have a patient with very high LDL-C and apoB levels that seemed to be a very poor responder to a statin. When he was finally started on Vytorin (simvastatin/ezetimibe) there was a good response but levels were certainly not at goal. The provider, like so many others, decided the heck with weak statin (simvastatin and ezetimibe) and switched to the most powerful HMGCoA reductase inhibitor rosuvastatin (Crestor) at the 20 mg dose. Unfortunately the Zetia (ezetimibe) was discontinued. To the providers amazement, on rosuvastatin monotherapy there was a drastic elevation of the LDL-C (170 to 250 mg/dL). Anyone still reading this newsletter should certainly recognize what is going on here. This person is for sure an over-absorber of cholesterol and there is no prayer for a statin by itself to correct the pathological sterol homeostasis. That explains why the LDL-C went way up when the cholesterol absorption blocker, ezetimibe, was stopped. Of course one might ask in an over-absorber of cholesterol, why did not ezetimibe get the patient to goal. The answer is in the sterol analysis, something very few physicians ever order.

On Crestor 20 mg:

Markers of cholesterol synthesis:

Desmosterol	18	normal range	(0-5)
Lathosterol	19	"	(0-7)

Markers of cholesterol absorption

Campesterol	20	"	(0-7)
Sitosterol	21	"	(0-5)

The labs provide the answer: The patient is both an over-producer and a severe over-absorber of cholesterol. The sitosterol and campesterol levels are really high and are fully compatible with homozygous absence of ABCG5 and G8 or phytosterolemia. How he made it to age 50 is a miracle. He is going to need potent therapies that can reduce cholesterol synthesis, decrease cholesterol absorption and promote cholesterol excretion.

The Diagnosis: Familial Hypercholesterolemia: including the phytosterolemia variant. Screen all first degree relatives. He will need as many meds as it takes:

1) Potent statin: Crestor 40 mg daily

2) Zetia has FDA approval to reduce sitosterol levels. One might even want to try 20 mg or more. Might also add a plant stanol (Benecol or 17 beta sitostanol).

3) Fenofibrate/fenofibric acid: fibrates have been used for the treatment for phytosterolemia before ezetimibe was discovered. As described above they decrease sterol absorption by down-regulation of NPC1L1. They also promote hepatic and biliary secretion of sterols via hepatic ABCG5,G8 upregulation (in actuality it is LXRs that upregulate the ABCG5,G8, but PPAR-alpha via "crosstalk" enhances LXR function).

4) Bile acid sequestrants were the primary treatment for those with Phytosterolemia prior to ezetimibe. Of course, by increasing excretion of bile acids (BA) they down-regulate the farnesoid receptor (FXR). FXR is the gene that prevents bile acid toxicity. The LXR regulates BA synthesis by inducing the enzyme that converts cholesterol to bile acids (7 alpha hydroxylase). Conversion of cholesterol to BA will deplete hepatic cholesterol pools and upregulate LDL receptors, leading to reductions in apoB, LDL-C and plasma sitosterol levels.

Getting apoB and the sterol levels to goal in this person will likely need Crestor 40 mg, Zetia 20 mg or more, fenofibrate or fenofibric acid (TriCor, Antara, Trilipix) and WelChol.

LIPID CASE 229 When is enough enough?

In the following discussion, lower case words are from the provider and CAPS are my thoughts:

In July, 2005, I took over care of this (then) 58 year old Caucasian male who was seeing another physician and was not happy with his care and he wanted to get closer to his home. He found me on the Internet. He was on Lipitor 20 and Zetia 10 for dyslipidemia and lisinopril 20 for HTN. He had not had a complete physical in over 10 years, had never been told to have a colonoscopy, did not know any of his lipid values because they never gave him any results, and was not sure of his BP. His BP here was 148/90. Labs on these meds were:

TC 183, HDL-C 81, LDL-C not calculated, TG 404, Non-HDL-C 102, TG/HDL-C 4.98.

LFT's, Thyroid, and other labs were normal. I began to adjust his BP meds for goal to < 120/80. I sent him for his colonoscopy, which removed a tubular adenoma. I added TriCor 145 mg daily to his Lipitor 20 mg and Zetia 10 mg.

THE TG/HDL-C RATIO AND NON-HDL-C IS NOT USUALLY ACCURATE WITH SUCH A HIGH TG, SO WE REALLY HAVE NO ACCURATE CLUE OF ATHEROGENIC PARTICLES OR NOT FROM THE ABOVE PROFILE. HE COULD HAVE FAMILIAL HYPERTIGLYCERDEmia WITH A NORMAL APOB AND VERY LARGE VLDLS: RISK WOULD BE PANCREATITIS BUT NOT CHD. HE ALSO EASILY COULD BE A HYPERAPO-B NIGHTMARE. THE PROVIDER ASSUMED THE LATTER AND PRESCRIBED A STATIN/FIBRATE/EZETIMIBE REALLY AGGRESSIVE! BUT IF HE HAS FAMILIAL HYPERTRIGLYCERIDEMIA THAT WOULD BE GROSS OVERTREATMENT. APO-B OR OTHER PARTICLE QUANTIFICATION IS

MANDATORY HERE. TO ALSO DEMONSTRATE THE SHORT-COMINGS ON NCEP-ATP-III, A PERSON ON THERAPY WITH AN NON-HDL-C OF 102 IS AT GOAL. TRUST ME, THIS MAN IS LIKELY NOT AT GOAL IF ONE ANALYZED LIPOPROTEINS!

The clinician got him in for his first physical Sept, 2005. He was 5'10", 184 lbs. (Ideal body weight 166-183 lbs), never smoked, and does Mall Walking for exercise. Family History is negative for Heart Disease.

Lipids now were:

TC 159, HDL-C 48, LDL-C 50, TG 306, Non-HDL-C 111, and TG/HDL-C 6.3.

Since the TG dropped some but was still high and the HDL-C dropped a lot, the doc stopped the TriCor and started Niaspan 500 and titrated up to 500 2 tabs at bedtime. This resulted in:

TC 158, HDL-C 80, LDL-C 13, TG 326, Non-HDL-C 78, and TG/HDL-C 4.0.

The provider increased the Niaspan to 1500 mg at bedtime.

THE CLINICIAN IS MAKING DECISIONS BASED ON LIPID CONCENTRATIONS WHICH, ESPECIALLY IN PATIENTS WITH HIGH TG IS FROUGHT WITH ERRORS. HE IS BASICALLY CHANGING LIPOPROTEIN CORE COMPOSITIONS AND CAN NOT KNOW WITH CERTAINTY WHAT HE MIGHT BE DOING TO POTENTIALLY ATHEROGENIC PARTICLES (IF INDEED THE PATIENT HAS ANY). PERSONALLY I WOULD HAVE BEEN LOATHE TO HALT THE ALREADY STARTED FIBRATE IN A PERSON WITH THAT TG, AND IF I DID AND USED NIASPAN INSTEAD I'D HAVE TITRATED IT TO 2000 MG, THE ONLY DOSE IN NIACIN CLINICAL TRIALS CAPABLE OF SERIOUSLY LOWERING TG.

On these meds:

TC 186, HDL-C 86, LDL-C not calculated, **TG 444**, Non-HDL-C 100, TG/HDL-C 5.2. The provider could not explain why the TG went back up when he increased the Niaspan, so he decreased the Niaspan back to 1000 at bedtime and then added, prescription strength N-3 fatty acid esters, Omacor (now called Lovaza), 4 grams daily. Of course, he was still on Lipitor 20 and Zetia 10.

THE MISTAKE IS IN BELIEVING THERE IS ANY CLINICAL DIFFERENCE WHATSOEVER BETWEEN A TG OF 444 AND 326. MANY ARE AWARE OF THE FRAMINGHAM DATA (Amer J Cardiol 1992;70:3H-9H) SHOWING NO DIFFERENCE IN CV RISK BETWEEN A TG OF 200 AND 500. TG TOLERANCE TESTS HAVE SHOWN THAT ANY TG LEVEL > 170-200 (FASTING OR POSTPRANDIAL) IS LIKELY PATHOLOGICAL. ALL THAT IS HAPPENING AT TG > 200 MG/DL IS VLDL SIZE IS ENLARGING, BUT VLDL-P (APOB) IS NOT INCREASING. THERE ARE SO MANY VARIABLES AFFECTING TG, YOU WOULD GO NUTS TRYING TO FIGURE OUT THE RISK ASSOCIATED WITH A 100 MG/DL CHANGE IN ALREADY HIGH TG: THUS, SINCE IT HAS NO ADDITIONAL RISK MEANING - WHO CARES? I AM ALSO HAPPY THE PROVIDER USED THE PROPER DOSE OF LOVAZA TO SLAY THE TG.

This change in therapy resulted in TC 172, HDL-C 106, LDL-C 15, TG 257, Non-HDL-C 66, and TG/HDL-C 2.4.

AS DISCUSSED; ALTHOUGH THE N-3 FA, AS EXPECTED SIGNIFICANTLY REDUCE THE TG LEVEL IT IS STILL IN THE HIGH RISK CATEGORY. THUS IN REALITY THE TG OF 257 HAS NO MORE OR LESS CVD RISK MEANING THAN THE TG OF 444. (See the Framingham data cited above). THE NON-HDL-C SUGGESTS HE IS AT GOAL AND NO FURTHER TREATMENT IS NEEDED DESPITE THE HIGH TG.

The patient was on the above meds until 11/08, when the provider had to stop his Lipitor 20 due to nonformulary status and started simvastatin 40 mg instead. Before he made the switch, however, labs were repeated:

TC 188, HDL-C 105, LDL-C 42, TG 205, VLDL-C 41, Non-HDL-C 83, TG/HDL-C 1.9.

Also, a Cardiac CT Calcium Score was done. The patient now is almost 62 years old. The score was 280, with 272 in the LAD and 8 in the circumflex. This put him in the 70th percentile for CHD risk. A Stress DIMPS (Stress Thallium in some hospitals) was done and was negative. Then, the formulary-mandated switch to the simvastatin 40 was done and everything else was continued.

SO NOW WE KNOW (BECAUSE OF THE CORONARY ATHEROSCLEROSIS) THIS IS NOT FAMILIAL HYPERTRIGLYCERIDEMIA AND THE PATIENT DOES HAVE (OR DID HAVE) A HYPERBETALIPOPROTEINEMIA OF SERIOUS SIGNIFICANCE. THAT WOULD HAVE BEEN MY GUESS FROM THE ORIGINAL PROFILE AS IT WAS OF THE CLINICIAN. THUS THE AGGRESSIVE RX HAS BEEN WELL WARRANTED. THE ONLY QUESTION IS WHETHER THE RX HAS THE PATIENT AT OR NOT AT LIPOPROTEIN GOAL (DESPITE THE STILL VERY ABNORMAL TG LEVEL).

The latest labs were done this week and the clinician also did an NMR LipoProfile (nuclear magnetic resonance spectroscopy) due to the positive Cardiac CT Calcium score to see what his LDL-P as well as other particle concentrations were (www.lipoprofile.com)

TC 186, HDL-C 118, LDL-C 22, TG 231, VLDL-C 46, Non-HDL-C 68, TG/HDL-C 1.9.

NMR:

Total LDL-P 302, (desirable < 1000 nmol/L)

Small LDL-P 36, (VIRTUALLY NONEXISTANT)

LDL size 22.5 nm, (large or Pattern A) THIS IS UNUSUAL IN A PATIENT WITH HIGH TG

Large HDL-P 26.5, (quite high) ALSO VERY UNUSUAL IN A PATIENT WITH HIGH TG

Large VLDL-P 8.6. (QUITE HIGH) COMMON IN PATIENT WITH HIGH TG

LipoProfile was done by LabCorp so one does not have the full detail that is available from LipoScience. (other VLDL species, IDL and other HDL species)

NOTE TO LIPIDOLOGY GEEKS READING THIS: HAVE YOU ALL COME TO A CONCLUSION AS TO WHY THE LDLs AND HDLs ARE SO LARGE IN A PATIENT WITH HIGH TG? TAHT IS VERY UNUSUAL. THIS IS THE FUN OF CLINICAL LIPIDOLOGY - FIGURING OUT WHT IS HAPPENING!!! WHAT IS THE LIKELY EXPLANATION OR DIAGNOSIS?

As the Lipid panel shows, his TG and VLDL-C are high, but his Non-HDL-C and TG/ HDL-C are great. The LipoProfile shows a fantastic LDL-P, but a high level of large VLDL-P. He is on simvastatin 40, Zetia 10, Niaspan 1000 mg at bedtime, and Lovaza 4 grams. He has lost 17 pounds over 3 years (never was overweight) and now weighs 167 lbs. dressed. (Ideal Body Weight for him at 5'10" is 166 lbs.)

BECAUSE FEW HAVE RECEIVED ANY SERIOUS CLINICAL LIPIDOLOGY TRAINING, MOST PROVIDERS OPERATE AT THE LEVEL OF A NOVICE (NO INSULT INTENDED) AND ONE OF THE BIGGEST SHORTCOMINGS IS A DISRESPECT OF TG: ONCE YOU HAVE LIPOPROTEIN NUMBERS, LIPID CONCENTRATIONS CAN MISLEAD YOU AND THEY ARE BEST IGNORED UNLESS YOU OPERATE AT WHAT I CALL LIPIDS 401.

LIPIDS 101 USING LDL-C

LIPIDS 201 USING NON-HDL-C

LIPIDS 301 USING APOB AND LDL-P

LIPIDS 401 USING ALL PARTICLE CONCENTRATIONS AND LIPID CONCENTRATION TOGETHER: HIGH LEVEL CLINICAL LIPIDOLOGY

VAST MAJORITY OF DOCS (NOT THE READERS OF MY NEWSLETTER) IN THE US ARE AT 101

Thoughts of the provider:

1. He has been on lipid meds since before coming to me, at least for more than 4 years. He has been on aggressive treatment from me for over 3 years. Maybe the high Cardiac CT Calcium score is due to old, calcified plaque that is well treated and not a risk. The Stress DIMPS did not show any reduction in flow.
2. The low LDL-P of 302 indicates excellent treatment and a low CHD risk.

I TOTALLY AGREE

3. I do not worry about the high TG and high VLDL-P or VLDL-C because everything else is optimally treated and his weight is excellent.

CORRECT ANALYSIS: I AM PROUD OF THE CLINICIANS DEDUCTIVE REASONING: HAVE MY READERS FIGURED OUT THE LIKELY EXPLANATIONS AS TO WHY WITH SUCH A HIGH TG HE HAS LARGE (IN FACT GIGANTIC) LDL PARTICLES AND A LOW LDL-C. MOST OF THE TIME THIS DISCONNECT IS EXPLAINED BY THE PRESENCE OF SMALL LDL PARTICLES. ALTHOUGH THE TG REMAIN HIGH - THEY ARE NOT HIGH ENOUGH TO PRECIPITATE PANCREATITIS AND SINCE THEY ARE NOT ASSOCIATED WITH TOO MANY APOB ATHEROGENIC PARTICLES THERE IS LITTLE IF ANY RESIDUAL CV RISK. THIS IS EXACTLY THE REASON NCEP ATP-III DID NOT PROVIDE A SPECIFIC TG GOAL OF THERAPY. IN RETROSPECT, THE NON-HDL-C, WHICH IS THE NCEP GOAL OF THERAPY IN SUCH A CASE WAS CORRECT; ON THERAPY NO ATHEROGENIC PARTICLES ARE PRESENT.

DID YOU ALSO NOTE THE INCREDIBLY HIGH CONCENTRATION OF LARGE HDL PARTICLES? HOW IS THIS POSSIBLE, AS MOST FOLKS WITH HIGH TG HAVE A LACK OF LARGE HDL-P? THE ANSWER IS OF COURSE IN CATABOLISM OF THE VERY HIGH CONCENTRATION OF LARGE VLDL-P. THERE IS CLEARLY AN OVERPRODUCTION OF LARGE VLDL-P AND A MARKEDLY DELAYED LIPOLYSIS OF THOSE PARTICLES;

THE TG-RICH LARGE VLDLS USING A LIPID TRANSFER PROTEIN CALLED CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) NORMALLY SEND THEIR TG TO THE LDLS AND HDLS AND ACCEPT CHOLESTERYL ESTER IN RETURN - THIS EXPLAINS WHY THE HDLS AND LDLS ARE SO LARGE: THEY ARE CARRYING A LOT OF LIPIDS, BUT NOT CHOLESTERYL ESTER (CE) AS THEY SHOULD BE, BUT RATHER TG. THE LDL AND HDL PARTICLE COMPOSITION IS LIKELY 80% TG AND 20% CE -- NORMALLY LDLS HAVE AN 80-20 CE/TG COMPOSITION AND HDLS HAVE ALMOST NO TG. OF COURSE ALSO NOTE THE HIGH VLDL-C -- THE VLDLS ARE NOW CARRYING CE THAT USED TO BE IN LDLS AND HDLS.

NORMALLY THE TG-RICH, CE-POOR HDLS AND LDLS UNDERGO FURTHER LIPOLYSIS (HYDROLYSIS OF TG AND SURFACE PHOSPHOLIPIDS) IN THE LIVER, USING AN ENZYME CALLED HEPATIC LIPASE. THE LIPOLYSIS USUALLY RESULTS IN THE FORMATION OF SMALL DENSE LDLS AND HDLS. THE LATTER ARE SO SMALL THEY SHED APOA-I WHICH IS EXCRETED VIA THE KIDNEY. IN THIS CASE THE PATIENT SHOULD HAVE A VERY HIGH LDL-P AND A VERY LOW LARGE HDL-P AND A VERY LOW HDL-C. BUT HE DOES NOT. SOMETHING IS AWRY. THIS TELLS ME VERY LITTLE LIPOLYSIS OF HIS LARGE TG-RICH LDLS AND HDLS IS HAPPENING. HIS LARGE HDLS ACCUMULATE IN NUMBER RAISING HDL-C. SINCE IT IS EASY FOR HEPATIC LDL RECEPTORS TO RECOGNIZE AND CLEAR

LARGE RATHER THAN SMALL LDLS, THE LDLS DO NOT ACCUMULATE AND THE LDL-P IS JUST FINE.

CONCLUSION; THE PATIENT HAS A HEPATIC LIPASE DEFICIENCY; THUS HIS HDLS AND LDLS STAY VERY LARGE. THEY HANG AROUND CONTRIBUTING TO THE HIGH TG. SUCH TG-RICH LDLS ARE CLOLESTEROL POOR AND THUS THE LDL-C IS FINE. THE HDLS ARE TOO LARGE (DUE TO THEIR TG CONTENT) TO BE EXCRETED AND TOO LARGE TO ATTACH TO THE USUAL HDL RECEPTORS, WHICH MAY RENBDER THEM DYSFUNCTIONAL (UNABLE TO PERFORM MACROPHAGE REVERSE CHOLESTEROL TRANSPORT). HDL-P AND HDL-C STAY HIGH. THE VERY LARGE LDLS CARRY TG AND VERY LITTLE CE: THEY ARE EASILY CLEARED BY LDL RECEPTORS; THUS LDL-C AND LDL-P ARE PERFECT.

At this point, my plan is to keep him on these same meds and consider that he is at low CHD risk.

KUDOS TO THIS PROVIDER: PASSING THE LIPID BOARDS PROVIDES A HIGHER LEVEL OF UNDERSTANDING TO UNDERSTAND AND TREAT THESE CASES

LIPID CASE 230 Asian Vegetarian with a Lipid Disorder

I was asked about a 65 year old Thai-American female vegetarian with no , family history of heart disease. She is a non-diabetic, non-smoker on no meds except Calcium +D and who is 5'3" and 128 pounds with a BMI of 22.7 and who is normotensive. Her lipid studies are:

with the following numbers:

Baseline: TC = 237, TG = 92, LDL-C = 149, HDL-C = 70 Non-HDL-C = 167 VLDL-C = 18

She was concerned about her LDL-C, and was counseled further on TLC to decrease and trans fats in diet.

3 months later: TC = 246, TG = 120, LDL-C = 162, HDL-C = 60 Non-HDL-C = 186 VLDL-C = 24

hs-CRP = 0.2

NMR LipoProfile

LDL-P = 1672 nmol/L (High risk: 80th percentile population cut point)

Small LDL-P = 438 (normal < 600)

LDL Size = 22.1 nm (Large or Pattern A)

Large HDL-P = 14.7 umol/L (high is > 9,0)

Large VLDL-P = 4.4 nmol/L (high: normal < 0.5)

The patient was concerned about her elevated cholesterol. The clinician asked me if she should be started on a statin to reduce LDL-P in spite of optimal small LDL-P?

DAYSRING ANALYSIS:

First: NCEP-ATP-III: She has two risk factors, namely age and elevated cholesterol so she qualifies for Framingham Risk Scoring (FRS): however her HDL-C is a "negative risk factor." Her ten year risk of an event is 2% (low risk) and thus drug therapy after lifestyle has been done should be considered if the LDL-C is > 160 mg/dL Her goal of therapy would be 130 mg/dL. Of course, if one reads the AHA Women's Guideline 2007 update, a desirable LDL-C is < 100 and non-HDL-C < 130. They also indicate in a woman > 50, a single CV risk factor (in this case the high cholesterol) would forecast a 50% lifetime chance of CVD. Therefore, I think most providers,

without even doing the NMR LipoProfile, would initiate a statin. Some might hesitate due to the elevated HDL-C. Very evidenced based docs would say that NCEP is only expert opinion, (Level III evidence) and the only clinical trial showing a statin helps a woman is JUPITER, and rosuvastatin helped women with normal LDL-C associated with elevated CRP. Note: data from baseline lipids in women with significant CHD (HER Study) revealed that 20% of women with CAD have an HDL-C between 60 and 80 (Am Heart J 2000;139:288-96.).

If we use population cutpoints, an LDL-C of 162 mg/dL is the 90th percentile in Multi-ethnic Study of Atherosclerosis (MESA) (2000-2002) and 80th percentile in Framingham Offspring (FOS) (1988-1991). Not exactly where you want to be. The 20th percentile (desirable) LDL-C is 93 in MESA and 100 in FOS.

We now know that lipids, including cholesterol, are trafficked within either apoB or apoA-I containing lipoprotein particles and atherogenic (apoB) particle number is the primary driving force facilitating their arterial entry. Particle cholesterol content and particle size do not retain their statistical significance as a CHD risk factor once adjustment is made for LDL-P or apoB.

From the brand new (**I BEG ALL TO READ**) Statement from the American Association of Clinical Chemistry (Clinical Chemistry 2009;55:407-419): "it appears prudent to consider using apoB along with LDL-C to assess LDL-related risk for an interim period until the superiority of apoB is generally recognized. -- When the lipoproteins were identified mid-twentieth century, the common practice was to quantify them based on their cholesterol content (1). Later, as the apolipoprotein constituents were recognized and characterized, awareness gradually developed that apolipoprotein B (apoB), occurring as 1 molecule per LDL particle, was a more representative indicator of the concentration of LDL. -- Results from prospective studies generally demonstrate the superiority of apoB or LDL-P over LDL-C measurement for the assessment of risk. -- LDL particles, not simply LDL-C, play a central role in atherogenesis. --- LDL-C concentration can vary widely between individuals with the same LDL particle concentration (2, 15). LDL-C content does not reflect LDL particle concentration because metabolic reactions involving lipids can alter both lipoprotein size and lipid composition. The relative amounts of cholesterol and triglycerides in LDL particles can vary widely between individuals. -- apoB is better considered an alternate measure of LDL-related risk because it largely reflects LDL particle concentration. LDL-C, non-HDL-C, LDL-P, and total apoB are all, to varying degrees, measures of LDL-related risk. These cholesterol and particle measures are highly intercorrelated, which explains why they have all been implicated as predictors of CVD risk in epidemiologic studies, but biologically they reflect different entities. Despite a high correlation, these markers are only modestly concordant, indicating that one cannot simply substitute for another in classifying patients into risk categories. -- We believe that the medical decision cutpoints should be set so that the apoB and LDL-P cutpoints are equivalent to those for LDL-C in terms of population percentiles. --- The NCEP-recommended cutpoints for non-HDL-C were arbitrarily set 30 mg/dL higher than LDL cutpoints because the VLDL cholesterol associated with a triglyceride concentration of 150 mg/dL is 30 mg/dL. In terms of population equivalence to LDL-C goals, however, lower cutpoints appear more appropriate -- it appears prudent at this point to consider using both apoB (or LDL-P) and LDL-C to assess LDL-related risk for an interim period until the superiority of apoB is generally recognized."

In this case unlike many others I have previously presented, the LDL-C and LDL-P are concordant. An LDL-C of 160 and an LDL-P of > 1600 is the 80th percentile of the MESA population - i.e. 80 percent of folks have a better level. 80th percentile is obviously high risk, so treatment is indicated. How can this woman have so many LDLs, if her LDL particle size is large? As mention in the AACC statement, we have no clue what the composition of her LDL particles is: it seems they must be cholesterol deficient, thus it will take more of those types of LDLs to traffic a given level of LDL-C than it would cholesterol enriched LDLs. Her LDLs may be carrying TG instead of cholesterol, which would change the normal 4:1 ratio of cholesterol to TG in the particle core. To me, the clue that makes this scenario likely is the increased numbers of large VLDLs (a TG-rich hepatic derived lipoprotein). Increased number of large VLDLs are common in insulin

resistant patients and many Asians, even vegetarians tend to be insulin resistant. The large VLDLs typically have increased plasma residence times (due to delayed catabolism or lipolysis) allowing their TG to be transferred to other lipoproteins including LDLs via cholesteryl ester transfer protein (CETP) -- causing the core composition of the LDLs to change to a TG-rich, cholesterol poor composition. In this case the LDLs are very large, the LDL-P is very high. Her LDLs are likely carrying TG (acquired from the large VLDLs) instead of cholesterol. They are cholesterol depleted LDLs and that is why she requires a lot of them. This may indicate hepatic lipase isoform variant (also note the high HDL-C). The kicker is that few would look at her TG of 120 mg/dL and think it might be a problem - yet it may be in this case.

Why the high non-HDL-C despite the high HDL-C of 186? Looks like it is being driven by the high LDL-C. But go back to a very key sentence in the new AACC statement: If guideline goals are based on the 20th percentile cutpoints for high risk patients and the 2nd or 5th percentile for very high risk patients, what are the 20th and 2nd percentile levels for non-HDL-C in FOS? We have all been taught that one simply adds 30 to the desirable LDL-C goal -THAT ASSUMES A VLDL-C OF 30 IS PHYSIOLOGIC AND DESIRABLE. VLDL-C is derived using the Friedewald formula by dividing TG by 5. $150/5 = 30$. But is a TG of 150 physiologic. Numerous epidemiological studies and TG tolerance studies show, no it is not: a physiologic TG is < 100 or even 70-75. Thus a physiologic VLDL-C is likely $100/5$ or $75/5$: i.e. 20 or 15. Therefore should we be adding 15-20 to get the non-HDL-C goal rather than 30 mg. The answer lies in the population cutpoints for non-HDL-C!

In FOS the LDL-C 20th% is 100 The 5th% is 78 The 2nd% is 70 mg/dL

FOS: 20th percentile = 119 ($100 + 30 = 130$ TOO HIGH) ($100 + 20 = 120$ DESIRABLE)
5th percentile = 94 ($70 + 30 = 100$ too high) ($70 + 20 = 90$ DESIRABLE)
2nd percentile: = 83 ($70 + 30 = 100$ too high) ($70 + 15 = 85$ DESIRABLE)

A non-HDL-C of 100 or 130 is the 10th and 30th cutpoints (too high)

One other question: How can a vegetarian have a high TC and LDL-C: almost certainly overproduction of cellular cholesterol with or without an ability to excrete it. Normally cells that have too much cholesterol export it to HDLs which return it to the liver or jejunum (directly) or via transfer to LDLs and VLDLs (indirectly using CETP) who return it to the liver. Once in the liver, directly secreted into bile or converted to bile acids. Biliary cholesterol and bile acids enter the jejunum and ultimately the ileum where they are subject to excretion or reabsorption (cholesterol via jejunal Niemann Pick C1 Like 1 or NPC1L1 protein) or ileum (Ileal bile acid transporter or IBAT). Ezetimibe blocks NPC1L1 and bile acid sequestrants bind bile acids and block their reabsorption. Thus both ezetimibe and BAS like colestevlam promote cholesterol excretion (last phase of reverse cholesterol transport). There is a study showing ezetimibe block cholesterol absorption identically in vegetarians or non-vegetarians, thus proving the vast majority of absorbed cholesterol is of biliary (endogenous), not exogenous origin and that ezetimibe main MOA is to block the reabsorption of biliary cholesterol not eaten cholesterol (J. Lipid Res. 2006. 47: 2820-2824).

Therapy: Need to upregulate LDL receptors: typically statin or statin plus ezetimibe are used. But do not forget the increased large VLDL-P, so in the back of our minds we have to think if there is trouble getting to goal, we may need a statin plus TG-synthesis inhibitor (fibric acid, niacin or N-3 FA). Be aware Asians are highly sensitive to statins so typically one starts with a very low dose and if not effective titrate up or add ezetimibe or colestevlam: if one cannot get to goal with that approach, consider a TG synthesis inhibitor: fibric acid like Trilipix (approved for statin use), or Niaspan, N-3 FA such as Lovaza). Keep in mind we have Japanese studies like JELIS showing benefit by adding N-3 FA to a statin.

LIPID CASE 231 Drugs and lowering LDL-P

The case up for discussion involves a 46 year old male with a history of hyperlipidemia and a family history of CAD.

TC = 211 LDL-C = 147 HDL-C = 55 TG = 46 VLDL-C = 9
TC/HDL-C = 3.8 TG/HDL-C = 0.8 Non-HDL-C = 156
Lp(a) 3

Framingham Risk Scoring 4% ten year risk

NMR LipoProfile

Total LDL-P 2177 (99th percentile)
Small LDL-P 1905 (quite elevated)
LDL particle size 20.0 (Pattern B) (small is <20.6 nm)
Large HDL-P 8.5 (borderline normal)
Large VLDL-P 0

The providers at the clinic were divided as to therapeutic options. One opinion was to just treat with extended release niacin (Niaspan) 500 mg, although they were unsure how much LDL-P lowering would be achieved, whereas another thought was to treat with Niaspan 500 mg and Lipitor (atorvastatin) 10 mg in light of very elevated LDL-P.

DAYSRING DISCUSSION

If one uses the lipid concentrations and goes strictly by existing NCEP ATP-III, lifestyle would be the recommended therapy. Of course an LDL-C of 190 mg/dL would call for immediate drug therapy. An LDL-C of 190 mg/dL is well over the 90th percentile population cutpoint. An LDL-C of 147 mg/dL is just under the 70th percentile in Framingham Offspring. Thus I believe and agree with the providers in the case that a patient with atherogenic particle number in the extremes of population cutpoints clearly also deserves drug therapy, no matter what the LDL-C is. In numerous epidemiological trials looking at CVD risk, apoB and LDL-P significantly out predicted cholesterol measurements. Why would this man with an LDL-C of 147 mg/dL have so many LDL particles? The only answer is that his LDL particles are fairly cholesterol depleted and it always takes more cholesterol depleted LDLs to traffic a given amount of cholesterol compared to cholesterol-rich LDLs. Why would this man have depleted LDL particles? The usual cause is elevated TG: cholesteryl ester transfer protein (CETP - also known as apolipoprotein D) swaps cholesteryl ester (CE) for TG between VLDLs and LDLs. The LDL particle thus becomes TG-rich and CE poor and the VLDL becomes CE-rich. Well it is sure hard to blame TG as the culprit in a patient with a TG of 46 and no large VLDLs. Many things are involved with the determination of lipoprotein sizes, including several lipases and other lipid transfer proteins (apolipoprotein F, A-II) that we do not measure. Speculation will get us nowhere fast. All we as clinicians need to know is this man is at risk because he has way too many apoB particles (almost all of which are small LDLs) and our therapeutic mission is to reduce their numbers.

Therapeutically apoB particles or specifically LDL-P can be reduced by inhibiting their formation or by enhancing their removal. It is much easier to do the latter. Statins of course inhibit HMGCoA reductase, the rate limiting enzyme of cholesterol synthesis. By depleting hepatic cholesterol pools, homeostatic forces go into play to restore it: the liver needs cholesterol for its cell membranes, to lipidate HDL particles and to make bile acids. The body can replace that cholesterol by increasing cholesterol absorption in the jejunum and having it delivered to the liver in chylomicrons, by reabsorbing it from the bile using hepatobiliary ATP Binding Cassette

transporters G5 and G8, or by increasing indirect reverse cholesterol transport by upregulating LDL receptors.

Lipidologist paragraph: statin-induced hepatic cholesterol deficiency suppresses the Liver X receptor (LXR) leading to release of the Sterol Regulatory Element Binding Protein (SREBP) Cleavage Activator Protein (SCAP). SCAP transports SREBP precursor proteins from the endoplasmic reticulum to the Golgi where two proteases (S1P and S2P) liberate the mature SREBP which enters the nucleus and generates mRNA. This leads to LDL receptor (LDLr) synthesis and translocation to the cell surface. The LDLr attach to any lipoprotein with apoB or apoE on it and internalizes them and their lipid content. This in effect is the last step of indirect reverse cholesterol transport (performed by VLDLs and mostly LDLs that have acquired cholesterol in part from HDLs via CETP).

In order of potency with respect to binding to and inhibiting HMGCoA reductase:

Rosuvastatin>atorvastatin> simvastatin > pravastatin/lovastatin > fluvastatin. It is not a fluke that rosuvastatin upregulates more LDL receptors than the other statins explaining it has better apoB lowering efficacy. The vast majority of the cholesterol synthesis inhibition and hence LDLr upregulation occurs with the lower starter dose of the statin. Further titration of the statin will therefore be much less efficacious than the starter dose explaining the "rule of 6" upon statin titrations. Because adding ezetimibe (Zetia) or colestevlam (WelChol) to a statin further depletes hepatic cholesterol (the first by reducing absorption and chylomicron delivery and the latter by preventing bile acid reabsorption (requiring hepatic cholesterol to be used for new bile acid synthesis), much more than doubling the dose of the statin, they will lead to further apoB or LDL-C reduction than will the statin monotherapy. Ezetimibe and colestevlam adds 15-20% additional LDL-C and variable LDL-P reductions.

VLDL-P secretion is in part determined by the liver lipid content. The more lipid substrate that exists in the liver the greater the VLDL-P production and secretion. In our insulin resistant patients who have lots of FA and TG in their liver, there is often an over secretion of large VLDL-P. Lipolysis will ultimately result in lots of LDLs, which tend to be small and therefore poorly cleared by LDLr - resulting in elevated apoB and LDL-P.

Extended-release niacin is a pretty much a lipoprotein placebo at 500 mg but at full dose (2000 mg) can drop LDL-P 15%. I presume the clinicians were starting Niaspan at 500 mg and then planned to titrate up to a relevant dose. With respect to apoB, Niaspan reduces it by 20% at the 1500 mg dose (Am J Card 2004;94:588-594) and with respect to LDL-P, Niaspan reduces total LDL-P by 15-20% (Am J Card 91;1432-36). As with most TG-synthesis inhibitors, the drop in total LDL-P is explained by significant decreases in small LDLs coupled with smaller increases in larger LDLs. Also see Journal of Clinical Lipidology (2009) 3, 45-50

When added to a statin, fibrates are very variable at dropping LDL-P, but excellent at reducing VLDL-P. N-3 FA added to a statin can also further reduce apoB when TG are very high. These are all TG-synthesis inhibiting drugs (reducing VLDL-P), that also expedite lipolysis (hydrolysis of TG). Although this hastens LDL-P production, the LDLs are larger and more easily cleared by hepatic LDLr. Reduction of VLDL-P production and enhanced lipolysis significantly reduces VLDL-P. Of course statins and ezetimibe have also been shown to somewhat reduce hepatic apoB particle production.

Anyone with an LDL-P > 2000 is in the 95th-99th percentile of humans: i.e. almost all people would have less. It carries an extremely high risk: this is called familial hyperbetalipoproteinemia: all first degree relatives should be screened. It will be a formidable task to reduce such a high LDL-P. Sniderman has published superb data showing that as good as statins are at achieving the 20th percentile population cutpoints of LDL-C they usually get to the 55th percentile cutpoints for apoB - i.e. they need lots of help in getting apoB to goal (Journal of Clinical Lipidology (2008) 2, 36-42).

Once hypothyroidism has been ruled out, usual therapy for such a patient is low fat diet and moderate to high dose statin plus ezetimibe day one: then add additional therapies as needed: Without CAD being present and with no TG/HDL axis disorder, niacin is not the best first add-on. However it is noteworthy that the patient has small LDL particles and significant increases of small LDL-P. Thus Niaspan titrated to 2000 mg might be a good third therapy if needed. By shifting LDL size it may induce better LDL receptor clearance of LDL-P. Simcor use would be more cost effective than statin plus niacin. Virtually never would I use a fibrate in a patient with perfect TG and HDL-C unless all other Rx fails. One might also consider, colesvelam and as a dietary adjunct perhaps a plant stanol (Benecol). The goal of therapy is total LDL-P, not LDL size.

Apropos to this case is very important data just published in the Journal of Lipid Research (J. Lipid Res. 2009. 50:730–739 from the great STELLAR trial (Thomas M. van Himbergen et al): a study comparing all of the statins on multiple lipid and lipoprotein parameters. In this analysis they looked at markers of cholesterol synthesis (lathosterol) and absorption (campesterol). "When using absolute values of these markers, subjects with the greatest reductions in both synthesis (lathosterol) and absorption (campesterol) had significantly greater reductions in total C than subjects in whom the converse was true (-46% versus -34%, P = 0.001), with similar effects for LDL-C. Rosuvastatin and atorvastatin decreased markers of cholesterol synthesis and increased markers of fractional cholesterol absorption, with rosuvastatin having significantly less effect on the latter parameter than atorvastatin. In addition, alterations in absolute values of plasma sterols correlated with the cholesterol lowering response. ----- Because ezetimibe very significantly reduces intestinal cholesterol absorption, but increases synthesis, and because statins have the opposite effect, it would appear that combination therapy would be ideal. In addition, because statin therapy is often long term, measuring sterols may prove to be a useful tool for optimizing therapy and reducing CHD risk." **I strongly advise all lipidologists to read and re-read this paper if you want to truly understand body cholesterol homeostasis.**

LIPID CASE 232 Goals of Therapy in the Elderly

This issue's case was sent to me for advice. The patient is an 82 year old female patient who has DM, but no known CAD. She was already on Vytorin (simvastatin/ezetimibe) 10/20 mg and her lipid results were as follows:

TC = 177 mg/dL LDL-C- 102 mg/dL , HDL-C-53 mg/dL , TG-112 mg/dL , VLDL-C = 22 mg/dL
Non-HDL-C = 124 mg/dL TC/HDL-C = 3.3

The provider had also ordered advanced lipoprotein testing, namely nuclear magnetic resonance spectroscopy.

Total LDL-P = 1654 nmol/L (high risk)
Small LDL-P = 961 nmol/L
LDL particle size 21.2 (large or Pattern A)
Large HDL-P 13.1 umol/L (desirable > 9.0)
Large VLDL-P = 0.1 nmol/L (desirable < 0.5)

The provider was going to change her to a more potent statin (rosuvastatin or Crestor) and Zetia (ezetimibe), but the woman gets her medications from the VA and they instead increased her Vytorin to the 10/40 mg dose. A month later her NMR LipoProfile was repeated:

TC = 170 mg/dL, LDL-C = 92 mg/dL, HDL-C = 53 mg/dL, TG =126 mg/dL, VLDL-C = 25 mg/dL

Total LDL-P = 848 nmol/L (51% reduction)
Small LDL-P = 183 nmol/L
LDL particle size = 22.3 (large)

Large HDL-P = 11.4 umol/L
Large VLDL-P = 3.2 nmol/L.

The clinicians were surprised that the LDL-C did not change very much (10 mg/dL), but were amazed at her particle numbers changes. Their question was whether we should push statin to get her particle number to less than 700 nmol/L.

DAYSRING DISCUSSION:

As with all patients' proper treatment and the aggressiveness of that treatment depends on both the ten year risk and lifetime risk of having a CVD atherothrombotic event. Those with the highest risk get very aggressive treatment and those with lower risk do not. The goals of therapy (lipids or lipoproteins) are more intense for those in the high and very high risk category. In an 82 year old woman, one likely assumes her ten year risk is her lifetime risk. We really cannot do Framingham Risk Scoring (FRS) in this woman as she is already treated. Many fail to realize that FRS has not been adjudicated (proven valid) in persons on medications. NCEP-ATP-III specifically warns not to recheck risk using the FRS equation once therapy is started. However if we assume her TC would be 30-40% higher had she not been on Vytorin 20 mg she has a 5-6 % risk of an event over the next decade. However the 2007 update to the AHA Women's Guidelines states that any women > age 50 who has a single risk factor has a high lifetime risk of an event. Since in this woman 10 year risk and lifetime risk is the same, which does a clinician believe? Personally I do not think FRS can help us much in this woman. What might be of more use is some indication of subclinical atherosclerosis: careful physical examination (retina, pulses, and bruits), carotid IMT testing or a coronary calcium score. For the purpose of this discussion I am assuming physical exam is negative and she cannot afford the imaging procedures (Please: no e-mails on the affordability of these tests in your area).

Of course 8 years ago NCEP called apolipoprotein B (a measure of atherogenic particles) as an emerging risk factor. We now know apoB (LDL-P has been validated in several trials and the 2008 ADA/ACC consensus statement made it a goal of therapy in patients with cardiometabolic risk. However there is nothing in the data we have that suggests cardiometabolic risk except her age (a major risk factor for insulin resistance) and the presence of large VLDL-P on the follow up profile. The recent AACC guidelines does give us a suggested apoB (80 mg/dL) and LDL-P (1000 nmol/L) goal for high risk persons.

If we are to play by NCEPATP-III this woman is low risk and is at goal using Vytorin (indeed she may have been at goal prior to Vytorin therapy) and nothing further need be done. However this case is complicated because we do have a high risk LDL-P of 1600 nmol/L (>80th percentile population cutpoints). Therefore we now must assume she is indeed high risk and therapy is indicated. However the Vytorin 10/20 blew away her LDL-P to the 5th population cut-point percentile in the Framingham study. Thus she is done and no further therapy is indicated. Judging by e-mails I receive I find way too many providers over-treating patients to absurd reductions in LDL-P based on no data whatsoever. The clinician treating this patient wanted to drop the LDL-P to less than 700. I might accept that in a very high risk person with CHD events but there is no way this woman qualifies as to that degree of risk. We also have to remember how easy it is to induce side effects as well as drive up cost in elderly patients. I really want to remind my readers that we cannot lose sight of evidence and we must base treatment goals, not so much on guidelines but on RISK! My own numbers are:

High risk: LDL-C < 100 mg/dL Non HDL-C < 120 (my number), apoB < 80, LDL-P < 1000

Very high risk: LDL-C < 70, Non-HDL-C < 85, apoB < 60, LDL-P < 700-800

Those are the 20th and 2nd to 5th percentile population cutpoints in Framingham and MESA. For a discussion why taking LDL-P to less than 1000 nmol/L is not indicated please if you have not done so read the Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices: Clinical Chemistry 55:3407-419 (2009). I really cannot

state how important this paper is in helping you make the transition from lipid to lipoprotein analysis. For how to obtain a reprint visit: <http://www.clinchem.org/> and search the article

Now, what about the tremendous response to Vytorin in this woman? Let's assume she was taking the meds as prescribed. Clearly if she was not, that would help explain some of the improvement when she finally started therapy. Clinical trials as well as the product information sheet for Vytorin shows that by going from Vytorin 20 to Vytorin 40 mg one should see a 3-6% further reduction in LDL-C. The apoB or LDL-P reduction should be similar or slightly less. Statins primarily upregulate LDL receptors, but the vast majority of that upregulation comes with the small starter dose of the statin. When one titrates from Vytorin 20 to Vytorin 40, one is simply doubling the dose of the simvastatin. Thus the desire to switch from Vytorin 20 to Crestor 20 mg/Zetia on face value makes sense in those where the LDL-P remains high on the Vytorin 20 (not the patient under discussion). But in lipidology it is always tough to predict individual responses to therapy. There are both hypo and hyper-responders to statins and ezetimibe.

The clinician was surprised that LDL-C did not change very much. Yet the LDL-C did drop by 10% which is more than one would have predicted reading the Vytorin package insert. The standard line is doubling the dose of a statin (no matter which one you use) gets you about 6% further LDL-C reduction. This is because the vast majority of statin-induced LDL receptor upregulation occurs with the smaller starting doses of the statins. If one needs more serious LDL lowering one would likely get more by adding a different drug than by titrating the statin and indeed NCEP ATP-III 2004 update gave that option to providers: the add-ons NCEP listed were ezetimibe, Niaspan (extended-release niacin) and Welchol (colesevelam: a bile acid polymer).

Of course there was an unexpected 50% reduction in LDL-P to doubling the statin dose and a much unexpected drastic increase in the LDL size. Accordingly, there was a hyper-response to doubling the dose of the statin on LDL-P but not LDL-C. Why? Most likely explanation is that the patient is simply an over producer (too much HMG CoA reductase), not an over-absorber of cholesterol and in these patients there are usually dramatic responses to statins. Over-absorbers sometimes have a high HDL-C (not the case in this lady). Over producers of cholesterol have high hepatic HMG-CoA reductase levels and therefore respond powerfully to statins.

Are there other clues in the lipid profile that something else may also be at play? Notice that the other parameters that differed between the two tests are 1) LDL size (particles went from normal to extremely large), and 2) large VLDL-P went up significantly, 3) TG increased by over 10%. The dramatic reduction in the LDL-P is explained by a big drop in small, not large LDL-P. Note that the original large LDL-P was 693 (1654 - 961) and the repeated large LDL-P was 665 (848 - 183): almost no change in large LDL-P (WHICH WERE NORMAL TO BEGIN WITH). Her small LDLs disappeared. What caused the particle size shift?

Looking just at the lipids: TC went down by 7 mg/dL, LDL-C went down by 10 mg/dL, HDL-C stayed the same, and VLDL-C went up. VLDL-C is of course TG/5, so it went from 22 to 25 (altered lifestyle?). Non HDL-C is VLDL-C plus LDL-C, so the change in Non HDL-C was 7 (from 124 to 117). That is a 9.5% reduction. So if Non HDL-C is supposed to correlate with LDL-P, why did the former drop 9.5% and the latter 50%? Why did LDL-C drop 10% and LDL-P 50%? This is a great example why **you really can never know with certainty what is happening** when you look at lipid concentrations as opposed to particle concentrations.

If you want some speculation: The above changes suggest something is inhibiting hepatic lipase or cholesteryl ester transfer protein. Statins, not Zetia, are known to do both in a dose related fashion to very variable degrees. Because the LDL particles are now larger, they hold much more core lipids cholesterol and/or TG and thus the patient does not need as many 22.3 nm sized LDLs as she did when LDL size was 21.2 to traffic her lipids. Some of the LDL size increase may be due to the slight increase TG and phospholipids (which were not measured) due to decreased

hepatic lipase or CETP activity or a combination of both. The IDL-P was not reported as it is not given on LabCorp versions of the NMR report. One would likely see that parameter also increased (one can look at the bar graphs on the LipoScience report form for IDL-P).

As far as additional treatment: None is needed other than some fine tuning of the lifestyle to lower the TG. Her LDL-P is way below goal. As discussed achieving an LDL-P of 700 is over treatment except perhaps for an extremely high risk individual which this lady is not. Check out the LipoScience report: An LDL-P of up to 1500 is called minimal elevated. Under 1300 is near optimal. An LDL-P of 1000 is not needed except in high risk patients.

Bottom line is the high-risk goal (LDL-C, Non-HDL-C, and LDL-P) was achieved. As long as you get LDL-P to appropriate goal one need not be a high level lipidologist to do well. But I believe the more we understand the underlying physiology/pathophysiology, the more fun managing patients is.

LIPID CASE 233 Severe Hypertriglyceridemia: When to use a statin

I was asked about a 31 year old man referred with an eye-catching lipid profile: I have little history to offer, so we will get into the lipid issues. One would suspect this person might be obese, hypertensive and even a T2DM. Since a cardiologist sent me this case I might assume the patient has coronary disease which at least puts him into the high risk category.

September:

TC = 232 mg/dL Direct LDL-C = 31 mg/dL HDL-C = 6 mg/dL TG = 1,933 mg/dL

The clinician started the patient on prescription strength N-3 fatty acids (Lovaza) at 4000 mg/day, and TriCor (145/day) and 6 weeks later a Berkeley Heart Lab analysis done:

TC = 180 mg/dL LDL-C = 81 mg/dL HDL-C = 23 mg/dL TG now 390

Non-HDL-C = 157 mg/dL

Apolipoprotein B (apoB) = 98 mg/dL

LDL III a+b = 35

LDL IVb = 1

Lp (a): 4 mg/dL

DAYSRING DISCUSSION:

At first glance this is simply a severe case of hypertriglyceridemia and excess cholesteryl ester transfer protein (CETP or apolipoprotein D) activity, which is an hepatic produced, but HDL trafficked protein, which transfers (swaps) one molecule of TG into the LDL and HDL particles in exchange for one molecule of cholesteryl ester (CE). It is TG that drives CETP activity. As a result of the increased CETP activity, the LDLs and HDLs are carrying (trafficking) significantly less cholesterol than they would if the TG were normal and there was no excess CETP activity. When TGs are extremely high, calculations such as the TC/HDL-C or non-HDL-C have no meaning and thus those parameters are not useful. The extreme excess of TG will alter particle compositions very significantly, especially HDL-C. Likewise a VLDL-C and therefore a calculated LDL-C would be erroneous. The provider ordered a direct LDL-C measurement, but in a person with extreme TG even a measured LDL-C will have virtually no correlation with the number of atherogenic lipoproteins (apoB or LDL-P or VLDL-P). As the HDLs, now carrying TG (instead of CE) pass through the liver, hepatic lipase hydrolyzes those TG and HDL surface phospholipids and the apoA-I breaks off and is excreted by the kidney: Hence the patient will have very few HDL particles: apoA-I or HDL-P (as well as HDL-C) would be very low. If one was looking at HDL subspecies, in addition to reduced HDL-P, there would be almost no large HDLs. Large HDLs carry about 80% of the total HDL-C and usually persons with declining HDL-C < 40 mg/dL, will

have fewer large HDL species. This TG-induced reduction of HDL-C is a hallmark of the metabolic syndrome and people with so called TG/HDL axis disorders. Likewise the TG-enriched, CE-depleted large LDLs will undergo further lipolysis by hepatic lipase and become small. The now small LDLs in such patients although very cholesterol-depleted are much too large (17-20 nm) to be excreted by the kidneys and hence they accumulate and in most such patients the LDL-P (apoB) is very high: The initial key to lowering apoB in such folks is reduce TG production with lifestyle.

High dose N-3 FA (Lovaza) with fenofibrate (TriCor in this case) is very appropriate first choices to "slay" the TG. Both share many actions and powerfully inhibit TG production. Of course the TSH must be checked, any glucose abnormalities brought under control and therapeutic lifestyle with total avoidance of alcohol are also indicated. I also presume the patient is not nephrotic. When approaching patients with hypertriglyceridemia it is really a two step approach: if the original TG level is > 500 mg/dL. According to NCEP ATP-III such levels are associated with very high risk and by that they mean both cardiovascular and of course pancreatitis risk. Triglyceride, correctly called triacylglycerol is a molecule with three fatty acids (or acyl groups) attached to a glycerol (a sugar-alcohol considered to be a carbohydrate). Acyl groups in reality are detergents, meaning they can disrupt cell membranes. Soaps are acyl compounds. In persons with extremely high levels of acyl groups, pancreatic cell membranes are disrupted, thereby releasing their peptidases, lipases, etc., which of course is why extreme hypertriglyceridemia is associated with pancreatitis. Usually it takes a TG well above 1000 mg/dL to cause pancreatitis. However if one has a fasting TG > 500 mg/dL, it is not unusual for a postprandial TG to rise to extreme levels (especially after a FA or glucose or maltose challenge - i.e. good living). If one reduces the fasting or PP TG to < 500 mg/dL pancreatitis is not likely to occur. Both high dose N-3 FA (remember there is a threshold effect of 4 gms for N-3s to lower TG) and fibrates (fenofibrate or fenofibric acid) will lower TG in the 40-50% range. I often use both together when TG levels are extreme as did the clinician in this case.

In this patient: what are the particles trafficking the excess TG? Well they have to be VLDLs or chylomicrons. NMR cannot separate those two particles (they would both be reported as large VLDLs. If one lets the turbid serum stand overnight, and there is a dense "heavy cream" layer on top of the turbidity the next morning then chylomicrons are present. That would surely suggest some degree of lipoprotein lipase (LPL) deficiency. Clearly in such patients there is marked increase residence time of these TG-rich particles: all the more time in which the CETP can transfer the TG causing pathological composition of the LDLs and HDLs as described above. Blood viscosity will be high, endothelial cells will express less nitrous oxide and both PAI-1 and fibrinogen will be elevated. It would not be surprising to find elevated apoC-III which would further delay particle lipolysis by blocking or displacing apoC-II, apoE and apoA-V.

On follow up, the two TG synthesis inhibitors (Lovaza and TriCor) have done a great job and the number of circulating chylomicrons (if present), VLDLs and their progeny (LDLs) has been reduced. The still high TGs are still via CETP activity swapping for cholesteryl ester in the LDLs and HDLs, but at a far less rate than previous: hence the rise in LDL-C and HDL-C (both desirable). The HDLs are larger now and less prone to renal excretion and thus apoA-I or HDL-P is rising. A major shortcoming of Berkeley (unlike LipoScience) is they not to report anything on VLDL-P (remnants) or HDL-P (or apoA-I). Fibrates and N-3 FA share many of the same mechanisms of action (via their effect on nuclear transcription factors): reducing hepatic lipogenesis, increasing mitochondrial beta-oxidation of FA, inhibiting DGAT (the enzyme that attaches the final acyl group to diacylglycerol), increasing lipoprotein lipase activity, decreasing CETP activity, reducing apoC-III, etc.

Note that on the follow up the TG were significantly reduced but the LDL-C seemingly went up. This often happens when powerful TG synthesis inhibitors (N3 FA and fibrates) are used and it is of no major concern. There are great slides explaining this on our web site www.lipidcenter.com (professionals). In patients with high TG, the composition of HDL and LDL particles is very abnormal: these lipoproteins are carrying TG instead of CE. Thus when TG are dramatically

lowered by fibrates or N-3 FA, CETP activity diminishes and TG no longer are transferred from VLDLs to LDLs and HDLs. Thus on these meds, HDLs and LDLs return to a more normal core composition and traffic CE instead of TG. This usually results in larger LDLs and HDLs, carrying more CE and less TG. LDL-C and HDL-C increases, but non-HDL-C (apoB) goes down. If you are wondering why the non-HDL-C level gets to goal even when LDL-C is rising, it is simply because the powerful TG lowering drugs, significantly reduce VLDL-C. The reduction in VLDL-C is much greater than the rise in LDL-C. Non HDL-C = VLDL-C plus LDL-C. It is easy to see how significant TG reduction is beneficial despite the occasional rise in LDL-C that might occur. Providers who stop N-3 FA (Lovaza) or fibrates because LDL-C goes up (if non-HDL-C and apoB are reducing) are not up to current knowledge on lipid and lipoprotein basics. They make a big mistake by stopping those therapies.

Now that the risk of pancreatitis is gone (with TG < 500 mg/dL), lowering apoB (if it is still elevated) remains the priority: In NCEP, once the TG are < 500 mg/dl, the goal of therapy becomes non-HDL-C. In this case, with the TG still high at 380 mg/dL, the clinician added Niaspan. Note the non-HDL-C is well above the high risk goal of 130 mg/dL. So for sure additional lifestyle and pharmacological therapies are indicated. But remember our mission (and never lose focus) is to eliminate the still high numbers of atherogenic apoB particles. Note the apoB of 98 mg/dL. The new ADA/ACC consensus statement calls for an apoB of 90 and most believe that is way too conservative. The AACC statement calls for an apoB of 80 and those of us who are very aggressive in patients with CAD often shoot for an apoB of 60. There is no guideline recommending an apoB of 60. This provider got his apoB on the Berkeley report and that company does suggest apoB of 60 for the high risk patients. An apoB of 98 is the 50th percentile population cut point (way too high). 90 would be the 40th percentile (still way too high and I cannot believe the ADA/ACC consensus panel chose 90). An apoB of 80 is the 20th percentile and that is reasonable. 60 mg/dL would be the 2nd percentile cut point (similar to an LDL-C of 70 mg/dL).

Although high dose (2000 mg) of extended release niacin (Niaspan) will further lower TG and apoB, it would not have been my choice in this patient. A potent statin (Like Crestor 20 mg) or atorvastatin 40-80 mg if insisted upon by a formulary) would be a better third line drug as properly dosed statins are better apoB lowering meds than Niaspan. It is likely, with the statin, the apoB would hit 80 mg/dL (the goal). Once there you are done. There is no need to raise HDL-C per se once apoB is normal. If you add the statin and apoB does not get to goal then one could consider niacin. I do like to use niacin in patients with CAD, because of its numerous beneficial angiographic trials (when used with a statin or bile acid sequestrant). However, if you really wanted to be aggressive, instead of adding the statin as I suggested, one could start Simcor and titrate up. (and save the patient some money). You have to have a statin on board. The new ACC/ADA statement on cardiometabolic risk mandates a statin as the first line drug if the TGs are < 500.

Personally I would have used a statin or statin/ezetimibe (added to the Lovaza and TriCor). The TGs are probably still too high to consider colesvelam (WelChol). We must remember that with the TG < 500 mg the NCEP goal of therapy is non-HDL-C (apoB or LDL-P). We need to upregulate LDL receptors to really lower apoB and thus a statin or statin/ezetimibe is the proper choice. Since the TGs are still 380 mg/dL, the two best statins at lowering TG are rosuvastatin (Crestor) 40 mg and atorvastatin (Lipitor) 80 mg (see STELLAR Trial data (Am J Cardiol 2003;93:152-160). There is a new pdf on my web site discussing statins and TG if you want to examine this topic more deeply. Although they are equal on TG, the Crestor is more powerful on reducing apoB so it would be my pick. One could argue that statin/ezetimibe (Vytorin) at 40 mg would be equally efficacious. Since this clinician already started the Niaspan and hopefully will titrate it up, one could wait 8 weeks and see what happens to the parameters. If apoB still is high on Lovaza/TriCor/Niaspan) I'd suggest stopping the Niaspan and switching it for Simcor at the equivalent dose.

In summary, the approach to very serious TG elevations after ruling out hypothyroidism is drop the TG to < 500 mg/dL:

- 1) Lifestyle with alcohol avoidance
- 2) N-3 FA (Lovaza) 4000 mg or more and/or fenofibrate/fenofibric acid
- 3) Once TG < 500 mg/dL, non-HDL-C (apoB or LDL-P) becomes the goal of therapy
- 4) Add potent statin or statin/ezetimibe as discussed above

On a molecular level, what you need to do is aggressively reduce FA and glucose intake [lifestyle and/or orlistat (Xenical)] or inhibit FA synthesis and increase hepatic mitochondrial beta oxidation of FA reduce CETP activity, increase lipolytic activity (stimulate LPL and decrease apoC-III). N-3 FA, fibrates, niacin do most of those. Statins and ezetimibe do not. However you must also upregulate LDL receptors to clear the excess numbers of apoB particles: statins, ezetimibe or colesvelam or combinations thereof.

LIPID CASE 234 Diagnosing Low HDL-C states

I was asked to comment about a 34 year old police officer who is not overweight. He came to the provider's office as he was not feeling well with nonspecific symptoms and as part of the work up a lipid panel was done. I have no other information or lab results. However, the lipid panel is worthy of a discussion.

TC = 132 mg/dL TG = 167 HDL-C = 10 LDL-C = 88 TC/HDL-C = 13.2

The provider wonders if the low HDL-C (he had never seen such a low value) required treatment. Because the LDL-C and TC were so good he was skeptical that therapy was indicated. A pharmaceutical rep advised Rx to raise HDL-C, based on Castelli's Framingham data which suggests low HDL-C and high TC/HDL-C ratio is an independent risk factor for CHD regardless of the LDL-C.

DAYSRING DISCUSSION:

There is a reason why reps that provide providers with information about their products do not have a license to practice medicine. They do not know (nor could they without years of clinical training) how to apply their specific drug-product knowledge to INDIVIDUAL patient care. Fortunately, the provider did not listen to the rep and immediately start some drug to raise HDL-C per se. The clinician's intuition was correct: based on the above info there is absolutely no way to make a rational therapeutic decision. Additional information is needed. Also one should never ask the simplistic question, if low HDL-C should be treated. There is no specific HDL-C goal of therapy in NCEP ATP-III and there is no certainly no NCEP statement that if the HDL-C drops below a certain value that treatment is indicated. NCEP certainly states low HDL-C is a major independent risk factor for CHD, but a full reading of the NCEP chapter on low HDL-C indicates that there are several low HDL-C states not associated with CHD.

Our mission as clinicians is to prevent atherosclerosis and the clinical events associated with it. All of our decisions are based on two facts: 1) is atherosclerosis present or has a clinical event occurred or 2) if #1 is not present are there any risk factors present that might indicate a person is at risk for atherosclerosis? Providers must do a careful search for historical risk factors (age, smoking, family, etc.), search for disease evidence on careful examination (skin, eyes, pulses, obesity, BP, bruits, etc.), and then turn to the laboratory and imaging sciences for as thorough an evaluations as deemed necessary realizing we cannot do every possible test on every patient. Once the proper degree of risk is ascertained, then treatment (lifestyle and drugs) are directed at whatever evidence-based treatable risk factors were found. I am unaware of any high level evidence that simply raising HDL-C per se is necessarily cardioprotective. There are certainly therapies that raise HDL-C that are not cardioprotective (Dilantin, estrogen in women with CHD, torcetrapib, high alcohol intake).

So let's apply those principles to this patient: 1) what more do I desire from the history?

Does his last name end with a vowel - if so is he or his ancestors from Northeast Italy? Family history of premature heart disease or any known genetic diseases. Is there knowledge that other family members have had very low HDL-C? If so, did they or did they not have heart disease. Are there any known eye problems or skin discolorations? Any special diet? And of course are any prescription, OTC or illegal drugs being used. The patient has to advise whether androgenic steroids are being used! One might suspect him to look like a body builder, but that may not be so.

2) Exam: lens clouding, palmar xanthomas, other xanthomas, tonsil exam, splenomegaly, and vascular exam

3) Lab: blood chemistry profile to include glucose, A1C, TSH, serum total and gamma protein (myeloma can present as low HDL-C), urine albumin, hs-CRP, and NMR LipoProfile. I really want the latter because I be very interested to see if lipoprotein (x) is present and of course I need to know the LDL-P. An apoB could obviously be done to assess atherogenic lipoproteins, but lipoproteins (x) if present would be missed by only doing apoB. How about apoA-I or the total HDL-P (available on the full NMR report). Or is this a case where the blood should be sent to Boston Heart Lab (see below) for HDL "fingerprinting."

Of course a complete evaluation would entail much more history and exam. But why did I specifically mention certain items above. Is everyone mentally starting to make a rule-out list of diagnostic possibilities? When I see someone with an HDL-C less than 10, we are dealing with severe hypoalphalipoproteinemia. Some of those conditions are associated with severe CHD, some with minimal CHD and some with no CHD. NHANES data shows that approximately 1 in 20,000 patients has an HDL-C of 10 mg/dL or less (Cur Opin Lipidol 2004;19:380-384).

A quick review of HDL biology and keep in mind that a defect in any one of these steps will affect serum HDL-C levels and clinical outcomes: HDLs start as hepatic or jejunal secreted unlipidated apoA-I which acquires phospholipids and unesterified cholesterol by attaching to cellular membrane ATP binding cassette transporters A1 (ABCA1). The cholesterol is esterified to cholesteryl ester by the enzyme lecithin cholesterol acyl transferase (LCAT): also called phosphatidylcholine-sterol O-acyltransferase. As a fatty acid (FA) transfers from HDL phospholipids (at the Sn-2 position), it attaches to unesterified cholesterol (3-hydroxy-cholesterol which has an -OH group at the 3 position). The FA makes the cholesterol more hydrophobic and the molecule moves away from particle surface and the aqueous plasma deep into the core of the unlipidated apoA-I, forming a prebeta HDL and then as the process proceeds a maturing, small HDL is formed: this is termed alpha-3 or 4 by Boston Heart Lab or HDL3 by Berkeley or H1 H2 by NMR. As the particle acquires more and more cholesterol which is constantly esterified it becomes more mature (larger) and is now called an alpha 2 and finally alpha 1 (HDL2 or NMR H4, H5). Once the particle is larger than prebeta, it can be additionally lipidated by attaching to different protein sterol transporters capable of lipidating larger HDLs: ABCG1 or G4 or the bidirectional transporter, called the Scavenger Receptors B1 (SR-B1) which can actually lipidate or delipidate HDLs depending on the cholesterol concentration gradients inside and outside the cell. Although the vast majority of HDL lipidation (acquisition of cholesterol) occurs at the liver and jejunum, arterial wall macrophages (macrophage RCT) and peripheral cells can also contribute to HDL lipidation. Ultimately the large, mature HDL is delipidated by hepatic, adipocyte or intestinal SR-B1 (direct RCT) or steroidogenic tissue SR-B1 or by cholesteryl ester transfer protein (CETP) activity where the CE in the HDL is exchanged for TG in the apoB particles (VLDLs and HDLs). During delipidation the HDL becomes smaller, transforming back into alpha HDL 3 or 4 (HDL3 or H1, H2) or even smaller prebeta HDL. Keep in mind that because of their larger size and volume about 80% of the total HDL-C value is trafficked in the larger mature HDL species. Cromwell in his classic paper notes that as HDL-C increases from 20 to 40 mg/dL there is a tremendous rise in small HDL species: after an HDL-C of 40-45 mg/dL there is very little

further increase in HDL-P, but rather an increase in HDL size. Because the volume of a sphere is a third power of the radius, increasing HDL size can be associated with substantial increases in HDL-C. One can speculate that HDL-P may be more important than HDL-C as a risk factor or perhaps even as a goal of therapy. When the particle volume characteristics are understood one can see how some low HDL-C values may be associated with substantial HDL-P levels (lots of small HDLs) and very high HDL-C levels may not be (low numbers of very large HDLs). Several key enzymes are very important in remodeling HDL particles especially hepatic (triglyceride lipase and phospholipase) and endothelial lipase (a phospholipase).

So with particle physiology (remodeling or flux) in mind: Let's go through the differential diagnosis in this patient:

- 1) Anabolic steroid abuse: causes decreased apoA-I synthesis and increased hepatic lipase: decreased numbers of small HDLs and low HDL-C. Acne may be present, an athletic build and with chronic use - reduced testicular size. Easy therapy: stop the steroids!
- 2) Other drugs: likely not the case but either fenofibrate alone or more commonly with fenofibrate in combination with rosiglitazone are known causes of the disappearing HDL syndrome. Etiology not well understood but likely an over upregulation of SRB1 with severe HDL delipidation (see reference 5 below). Likewise a drug formerly available in the US, and still available in other countries, probucol (formerly sold here as Lorelco) has a positive postangioplasty angiographic trial. Formerly thought to be an antioxidative drug, it is basically a CETP and SRB1 inducer and thus lowers HDL-C. (Future Lipidology 2009;4:63-78). Of course this patient is not likely on probucol.
- 3) Tangier's Disease: a rare genetic disorder where ABCA1 is not present. Sterol accumulation occurs in lymphoid tissue (tonsils, spleen, and liver). ASHD occurs if apoB is high. The degree of atherosclerosis is less than one would suspect with virtually absent HDL-C levels.
- 4) Hypoalphalipoproteinemia due to marked decrease in apoA-I production: severe CHD usually present. Skin manifestations (palmar xanthomas, lens clouding can occur)
- 5) Hypoalphalipoproteinemia due apoA-I Milano: Rare gene and apoA-I mutation found in folks from a small town in NE Italy (Alps area). An extremely functional apoA-I not associated with CHD. The HDLs are extremely functional on sterol efflux.
- 6) Low HDL-C due to heterozygosity of ABCA1: 50% reductions in HDL-C due to decreased cell and hepatic ABCA1 transporters resulting in reduced lipidation of HDLs, not usually associated with CHD unless apoB is elevated (higher TG (indicative of potential apoB elevations). Think about it: in these patients there is less hepatic lipidation of HDL particles with cholesterol (resulting in reduced HDL-C) - why would that cause CV risk? I doubt if this applies to the patient at hand as this condition does not cause extremely low HDL-C values (10 mg/dL)
- 7) LCAT deficiency (Fish eye disease in its milder form): Problems with the enzyme LCAT. Various deficiencies of the esterification enzyme LCAT, prevents the formation of the lipophilic cholesteryl ester (CE). If free cholesterol does not become esterified (UC) it remains partially hydrophilic and therefore UC stays on the surface of the HDL particle whereas the lipophilic CE would go from particle surface to particle interior, in effect filling the particle, ultimately causing the discoid prebeta HDL to transform into a spherical larger HDL particle. If the HDL does not "fill up and enlarge" the apoA-I breaks off and is prone to renal excretion. Thus these patients with LCAT deficiency will have very low HDL-C levels (5-10) and interestingly the risk of atherosclerosis is not significantly increased (the activity of LCAT in HDLs is LCAT alpha). Many of these patients form bilayer phospholipid discs which are referred to as lipoprotein x. NMR spectroscopy can detect Lp(x). Since LCAT assays are not available to the average practitioner, Lp(x) on an NMR LipoProfile can be a big help in diagnosing LCAT deficiency. Many of these patients develop lens clouding - hence "Fish Eye Disease." Although often not recognized, LCAT

is also present in the apoB particles (LCAT beta activity) and this interferes with the composition of those particles creating what is called "polydisperse particles" meaning they have variable core contents of CE and TG. Often the TG is slightly elevated.

So why not send the blood up to Boston Heart lab (www.bostonheartlab.com) for their "HDL fingerprinting analysis. Developed by Bela Asztalos and Ernie Schaefer using nondenaturing two-dimensional PAGE, immunoblotting, one can very rapidly diagnose most HDL particle disorders. Please visit their web site for details or check out the following reference pertinent to this case which is a must for lipidologists (J. Lipid Res. 2007. 48:592–599). In this case one would not find any mature HDL particles. This lab also offers testing tough to get elsewhere such as markers of cholesterol synthesis and absorption. Lipidologists: Please check them out.

8) Is this simply a case of insulin resistance related isolated low HDL-C (which would be seriously related to CHD risk). I would certainly perform: glucose, insulin level, urine microalbumin. I'd want an apoB or preferably a full NMR LipoProfile (not the LabCorp partial NMR analysis) and I'd look for large VLDL, increased # of total and small LDL-P. I'd also look at the total HDL-P (a sum of small, medium and large HDL-P). Insulin resistant patients typically have reduced numbers of large and increased numbers of small HDL species.

It is unusual to see HDL-C of 10 in insulin resistant patients who do not have massive hypertriglyceridemia. However this could be insulin resistance on top of a heterozygous ABCA1 deficiency. The key is are there or are there not too many atherogenic apoB (predominantly LDL particles) present or not. If to the person is at high risk for CHD and therapy would be directed at the elevated apoB (LDL-P): statin, statin/ezetimibe or statin/Niaspan (Simcor to save a copy). If LDL-P is not high none of those drugs are indicated.

Rumor has it that the Official NMR report will soon start reporting total HDL-P and thus save me the addition exercise just described. I think we will all soon find out that total HDL-P (above and beyond HDL-C) is a very valuable parameter. Keep in mind that NMR spectroscopy cannot evaluate unlipidated apoA-I or prebeta HDLs. These do not contribute much to total HDL-P (maybe 5%) but of course the prebeta HDLs are a very crucial "prebeta HDL particle" and are the crucial first step in HDL lipidation at the liver or the arterial wall macrophage. In LCAT the NMR report would show reduced numbers of HDLs, no large or medium HDLs and possibly lipoprotein x.

So a good history and proper laboratory testing will differentiate from all of the above possible diagnoses. If apoB or LDL-P is high or one of the hypoalphalipoproteinemia disorders known to be associated with CHD is present, I'd also order hs-CRP, Lp-PLA2 and do a carotid IMT or coronary calcium score. Depending on the results of above, treatment proper treatment could be suggested. If it is IR with high LDL-P then Simcor (likely with Zetia) would be indicated. Should isolated low HDL-C be treated? There would be zero clinical trial data from which to draw a conclusion. NCEP ATP-III suggests that in high risk patients (i.e. patients with known CHD, or CHD risk equivalents it is appropriate to prescribe a fibrate or niacin. I disagree with that. I know of no evidence that fibrates work if TG are not elevated and the vast majority (if not all) of patients with low HDL-C who get CHD have too many atherogenic apoB particles and the best treatment for that is a statin, statin/niacin combo or statin/ezetimibe combo.

Lipid Case 234 Diagnosing Low HDL-C States (Illustrated)

The sophisticated graphics are supplied by Boston Heart Lab, who offer sophisticated HDL analyses (called HDL Map). Please see www.bostonheartlab.com and view their excellent video on HDL particle formation, lipidation and delipidation. Please note: in their animation they do not mention that the organs

providing the vast majority of HDL lipidation are hepatocytes and jejunal enterocytes, not peripheral cells or arterial wall macrophages.

This issue's case is a challenge and I'll take a theoretical stab at it. I was asked to comment about a 34 year old police officer who is not overweight. He came to the provider's office as he was not feeling well with nonspecific symptoms and as part of the work up a lipid panel was done. I have no other information or lab results. However, the lipid panel is worthy of a discussion.

TC = 132 mg/dL, TG = 167, HDL-C = 10, LDL-C = 88, TC/HDL-C = 13.2

The provider wonders if the low HDL-C (he had never seen such a low value) required treatment. Because the LDL-C and TC were so good he was skeptical that therapy was indicated. A pharmaceutical rep advised therapy to raise HDL-C, based on William Castelli's classic Framingham data which suggests low HDL-C and high TC/HDL-C ratio is an independent risk factor for CHD regardless of the LDL-C.

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All of our decisions are based on two facts:

- 1) is atherosclerosis present or has a clinical event occurred or
- 2) if atherosclerotic disease is not present are there any risk factors present that might indicate a person is at risk to develop atherosclerosis?

Providers must do a careful search for historical risk factors (age, smoking, family, etc.), search for disease evidence on careful examination (skin, eyes, pulses, obesity, BP, bruits, etc.), and then turn to the laboratory and imaging sciences for as thorough an evaluations as deemed necessary realizing we cannot do every possible test on every patient. Once the proper degree of risk is ascertained, then treatment (lifestyle and drugs) are directed at whatever evidence-based treatable risk factors were found. In cases of low HDL-C, sometimes advanced sophisticated lipoprotein (HDL and LDL) testing can be very helpful.

I am unaware of any high level evidence that therapeutic raising HDL-C with a drug per se is necessarily cardioprotective. There are therapies that raise HDL-C that are not cardioprotective (Dilantin, estrogen in women with CHD, torcetrapib, high alcohol intake).

So let's apply those principles to this patient: 1) what more do I desire from the history?

Does his last name end with a vowel - if so is he or his ancestors from Northeast Italy? Family history of premature heart disease or any known genetic diseases? Is there knowledge that other family members have had very low HDL-C? If so, did they or did they not have heart disease. Are there any known eye problems or skin discolorations? Any special diet? And of course are any prescription, OTC or illegal drugs being used. The patient has to advise whether androgenic steroids are being used! One might suspect a steroid user to look like a body builder, but that may not be so (Presence of acne and low HDL-C can be telling).

2) Exam: lens clouding, palmar xanthomas, other xanthomas, acne, tonsil exam, splenomegaly, and vascular exam.

3) Lab: blood chemistry profile to include glucose, A1C, TSH, serum total and gamma protein (myeloma can present as low HDL-C), urine albumin, hs-CRP, and NMR LipoProfile (to include total HDL-P). I really want the latter because I would be very interested to see if lipoprotein (x) is present and of course I need to know the LDL-P. An apoB could obviously be done to assess atherogenic lipoproteins, but lipoprotein (x) if present would be missed by only doing apoB. How about apoA-I or the total HDL-P (available on the full NMR report). Or is this a case where the blood should be sent to Boston Heart Lab (see below) for HDL Map (formerly called HDL Fingerprint)."

Of course a complete evaluation would entail much more history and exam. But why did I specifically mention certain items above. Is everyone mentally starting to make a rule-out list of diagnostic possibilities? When I see someone with an HDL-C less than 10, we are dealing with severe hypoalphalipoproteinemia. Some of those conditions are associated with severe CHD, some with minimal CHD and some with no CHD.

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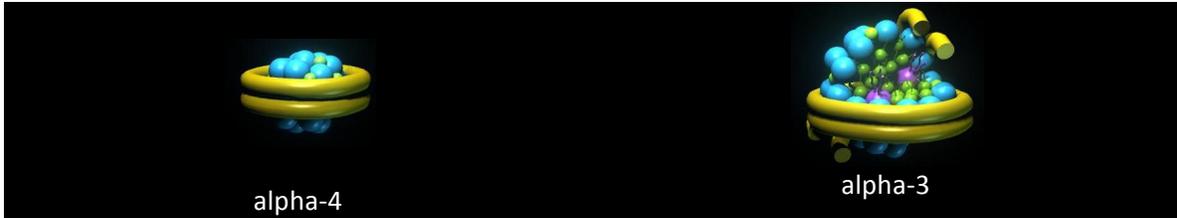
A quick review of HDL biology and keep in mind that a defect in any one of these steps will affect serum HDL-C levels and clinical outcomes:

HDLs start as hepatic or jejunal secreted unlipidated apoA-I which acquires phospholipids and unesterified cholesterol by attaching to cellular membrane ATP binding cassette transporters A1 (ABCA1). The new lipidated apoA-I is termed a pre-beta-1 HDL (note the belt like two molecules of apoA-I)



Courtesy of Martin Jacob

The cholesterol is esterified to cholesteryl ester by the enzyme lecithin cholesterol acyl transferase (LCAT): also called phosphatidylcholine-sterol O-acyltransferase. As a fatty acid (FA) transfers from HDL phospholipids (at the Sn-2 position), it attaches to unesterified cholesterol (3-hydroxy-cholesterol which has an -OH group at the 3 position). The FA makes the cholesterol more hydrophobic and the molecule moves away from particle surface and the aqueous plasma deep into the core of the unlipidated apoA-I, forming a maturing, small HDL is formed: this is termed alpha-4 or and then 3 by Boston Heart Lab or HDL3 by Berkeley or H1 H2 by NMR.

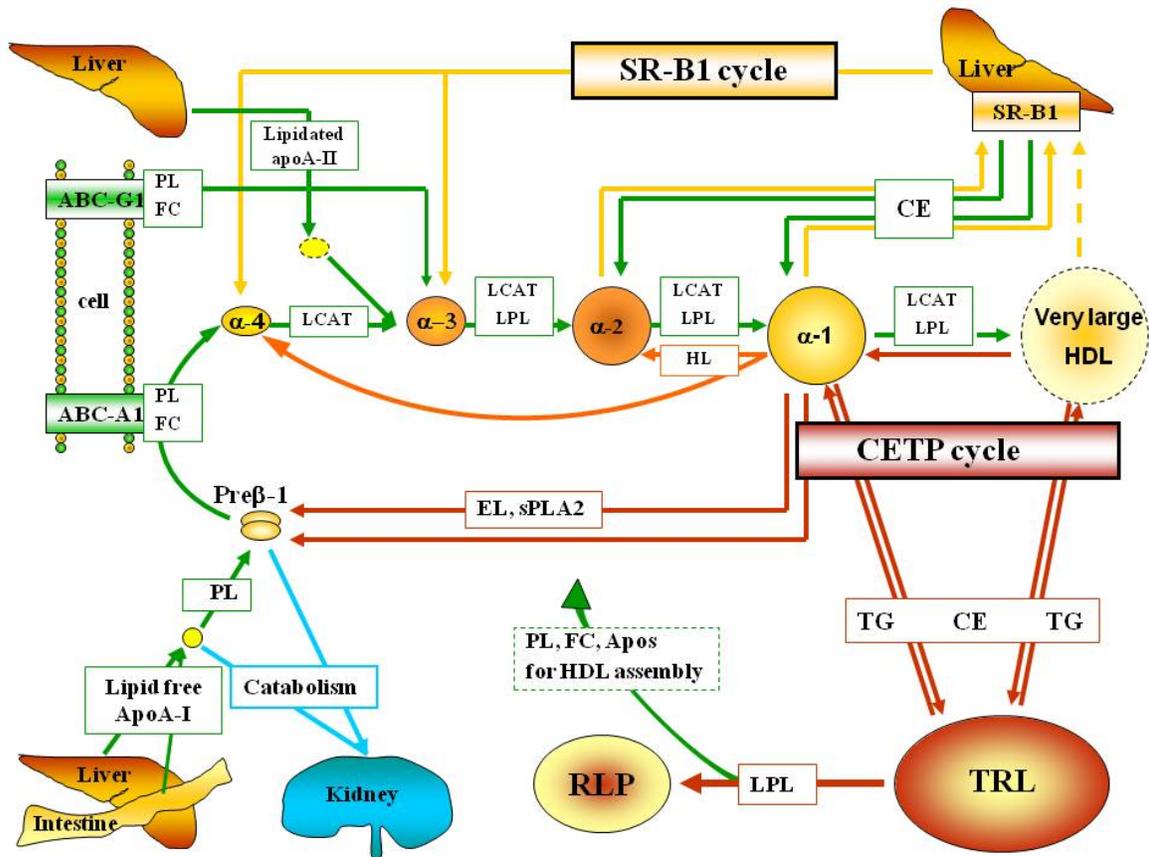


As the particle acquires more and more cholesterol which is constantly esterified it becomes more



mature (larger) and is now called an alpha 2 and finally alpha 1 (HDL2 or NMR H4, H5). HDLs are further lipidated and by attaching to additional protein, sterol transporters capable of transferring cholesterol from cells into the HDL, resulting in larger HDL particles: ABCG1 or G4 or the bidirectional transporter, called the Scavenger Receptors B1 (SR-B1) which can actually lipidate or delipidate HDLs depending on the cholesterol concentration gradients inside and outside the cell. Although the vast majority of HDL lipidation (acquisition of cholesterol) occurs at the liver and jejunum, arterial wall macrophages (macrophage RCT) and peripheral cells can also contribute to HDL lipidation.

Ultimately the large, mature HDL is delipidated by hepatic, adipocyte or intestinal SR-B1 (direct RCT) or steroidogenic tissue SR-B1 (forward cholesterol transport) or by cholesteryl ester transfer protein (CETP) activity where the CE in the HDL is exchanged for TG in the apoB particles like VLDLs and LDLs (indirect RCT).



Courtesy of Asztalos 2009

In the sophisticated diagram above, it is not depicted that HDLs also traffic cholesterol to steroidogenic tissues and adipocytes where they can be delipidated by SR-B1.

During delipidation the HDL becomes smaller, transforming back into alpha HDL 3 or 4 (HDL3 or H1, H2) or even smaller prebeta HDL. Keep in mind that because of their larger size and volume about 80% of the total HDL-C value is trafficked in the larger mature HDL species.

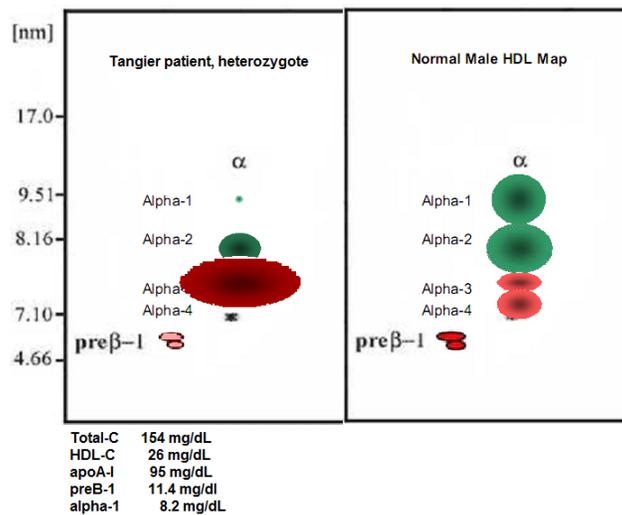
Cromwell in his classic paper (*Journal of Clinical Lipidology* (2007) 1, 57–64) notes that as HDL-C increases from 20 to 40 mg/dL there is a tremendous rise in small HDL species: after an HDL-C of 40-45 mg/dL there is very little further increase in HDL-P, but rather an increase in HDL size. Because the volume of a sphere is a third power of the radius, increasing HDL size can be associated with substantial increases in HDL-C. One can speculate that HDL-P may be more important than HDL-C as a risk factor or perhaps even as a goal of therapy. When the particle volume characteristics are understood one can see how some low HDL-C values may be associated with substantial HDL-P levels (lots of small HDLs) and very high HDL-C levels may not be (low numbers of very large HDLs). Several key enzymes are very important in remodeling HDL particles especially hepatic (a triglyceride lipase and phospholipase) and endothelial lipase (a phospholipase). So with particle physiology (remodeling or flux) in mind: Let's go through the differential diagnosis in this patient:

1) Anabolic steroid abuse: causes decreased apoA-I synthesis and increased hepatic lipase: decreased numbers of small HDLs and low HDL-C. Acne may be present, an

athletic build and with chronic use - reduced testicular size. Easy therapy: stop the steroids!

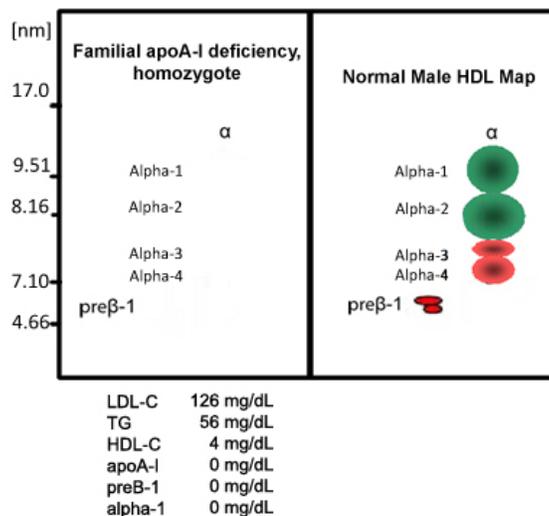
2) Other drugs: likely not the case but either fenofibrate alone or more commonly with fenofibrate in combination with rosiglitazone are known causes of the disappearing HDL syndrome (Journal of Clinical Lipidology 2007;1:41–56 or J Clin Pharm OnlineFirst, published on April 29, 2009 as doi:10.1177/0091270009335766). Etiology not well understood but likely an over upregulation of SRB1 with severe HDL delipidation. Likewise a drug formerly available in the US, and still available in other countries, probucol (formerly sold here as Lorelco) has a positive postangioplasty angiographic trial. Formerly thought to be an antioxidative drug, it is basically a CETP and SRB1 inducer and thus lowers HDL-C. (Future Lipidology 2009;4:63-78). Of course this patient is not likely on probucol.

3) Tangier's Disease: a rare genetic disorder where ABCA1 is not present. Sterol accumulation occurs in lymphoid tissue (tonsils, spleen, and liver). ASHD occurs if apoB is high. The degree of atherosclerosis is less than one would suspect with virtually absent HDL-C levels.



Modified from Asztalos et al., Atherosclerosis 156 (2001) 217-225

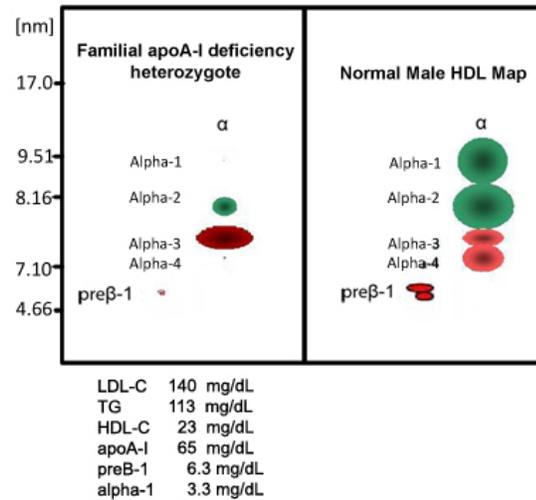
4) Hypoalphalipoproteinemia due to marked decrease in apoA-I production: severe CHD usually present. Skin manifestations (palmar xanthomas, lens clouding can occur).



Modified from Asztalos et al, Atherosclerosis 125 (2001) 217-225

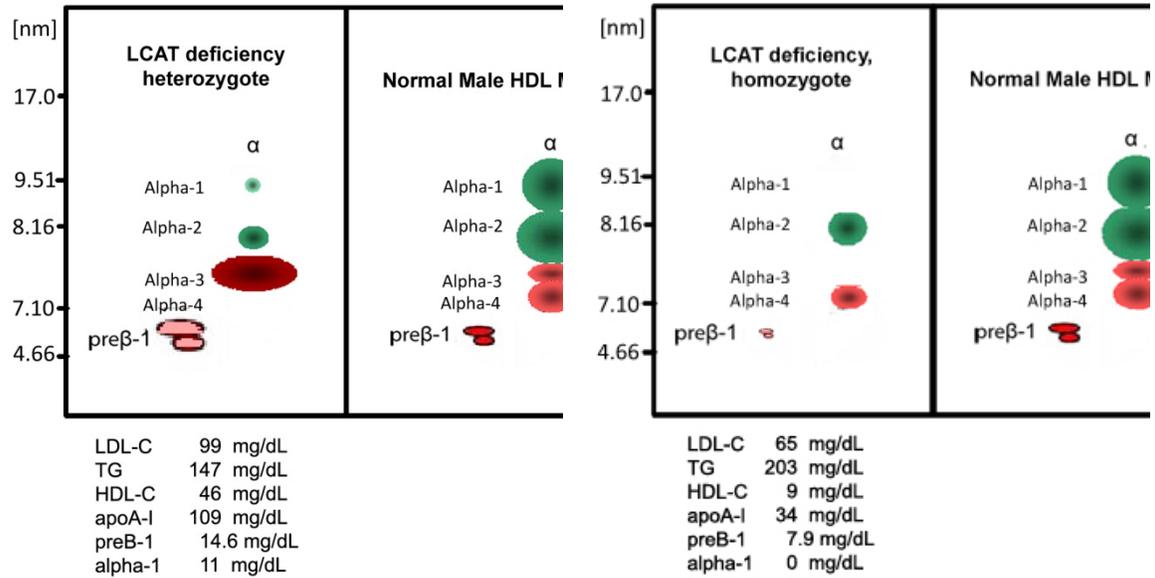
5) Hypoalphalipoproteinemia due apoA-I Milano: Rare gene and apoA-I mutation found in folks from a small town in NE Italy (Alps area). An extremely functional apoA-I not associated with CHD. The HDLs are extremely functional on sterol efflux.

6) Low HDL-C due to heterozygosity of apoA-I deficiency or of ABCA1 deficiency: 50% reductions in HDL-C due to decreased apoA-I or cell and hepatic ABCA1 transporters resulting in reduced lipidation of HDLs. The latter is not usually associated with CHD unless apoB is elevated (higher TG of ten present indicative of potential apoB elevations). Think about it: in these patients there is less hepatic lipidation of HDL particles with cholesterol (resulting in reduced HDL-C) - why would that cause CV risk? I doubt if this applies to the patient at hand as this condition does not cause extremely low HDL-C values (10 mg/dL)



Modified from Santos et al., JLR, 49, 2009, p 349-357

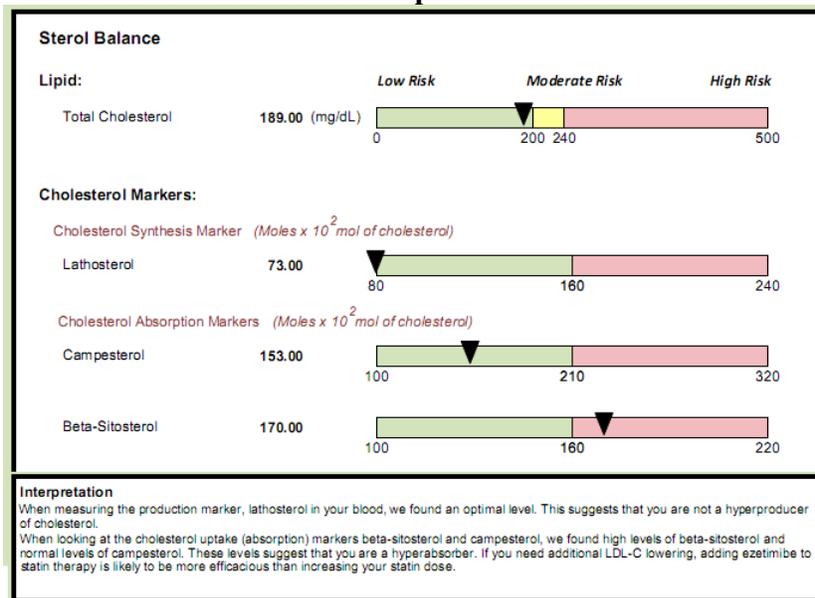
7) LCAT deficiency (Fish eye disease in its milder form): Problems with the enzyme LCAT. Various deficiencies of the esterification enzyme LCAT, prevents the formation of the lipophilic cholesteryl ester (CE). If free cholesterol does not become esterified (UC) it remains partially hydrophilic and therefore UC stays on the surface of the HDL particle whereas the lipophilic CE would go from particle surface to particle interior, in effect filling the particle, ultimately causing the discoid prebeta HDL to transform into a spherical larger HDL particle. If the HDL does not "fill up and enlarge" the apoA-I breaks off and is prone to renal excretion. Thus these patients with LCAT deficiency will have very low HDL-C levels (5-10 mg/dL) and interestingly the risk of atherosclerosis is not significantly increased (the activity of LCAT in HDLs is LCAT alpha). Many of these patients form bilayer phospholipid discs which are referred to as lipoprotein x. NMR spectroscopy can detect Lp(x) if it is present. Lp(x) is not a test to order: if present it will be detected. Its presence is rare other than LCAT deficiency or cholestatic states. Since LCAT assays are not available to the average practitioner, Lp(x) on an NMR LipoProfile can be a big help in diagnosing LCAT deficiency. Many of these patients develop lens clouding - hence "Fish Eye Disease." Although often not recognized, LCAT is also present in the apoB particles (LCAT beta activity) and this interferes with the composition of those particles creating what is called "polydisperse particles" meaning they have variable core contents of CE and TG. Often the TG is slightly elevated.



Modified from Asztalos et al., *JLR*, 48, 2007 p592-599

So why not send the blood up to Boston Heart lab (www.bostonheartlab.com) for their "HDL Map" analysis. Developed by Bela Asztalos and Ernie Schaefer using nondenaturing two-dimensional PAGE, immunoblotting, one can very rapidly diagnose most HDL particle disorders. Please visit their web site (www.bostonheartlab.com) for details or check out the following reference pertinent to this case which is a must for lipidologists (*J. Lipid Res.* 2007. 48:592–599). In this case under discussion one would not find any mature HDL particles. Boston Heart Lab also offers testing tough to get elsewhere such as markers of cholesterol synthesis and absorption. Lipidologists: Please check it out.

Cholesterol Balance Test Report from Boston Heart Lab



8) Is this simply a case of insulin resistance related isolated low HDL-C (which would be seriously related to CHD risk). I would certainly perform: glucose, maybe an insulin level (although that can vary), and a urine microalbumin. I'd want an apoB or preferably a full NMR LipoProfile (not the LabCorp partial NMR analysis as it does not provide total HDL-P) and I'd look for large VLDL, increased # of total and small LDL-P. I'd also look at the total HDL-P (a sum of small, medium and large HDL-P). Insulin resistant patients typically have reduced numbers of large and increased numbers of small HDL species.

It is unusual to see HDL-C of 10 in insulin resistant patients who do not have serious hypertriglyceridemia. However this could be insulin resistance on top of a heterozygous ABCA1 deficiency. The key is, are there or are there not too many atherogenic apoB (predominantly LDL particles) present or not. If so the person is at high risk for CHD and therapy would be directed at the elevated apoB (LDL-P): using statin, statin/ezetimibe or statin/Niaspan (Simcor to save a copay). If LDL-P is not high none of those drugs are indicated.

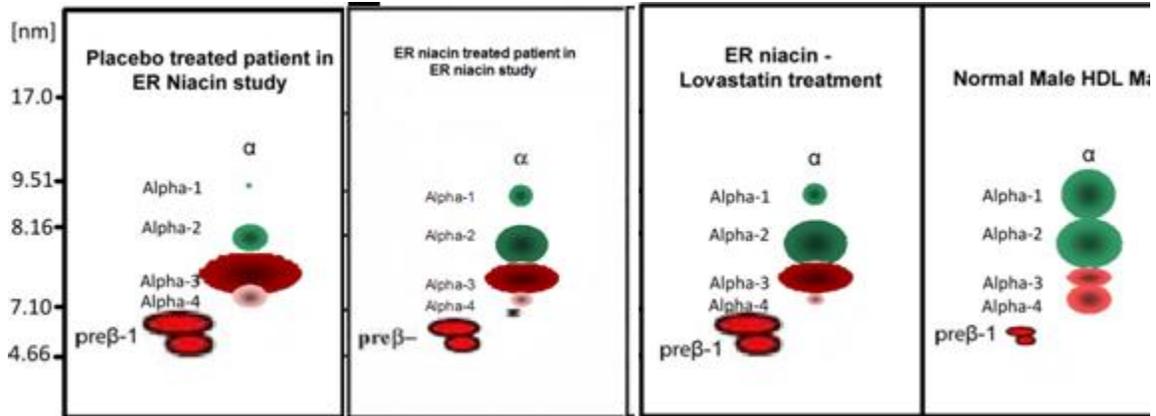
Rumor has it that the Official NMR report will soon start reporting total HDL-P and thus save me the addition exercise (adding small + medium + large HDL-P) just described. I think, as was seen in the VA-HIT, that total HDL-P (above and beyond HDL-C) is a very valuable parameter to judge both risk and response to therapy. Keep in mind that NMR spectroscopy cannot evaluate unlipidated apoA-I or prebeta HDLs (need Boston Heart Lab for that). Those HDL species do not contribute much to total HDL-P (maybe 5%) but of course the prebeta HDLs are a very crucial HDL particle as they perform the first step in HDL lipidation at the liver, jejunum or the arterial wall macrophage. In LCAT deficiency the NMR report would show reduced numbers of HDLs, no large or medium HDLs, perhaps some VLDL abnormalities and possibly lipoprotein x.

So a good history and proper laboratory testing will differentiate from all of the above possible diagnoses. If apoB or LDL-P is high or one of the hypoalphalipoproteinemia disorders known to be associated with CHD is present, I'd also order hs-CRP, Lp-PLA2 and do a carotid IMT or coronary calcium score. Depending on the results of above, treatment proper treatment could be suggested. If this man has insulin resistance with high LDL-P then Simcor (likely with Zetia) would be indicated. Should isolated low HDL-C be treated? There would be zero clinical trial data from which to draw a conclusion. NCEP ATP-III suggests that in high risk patients (i.e. patients with known CHD, or CHD risk equivalents) it is appropriate to prescribe a fibrate or niacin. I disagree with that. I know of no evidence that fibrates work if TG are not elevated and the vast majority (if not all) of patients with low HDL-C who get CHD have too many atherogenic apoB particles and the best treatment for that is a statin, statin/niacin combo or statin/ezetimibe combo.

The following HDL Maps are added to text by Boston Heart Lab showing how niacin affects the HDL Map.

Effects of ER niacin and Lovastatin on HDL Map, Lamon-Fava et al. ATVB 2009

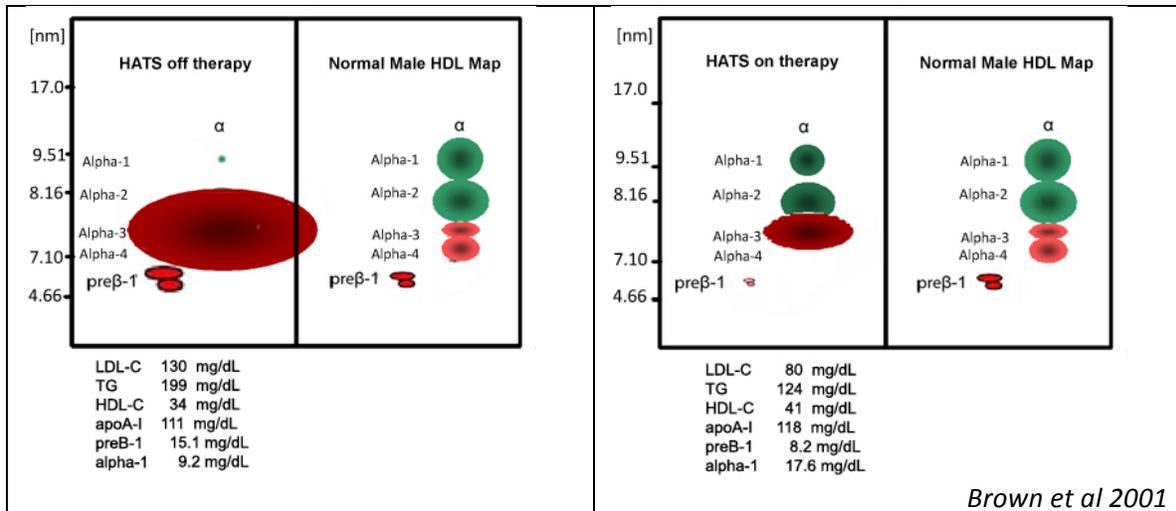
Five male subjects with combined hyperlipidemia; LDL-C > 130 mg/dL, TG > 150 mg/dL, HDL-C < 40 mg/dL. Patients subjected to TLC. Random crossover, double blind, 12 week treatment phases with a 4 week wash out period in between. The results were as follows:



LDL-C	126mg/dL	124 mg/dL	87 mg/dL	128 mg/dL
TG	343mg/dL	174 mg/dL	164 mg/dL	120 mg/dL
HDL-C	34	46 mg/dL	46 mg/dL	44 mg/dL
mg/dL		118 mg/dL	119 mg/dL	124 mg/dL
apoA-I	103 mg/dL	16.3 mg/dL	18.5 mg/dL	12 mg/dL
preB-1	18.1 mg/dL	14.1 mg/dL	13.5 mg/dL	16.7mg/dL
alpha-1	7.1 mg/dL			

Normal male, for comparison, from Framingham Offspring Study

HDL Maps from the HATS trial: patients on and off statin-niacin therapy



LIPID CASE 235 LDL-C = 7

In this issue of the newsletter I present a bizarre case. It is a 69 year old hypertensive Caucasian male with extreme obesity and claudication in the left leg due to PVD. The HTN is treated with Quinapril. He does not exercise and has not had a coronary event. For his dyslipidemia he takes rosuvastatin (Crestor) 5 mg and extended release niacin (Niaspan) 2000 mg daily. The labs are as follows:

TC = 101 mg/dL, LDL-C (calculated) = 7 mg/dL, TG = 308 mg/dL, HDL-C = 32 mg/dL VLDL-C = 61 mg/dL
 TC/HDL-C = 3.0 Non-HDL-C = 69 mg/dL

Lipoprotein assessment with the NMR LipoProfile

Total LDL-P 831 nmol/L (perfect)
 Small LDL-P = 716 nmol/L (perfect)
 LDL Particle size is 20.0 (small or Pattern B) (small is < 20.5 nm)
 Large HDL-P 6.9 umol/L (slightly reduced)
 Large VLDL-P 5.5 (normal < 0.5 nmol/L) significantly elevated

FBS-128 (1st time over 120); Meets the diabetes mellitus criteria
 Microalbumin elevated 581.4
 hs-CRP-5.28 (elevated); PLAC test (Lipoprotein associated phospholipase A2) = 106 (normal)

The provider states: "I know that particle size and composition are the problem, and the # of particles would seem to be adequate to transport lipids, vitamins etc., but what about an LDL-C of 7 mg/dL? Is it dangerous?"

DAYSRING DISCUSSION:

As long as the patient feels well, I certainly would not be too concerned about the LDL-C of 7 per se. The patient has adequate (physiologic) numbers of LDL particles. A recently published editorial by Larry Goldstein, correctly points out the adverse effects such as CNS hemorrhage is not from drug-induced cholesterol reductions. (Circulation. 2009;119:2131-2133.) Patients who have complex hypobetalipoproteinemia (a genetic condition) do not synthesize much apoB and typically have an LDL-C of 5-20 and most live long and healthy lives without any problems related

to cholesterol deficiency. Virtually all meta-analyses of statin trials have shown no adversity from lipid-modulating drugs and low cholesterol levels. LDLs are basically the waste products of VLDLs and IDLs (after they, via the lipolytic cascade) lose their core TG. The LDLs can gather additional cholesteryl ester (CE) from HDLs (via cholesteryl ester transfer protein or CETP mediated transfer) and basically bring the remaining cholesterol back to the liver where the particles are endocytosed via the LDL receptor (LDLr). Thus, most of the LDLs simply perform INDIRECT reverse cholesterol transport (RCT). Lipidated HDLs deliver cholesterol to the steroidogenic cells (gonads and adrenal cortex), adipocytes or perform DIRECT RCT at the liver or jejunum. An HDL-C of 32 mg/dL (the cholesterol carried within all of the HDLs, regardless of size that exist in a deciliter of plasma) is more than enough cholesterol to serve those organs.

Can we explain why the LDL-C is so low? First of all, it is a calculated LDL-C using the Friedewald formula. Although the formula historically carries the Friedewald name after William T Friedewald, the actual formula was developed in conjunction with Donald S Fredrickson and Robert I Levy. Lipidologists, please check out the original historic paper at *Clinical Chemistry* 1972;18:499-502. In the original paper, the authors warned the formula is inaccurate if chylomicrons are present (Type I and V hyperlipidemias), Type III (in which case some VLDLs and IDLs carry more cholesterol than usual) and Type IV hyperlipidemia (common in diabetics) when the TG is > 400 mg/dL

$LDL-C = TC - [HDL-C + VLDL-C]$ VLDL-C is a calculation based on TG $VLDL-C = TG/5$
Thus LDL-C calculations are directly related to TG, and the calculation is the reason patients have to fast for the lipid profile.

For the Friedewald equation to be accurate we must assume all of the TG are trafficked within VLDL particles and no others. We also assume the core TG/cholesterol composition is five times more TG than cholesterol and cholesteryl ester. The assumption is accurate when TG levels are physiologic (<70-100) and gets considerably inaccurate as the TG levels rise. As TG rise (I suspect somewhere around 130-160 (perhaps even lower- certainly much lower than described in the original paper) TG become, via CETP mediated transfer becomes part of the core composition of all lipoproteins. Note that the formula was developed long before potent cholesterol-lowering drugs became available and LDL-C levels below 100 mg/dL were unusual. The formula has never been validated at LDL-C levels < 100 mg/dL. For a thorough discussion of this please see: *The Friedewald Formula Underestimates LDL Cholesterol at low Concentrations Clin Chem Lab Med* 2001; 39(5):426-431.

The large VLDLs are the problem. This obese, T2DM male is significantly overproducing TG. He almost certainly has a fatty liver. There is a major over production and secretion of TG-rich large VLDLs (as noted on the NMR LipoProfile). Normally composed VLDLs carry several apolipoproteins: a single molecule of apoB100 and several copies of apoE and C-II, and variable amounts apoA-V, apoC-I, and C-III. VLDLs also traffic vitamins. Let's review their function:

ApoB100 - structure, stability and solubility of the particle as well as ligand for LDLr
ApoE - ligand for the VLDL receptor (in muscles and adipocyte capillaries) and LDLr
ApoA-V - binds to the endothelium in capillaries where lipoprotein lipase (LPL) is expressed
ApoC-II - binds to and activates LPL
ApoC-III - when present in physiologic amounts, delays binding of C-II to LPL. The apoC-II/apoC-III ratio is a measure of the rate of lipolysis (hydrolysis of TG from the VLDL). Low ratios indicate delayed lipolysis and are a CHD risk factor.
ApoC-I - activates LCAT, inhibits C-II as well as apoD (CETP)

In pathologic states VLDLs carry decreased apoA-V, and increased apoC-III and apoA-II, all of which lead to delayed VLDL lipolysis (TG hydrolysis) and hypertriglyceridemia (fasting and postprandial). Of course there are other problems associated with delayed clearance (increased plasma residence time) of TG-rich particles. They increase blood viscosity, are associated with

increased markers of coagulation (PAI-1, fibrinogen) as well as inflammatory proteins (perhaps in part mediated by apoC-III).

The longer TG-rich particles hang around, CETP activity swaps a single molecule of CE for TG between the TG-rich VLDLs and normally composed HDLs and LDLs. Thus the LDLs and HDLs become TG-rich and CE poor - explaining why as TG rise, LDL-C and HDL-C drops and VLDL-C dramatically increases: the VLDL in effect is stealing CE from both HDLs and LDLs. Thus, CE goes from a theoretically nonatherogenic particle to a potentially atherogenic apoB-containing VLD particle. Once the HDL acquires TG it is on the fast track to becoming a dysfunctional, proatherogenic HDL particle. TG-induced, dramatic rises in VLDL-C and reductions of HDL-C lead to increased non-HDL-C. It is so tragic that so many providers do not appreciate the lipoprotein havoc that is caused by rising TG levels (at much lower levels than we ever imagined). In the patient under discussion, his LDLs, thanks to increased CETP mass and activity (due to delayed, likely C-III mediated, lipolysis of VLDLs). In the patient under discussion, because of the TG, his LDL core composition is drastically abnormal: instead of having 4 times more cholesterol than TG, his LDLs have just the opposite. The LDLs are significantly depleted in CE and enriched in TG – who really knows (or cares) what his calculated LDL-C is: it might be 7 – might be 30 mg/dL. It is the LDL-P that really matters.

Atherosclerosis results when too many apoB particles exist and enter the arterial wall where they are subject to oxidation and internalization by macrophages, creating "foam cells." The vast majority of apoB particles are LDLs and the LDL-P is perfect in this man. He still has way too many large VLDLs (typical of IR patients) which are still, via CETP, distorting the composition and size of HDLs and LDLs. Is there anything else to offer such a patient taking a statin and niacin? Should the TG be lowered further? Do we need to raise HDL-C? NCEP ATP-III notes that the goal of therapy in patients with elevated TG is to normalize LDL-C and then non-HDL-C (both already accomplished). ATP-III advises that proper goal for those with low HDL-C (and TG > 200 mg/dL) is to likewise normalize LDL-C and non-HDL-C (both of course are apoB or LDL-P surrogates). Therefore according to NCEP, this man is at goal and needs no further Rx.

Personally I would try to further reduce the TG - as I suspect it would improve blood viscosity, coagulation and inflammation (note the elevated CRP). Thus I would prescribe 4000 mg (lower doses have little effect on lowering TG) of prescription strength N-3 fatty acids, namely Lovaza. The hypertriglyceridemia is a serious disease state and both the FDA documented accurate dose and purity of Lovaza comes into play. What would we expect to happen to the lipid and lipoprotein analysis after N-3 FA use?

- Decreased TG (fasting and especially postprandial)
- Reduced CETP activity - leading to an increase in LDL-C and HDL-C, but a serious reduction in VLDL-C
- Increase in LDL and HDL size
- Reductions in large VLDL-P and no major change in LDL-P.

On occasion N-3 FA (or even fibrate) induced lipolysis of VLDLs can raise LDL-P, by converting some VLDLs into LDLs. Normally the latter due to an upward shift in size are rapidly cleared by LDLr. This man has such a low LDL-P (and is on a statin) to begin with so pathological rising of LDL-P is unlikely to occur.

N-3 FA and co administration of niacin work well together (Journal of Clinical Lipidology 2007;211–217), and we have beneficial statin/N3 FA lipid/lipoprotein data from COMBOS and outcome data from the Japanese in JELIS on the benefits when combined with statins. For those who would like to understand N-3 Fatty acid therapy in depth I surely recommend Drug Therapy for Hypertriglyceridemia: Fibrates and Omega-3 Fatty Acids by Peter P. Toth, Thomas D. Dayspring, and Gregory S. Pokrywka in Current Atherosclerosis Reports 2009;1:71–79. Last but certainly not least, sooner or later consideration of obesity surgery should be considered and it

usually has dramatic positive effects on glucose and lipid metabolism. If that is not an option it is probably time to get metformin into the regimen (presuming renal function is still fine).

LIPID CASE 237 Those Misunderstood triglycerides?

Of all of the lipids in the lipid profile, it is indeed triglycerides that are the least understood by clinicians. Their relationship to CV risk is so underestimated and you can get as many ideas on should high levels of TG dictate treatment as you want. Some think a level of 500 dictates therapy and others get nervous with a TG > 100 mg/dL. Let's look at the following case and kick TG around a bit.

A provider has been closely following LDL particle concentration (LDL-P), via the NMR LipoProfile (nuclear magnetic resonance spectroscopy), with LabCorp and has a patient with CHD who is on a statin. The patient has achieved an LDL-P 700 nmol/L (very physiologic level putting him in the bottom 5th percentile population cutpoint). However the lipid profile still raises some areas of concern:

TC = 136 mg/dL HDL-C = 41 mg/dL TG = 356 mg/dL
Calculated VLDL-C = TG/5 = 71
Calculated LDL-C = TC - [HDL-C + VLDL-C] = 136 - [41 + 71] = 24
TC/HDL-C = 3.3 Non HDL-C = 95

. The clinician asks: "Where's the evidence of adding a fibrate in such a patient to reduce CV risk?"

DAYSRING DISCUSSION:

Before we start, realize that a serum TG level reflects the total amount of TG (triacylglycerol) that is carried within every lipoprotein that exists in 100 ml (deciliter) of plasma. Normally the TG are carried in chylomicrons after a meal and VLDLs during the day: other lipoproteins carry very small amounts of TG under physiologic circumstances. So, let me phrase the clinicians question another way - Where is the evidence that any combination lipid-modulating therapy reduces cardiovascular risk? Let's start with what drugs (or drug classes) have Level 1 (empowered randomized double blind, prospective) monotherapy outcome evidence. The answer may surprise you:

- 1) Statins: All have solid outcome data
- 2) Fibrates: Clofibrate and gemfibrozil
- 3) Bile acid sequestrants: cholestyramine

Drugs with no empowered Level 1 outcome evidence:

Niacin (failed to meet primary outcome in Coronary Drug Project which is its only outcome trial)

Fenofibrate & Bezafibrate (failed to meet primary endpoint in FIELD and BIP),

Ezetimibe

Omega-3 fatty acids

How about outcomes with combo products: there is actually only one positive combo outcome trial which few have ever heard of:

Advicor and Simcor: neither has an FDA indication to reduce CV events due to lack of data

FATS, HATS are small angiographic trials not empowered to address outcomes meeting FDA criteria. HATS had no statin only group to compare statin/niacin to and there were only 38 patients in statin/niacin group.

Niacin/cholestyramine: FATS small angiographic trial with some statin use

Vytorin: simvastatin/ezetimibe did reduce ischemic events in SEAS vs. placebo (secondary endpoint)

Statin/Omega-3: Positive data in open label Japanese trials

Niacin/fibrate: Stockholm Ischemic Trial Positive primary and secondary outcomes. Clofibrate and immediate release niacin were used. (Acta Med Scan 1988;223:405-418)

So what: we use all sorts of cardiovascular (BP) and diabetes drugs in untested combinations or else we would not achieve BP or A1C goal in many patients. To achieve goal I would use any of the above drugs in combination except for gemfibrozil and clofibrate (too many contraindications and warnings, i.e. medicolegal issues with a statin or ezetimibe). Note: we have all used fenofibrate (TriCor, Lipofen, etc) for years with statins, and their combined use seemed quite safe in FIELD, but the only fibric acid with solid safety data when used with a statin and an FDA indication to use with a statin is fenofibric acid.(Trilipix).

There has never been an outcome trial where the entry criteria was elevated TG, and thus without ever testing the hypothesis "does lowering TG reduce clinical events" no data exists. All of us should be lowering TG, but there is no specific level which assures event reduction. This is the reason there is no TG goal of therapy in NCEP ATP-III. Numerous epidemiologic trials have demonstrated that either elevated fasting or postprandial TG levels are an independent risk factor for CHD and accordingly eight years ago NCEP established the following "risk of TG" chart:

TG = 150-200: Borderline CV risk

TG of 200-500 High CV risk

TG > 500 Very high risk (as pancreatitis now enters the picture)

NOTE: THAT IS NOT THE NCEP GOAL OF THERAPY CHART: Simply the "associated risk chart." There is tremendous confusion on this: so many erroneously think a TG of 150 mg/dL is the desired NCEP goal of therapy or the level at which TG-lowering therapy is to be initiated.

Interestingly NCEP lists the following as the known causes of elevated TG:

Obesity, lack of exercise, XS alcohol, cigarette smoking, high carb diets, various drugs, genetic causes and other diseases (diabetes, renal disease). What is a physiologic TG??? The following NCEP statement will shock many: if a patient does not have any of the conditions listed in the first sentence of this paragraph, it is extremely unlikely a human could ever have a TG > 100 mg/dL. TG tolerance tests in noninsulin resistant patients reveal that a normal fasting TG is 10-70 with a mean of 30 mg/dL. A normal postprandial response to a fat challenge would raise the TG to 70 mg/dL with one standard deviation being 170 mg/dL. Therefore anyone with a TG > 170 has an abnormal level, whether fasting or not. There is never a need to repeat a nonfasting TG level: because if it is > 170 mg/dL, it is abnormal. Of course without a fasting TG, the VLDL-C and hence the LDL-C cannot be accurately calculated using the Friedewald formula. However as pointed out by NCEP, if we all just looked at non-HDL-C (the cholesterol that is not in our HDL particles), fasting is not required and it is as good and most often superior to LDL-C as a marker of atherogenic apoB-containing lipoproteins. Non-HDL-C is not affected by fasting.

So if I use the NCEP risk chart cited above - is treatment indicated in everyone with a TG > 150 mg/dL (borderline risk) or > 200 mg/dL (high risk)? The correct and technical answer is NO. When a patient has a TG between 200-499 mg/dL there is nothing per se in NCEP that triggers anything other than lifestyle recommendations. As you know the only lipid levels used for initiating drug therapy are LDL-C levels or a TG > 500 mg/dL. However in 2001 (8 long years ago) NCEP established a secondary goal of therapy in patients who are at LDL-C goal but still have an elevated TG and that goal is non-HDL-C. **Tragically that is the most ignored dictum in the guidelines.** Any clinician getting patients to NCEP LDL-C goal, but ignoring non-HDL-C goal is providing substandard lipid management (vast majority of providers in the country on any published survey). I know my readers all understand this concept, but please spread the word to your colleagues who are still following the 1994 NCEP ATP-II guidelines and not calculating or acting upon non-HDL-C. NOTE: IF YOU ARE ROUTINELY USING NMR PARTICLE MEASUREMENTS OR APOB, then lipid measurements including non-HDL-C are misleading or often discordant. As good as non-HDL-C is (as an apoB or LDL::P surrogate) there is still moderate discordance between it and particle measurements. One last caveat: ignore the NCEP statement that non-HDL-C only matters when TG are > 200 mg/dL. Framingham data collected by none other than NCEP chairman Scott Grundy reveals that once non-HDL-C is know, LDL-C is no longer a risk factor for CHD, regardless of a TG above or below 200 mg/dL (Am J Cardiol 2006;98:1363–1368).

Is there anything I can point to that lowering TG per se is associated with better outcomes? Sure: In a recent post-hoc analysis of the PROVE IT (TIMI22) trial, those patients on a statin who achieved a TG < 150 mg/dL had a 27% relative risk reduction in events than did those not achieving a TG of < 150 mg/dL (J Am Coll Cardiol 2008;51:724–30). At best that is suggestive data. Yet in the VA HIT study where gemfibrozil monotherapy was associated with a > 30% reduction in TG, there was no associated outcome benefit. In further analysis, gemfibrozil only worked in those with IR determined via the HOMA equation. The benefit of the fibrate in those patients had no

relationship to the baseline or on treatment HDL-C or TG levels (Diabetes Care 26:1513–1517, 2003).

Where am I going with this? Be patient! If TG is a beyond a doubt established risk factor, but there is little evidence relating outcome improvement to the drop in TG per se, then maybe we have to look at it in a different way. Ask yourselves- why is TG an independent risk factor? Maybe elevated TG is simply a marker of a more validated cause of atherosclerosis and if so, those with high TG who have abnormalities of that marker are at risk and perhaps improving that marker should be the real goal of therapy. Those with high TG, who do not have abnormalities of that marker, are not at risk despite the high TG and therefore require no treatment. Of course Lipidaholics and clinical lipidologists, but few others know that the marker referred to above is apolipoprotein B or apoB for short (atherogenic particle concentration), the best validated marker of atherosclerotic risk as well as goal of therapy. There is one apoB on every chylomicron, VLDL, IDL, LDL and Lp (a) particle. HDLs carry no apoB. Thus non-HDL-C levels reflect the cholesterol within the apoB particles.

Have a high apoB, you are at risk for CHD regardless of the TG or HDL-C level and vice versa, have a perfect apoB, it is unlikely the TG or HDL-C have much meaning (See ADA/ACC Consensus paper on Lipoprotein management in patients with cardiometabolic risk: Diabetes Care 2008;31:811-822). Is there a relationship of TG to apoB - if so I think we have solved the puzzle! In study after study apoB is as good (in a few trials) or significantly better (in vast majority of trials) in predicting risk or as a goal of therapy than any lipid measurement including non-HDL-C. What are the atherogenic apoB particles associated with atherosclerosis? They are chylomicron, VLDL and IDL remnants, IDLs, LDLs (of any size) and Lp(a). As the liver accumulates TG, there are two possible consequences: 1) Production of normal amounts of large VLDLs - this would raise TG but not raise apoB (seen in those with Familial Hypertriglyceridemia who despite very high TG have no CV risk) or 2) overproduction of VLDLs with resultant increased numbers of its apoB-containing progeny, IDLs and LDLs (seen in the vast majority of insulin resistant patients). This latter scenario would be associated with both high TG and high apoB. This explains much of the risk in our metabolic syndrome and T2DM patients (majority of who have high TG. For those doing NMRs: apoB consists of VLDL-P + IDL-P + LDL-P. However due to half life differences the vast majority of the apoB particles (90% or more) are LDLs. A normal total VLDL-P is 40-50 nmol/L whereas a normal total LDL-P is ~ 1000 nmol/L. Thus there are a hell of lot more LDLs than other apoB particles. This is not to say VLDL and chylomicron remnants are not a big part of the atherosclerotic picture: they are - but for reasons other than their contribution to particles counts (discussed below).

Are there apoB particles that would contribute to elevated apoB (VLDL-P and LDL-P) but have no effect on raising LDL-C? If so, they could explain a lot of the residual risk in patients with at goal, LDL-C who still have residual risk. Unfortunately yes, and it is the presence of these particles that renders LDL-C as a fairly useless marker of risk and goal of therapy. Those apoB particles are remnants, large TG-rich, cholesterol poor LDLs, and small LDLs: of course the patients who have those particles that drastically raise

apoB (LDL-P0 but not LDL-C are called metabolic syndromes and T2DM. What do those two patient groups have in common? You guessed it - HIGH TG (especially if you consider a TG of > 100 as potentially abnormal). If you cannot get an apoB or LDL-P assay do you have any hope? Yes, that is why NCEP ATP-III introduced non-HDL-C as the goal of therapy in patients with TG between 200-500 mg/dL.

Moral of the story: Do we (should we) treat high TG? It is a matter of semantics. The answer is definitely yes if the TG are > 500 mg/dL because the FA within TG molecules act as soaps disrupting pancreatic cell membranes and can cause pancreatitis. However once the TG are less than 500 mg/dL, non-HDL-C (apoB), not TG becomes the goal of therapy to reduce CVD risk. Look at the patient under discussion. The TG remain high, yet LDL-C and non-HDL-C are at goal, so NCEP would want you to do nothing further despite the TG of > 300 mg/dL (not high enough to cause pancreatitis and clearly in this man not raising his LDL-P or atherogenic particle count).

Is there any other way high TG can injure the arteries if apoB is under control? TG-rich lipoproteins can raise blood viscosity, down-regulate endothelial nitrous oxide, increase PAI-1 and fibrinogen, carry apoC-III (a potentially pathological apoprotein known to be a predictor of risk), induce endothelial inflammation, etc. Thus if one wants to be super aggressive (way beyond evidence based medicine) one could make a theoretical case for further reducing the high TG. If he was a T2DM, fenofibrate (fenofibric acid) would provide microvascular benefits as well as reducing any remnants (VLDL-P) and further increase HDL-P. There would be little additional LDL-P lowering (but it is already quite low). Niaspan would have to be used at 1500- 2000 mg to achieve serious TG lowering. In a recently published trial extended release niacin added to statin did not provide additional LDL-P lowering but dramatically shifted LDL size (increased large LDL-P but equally reduced small LDL-P) and raised HDL-P. I often make the case because of its multiple positive imaging trials it is hard to argue against using niacin in patients with significant CHD. Lastly, do not forget prescription strength (4000 mg or more) omega-3 (N-3) fatty acids (Lovaza). The TG-rich lipoproteins would rapidly disappear. So should we add fenofibrate or fenofibric acid, Niaspan, or Lovaza? If he is not a diabetic and does not have microalbuminuria, I would forego the feno. To me it comes down to Niaspan (or switch to Simcor for compliance reasons) or simply add Lovaza (4 gms) to the regimen. The latter is certainly a more tolerable therapy for most patients, but Niaspan slowly titrated over 6-8 weeks is tolerable by a majority of high risk patients. If pressed I'd probably go with the Lovaza.

So until proven otherwise your patients with high TG or high TG and low HDL-C should be considered apoB or LDL-P nightmares. Get either (or their lipid surrogate, non-HDL-C) to goal. If those levels are at goal and the TG are between 150-500, do whatever you think is best - nothing or some of the potential TG-modulating therapies I have outlined above. Final caveat, because normal TG levels are much lower than what NCEP suggested in 2001 (150 mg/dL), perhaps a normal VLDL-C should not be 150/5 or 30 mg/dL but rather 75 or 100 divided by 5 or 15-20 mg/dL. If we accepted that a more normal VLDL-C is 15 or 30 mg/dL, then our non-HDL-C goals should change to LDL-C goal + 15 or 20 mg/dL. Indeed, in their new position paper AACC (American

Association of Clinical Chemists: Clinical Chemistry 2009;55:407–419) call for a non-HDL-C goal of 85 in very high risk patients (instead of NCEPs 100) and a goal of 120 (not NCEP's 130) in high risk patients. In reality, if TG are > 500 you do treat the TG and if the TG are less than that you are treating not the TG per se but rather the associated atherogenic apoB particles that are almost always present when TG start to rise above 100-130 mg/dL.

I close with a memorable quote by one of our country's top Cardiovascular gurus, William Castelli of Framingham fame. In his classic Risk of TG paper published in 1992 (Am J Cardiol 1992;70:3H—9H) he states: "All that need be known is that the triglyceride level is > 136 mg/dL and the HDL level is < 40 mg/dL, and that the patient is not a vegetarian. This suggests the presence of the dangerous kind of VLDL (*remnants*) and most probably the more dangerous variety of LDL (*cholesterol poor*). If the patient's insulin level is also known, it is possible to suggest prospectively that these conditions will be concomitant with blood sugar > 100 mg/dL, uric acid > 6.0 mg/dL, a waist to hip circumference ratio > 0.85, an elevated apolipoprotein B level, a total cholesterol:HDL cholesterol ratio > 4.5, and hypertension. In other words, a person who is on the fast track to atherosclerotic vascular disease." **BE HONEST, HOW MANY OF YOU LOOK AT A TG OF 132 AS ANYTHING OF POTENTIAL CONSEQUENCE? Please check the particles!**

LIPID CASE 238 An LDL-P that will not come down

A physician contacted me as follows: "Please point me in the right direction for this patient. I have been his PCP for about 1 year now. He is a 56 year old white male with a family history of CAD/MI/CHF starting around age 60. He is an avid cyclist. He is 5'6" and weighs 208 lbs. He only had a diagnosis of hyperlipidemia at that time of initial visit and was on Lipitor 40 mg with following labs:"

TC = 287 LDL-C = 191 HDL-C = 70 TG = 132 Non-HDL-C = 217 mg/dL

LDL-P = 2648, with small LDL-P = 1926 nmol/L

Large HDL-P = 14.9 umol/L

VLDL-P = 4.3 nmol/L

LDL Particle size 20.2 nm (Pattern B or small is < 20.6 nm)

In his initial visit with me, he complained of exertional dyspnea. An EKG had infero-lateral T-wave inversions, and 3 days later he had a triple bypass. In the following weeks, he was diagnosed as having hypertension, hypothyroidism, hypogonadism, and "fluid retention" and is currently stable with respect to all of those medical problems on about 10 medications. His TSH, glucose, testosterone and HgbA1c are all normal consistently for the past 6 months. I initially switched his Lipitor (atorvastatin) 40 mg to Crestor (rosuvastatin) 20 mg and Zetia (ezetimibe) 10mg. He committed to a better diet and really could not increase his exercise since he cycled upwards of 20+ miles 4 times per week. He is compliant with all of his medications. Subsequent labs on Crestor and Zetia:

TC = 175 LDL-C = 101 HDL-C = 49 TG = 126 Non-HDL-C = 126 mg/dL
LDL-P: 1751, with small LDL-P at 1391
HDL-P: 10.7
VLDL-P: 2.8
LDL Particle size is small (Pattern B) at 20.1 nm

The clinician was happy with the LDL-C reduction, but the LDL-P was still >1000 and the HDL-C dropped quite a bit. He gave him a Niaspan (extended release niacin) sample which he did not tolerate. He then started Trilipix (fenofibric acid) with the following labs:

TC = 213 LDL-C: 130 HDL-C = 60 TG = 115 Non-HDL-C = 153 mg/dL
LDL-P = 2203, with small LDL-P and 1488
Large HDL-P = 4.7
VLDL-P = 2.8
Particle size is now larger (Pattern A) at 20.6 nm

I was asked: "Any suggestions on how to drive his LDL-P down to <1000 nmol/L? Am I missing something here? Would Welchol help at all?"

DAYSRING DISCUSSION:

At the time of presentation, both the very high LDL-C and extremely high LDL-P identified this person as having serious lipid/lipoprotein risk. However with treatment things seem confusing as the LDL-C response is very nice and at goal, but the LDL-P remains in the high risk category. No wonder the provider is perplexed.

The first issue is - do you believe the disconnect between the on-treatment lipid concentrations and the NMR-determined LDL-P. The on-treatment LDL-C of ~ 100 mg/dL is the 20th percentile population cutpoint (low risk) whereas the LDL-P of 1700 is somewhere between the 75th and 90th percentile population cutpoint (high risk) depending which population you look at (Framingham or MESA). Since there are multiple published trials attesting to the fact that risk virtually always follows LDL-P over LDL-C, I do believe there is residual risk present in this patient at LDL-C goal based on the very high LDL-P.

The problem in this case is not only explaining the on-treatment disconnect but why the LDL-C and LDL-P went up in this patient with the prescribed fibric acid therapy. No doubt others may be uneasy with the drug (statin-ezetimibe) induced drop in HDL-C. And did everyone notice that the administration of the fibrate, raised the HDL-C but significantly dropped the large HDL-P concentration --- what gives?

Perhaps initially his endocrine abnormalities played a role in some of the lipid/lipoprotein abnormalities. Certainly the hypothyroidism, leads to down-regulation of LDL receptors and elevated LDL-P, apoB, LDL-C, non-HDL-C etc. However the normal TSH assures us this has been corrected. Hypogonadal men are at higher risk for developing a host of metabolic derangements, including dyslipidemia, type 2 diabetes mellitus, obesity, and

hypertension (*Journal of Clinical Lipidology* (2008) 2, 71–78). However, proper testosterone therapy has eliminated the hypogonadism.

The most important discussion is what is the CV risk of this man and what is an appropriate goal of therapy? His original lipid/lipoprotein values identify him as high risk: severe elevations of a single risk factor (i.e. and LDL-C > 190 mg/dl) qualifies (and do not forget his initial terrible lipid/lipoprotein concentrations were while he was taking a powerful statin, Lipitor 40 mg. The ACS and CABG likely push him into the very high risk category. Why did not his high HDL-C protect him - isn't that value (> 60 mg/dl) supposed to be a negative CHD risk factor? We now know NCEP likely made a big error by uniformly suggesting a high HDL-C is a negative risk factor. In many it is, in some it is not. Many patients with extremely high cholesterol levels have too much cholesterol in all of their particles. Their tissues are full of excess cholesterol and the HDLs delipidate those tissues (especially the liver and small intestine). The very high non-HDL-C in the face of the high HDL-C should make us suspect we are dealing with too many atherogenic particles and indeed the nightmare LDL-P value confirms that we are: the diagnosis is severe hyperbetalipoproteinemia. The old Fredrickson classification would be Type IIa. Most persons with an LDL-C of 190 mg/dL do not have an extreme LDL-P of > 2600 nmol/L. Yet, because he had small LDL particles, it always requires more small LDLs (compared to larger LDLs) to traffic a given LDL-C concentration. One other factor that may have further depleted the number of cholesterol molecules per LDL particle is the TG level of 132 mg/dL. If for whatever reason he had increased CETP activity (the protein that swaps cholesteryl ester or CE for TG between TG-rich VLDLs and TG-poor particles (LDLs and HDLs) his LDLs might be carrying more TG than expected and thus would be carrying less CE than normal. If his LDLs are both small and TG-rich, they will be extremely cholesterol depleted and all of a sudden we have a reasonable explanation for the very high LDL-P. Although the TG were only 132, not considered alarming by most, there was a significant increase in his large VLDL-P - these are very TG-rich VLDLs that are the perfect substrate for CETP activity. It is the large VLDLs that can supply the TG to be exchanged for CE on the LDLs.

Sounds like the patient got great care: His endocrine and other problems were solved and he was started on aggressive lipid-modulating therapy. Clearly nothing further could be done to lifestyle. In an attempt to further reduce the LDL-C, non-HDL-C and especially the LDL-P, the clinician turned to the most powerful apoB (LDL-P) combo therapy we have: Crestor/Zetia. There is no more powerful therapy to upregulate LDL receptors (LDLr). The validity of this therapy was proven in the EXPLORER trial Crestor 40 plus ezetimibe was tested and a 70% LDL-C and 57% apoB reduction was seen (*Am J Cardiol* 2007;99:673–680). Personally I would have used Crestor 40 plus Zetia, but careful reading of the Crestor package insert advises not starting 40 mg as the initial Crestor dose. One should titrate up after a trial of 20 mg.

Well as expected, there was a wonderful LDL-C and non-HDL-C response where an LDL-C goal for a high risk patient was attained (100 mg/dL). If we consider the man very high risk: he is not at the desirable LDL-C of < 70 mg/dL. Although the LDL-P was significantly reduced by almost 1000 nmol/L, it was still in the high risk category. Please review Alan Sniderman's classic article (*Journal of Clinical Lipidology* 2008;2:36–42)

where he shows: “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.” Is there a reason for the drop in HDL-C: first of all is it real? HDL-C is very prone to lab errors or variability. Sometimes when one significantly drops TC (112 mg/dL in this case), all cholesterol levels, including HDL-C can occur. Dean Ornish, many years ago, was the first to show this by demonstrating CHD patients using extremely low fat diets dramatically reduced both TC and HDL-C and had angiographic improvement despite the HDL-C reductions (of 20-30%).

In an attempt to get to goal, the provider prescribed Niaspan. He does not indicate the starting dose, but obviously it was rapidly discontinued due to flushing. I think Niaspan was an appropriate add on. There are many positive angiographic trials that are testimony to niacin's benefit in persons with CHD. I often say if one has serious CHD, and there are no obvious reasons not to use it (uncontrolled diabetes, gout, intolerance, etc.) why is the patient not on a statin/niacin combo. A recent study of triple combination therapy (simvastatin/ezetimibe/niacin) of > 1200 patients showed significant efficacy with a 48% apoB reduction (J Am Coll Cardiol 2008;51:1564–72). High dose Crestor/Zetia/Niaspan would be one powerful therapy. Perhaps a more slowly titrated Niaspan regimen, with a full explanation to the patient that most flushing is self limited over a 4-6 week period would have helped compliance for this wonderful and powerful therapy. I believe docs give up way to early on niacin and do not advise patients that they have a malignant lipoprotein disorder. Be persistent: start off with a low dose and titrate slowly!

The doc then decided to add Trilipix (fenofibric acid). This was probably a mistake and indeed the resultant lipid/lipoprotein values prove that. A review of the extensive fibrate literature (way more studies than any class of lipid drugs except statins) reveal fibrates are most beneficial in persons with insulin resistance, metabolic syndromes, T2DM with insulin resistance who have TG levels > 200 mg/dL with accompanying low HDL-C (< 50 mg/dL in women and 40 mg/dL in men). This man has no clinical criteria for insulin resistance, especially after his hypogonadism was corrected. If one carefully reviews the published data on Crestor/Trilipix combination therapy, you will see to be enrolled in the studies the patients had to have elevated TG and low HDL-C. Researchers did no testing of the combo in patients without TG/HDL axis disorders. In patients studied the combo did attenuate the rosuvastatin induced LDL-C reduction, but so thoroughly reduced VLDL-C and raised HDL-C beyond the capability of the statin, that non-HDL-C and apoB was improved somewhat over time. Therefore no one should care that the LDL-C goes up if apoB or LDL-P does not go up. The explanation is clear: the fibric acid (an excellent TG-reducing drug) reduces then TG in the core of the LDLs: this increases the CE content of the LDL, but also shifts LDL size upward facilitating LDLr removal: i.e. LDL-C may rise, but LDL-P does not and usually goes down a bit.

What about the HDL changes? In VA-HIT using gemfibrozil there was a tiny fibrate induced HDL-C rise, and a dramatic HDL-P rise despite a reduction in large HDL-P (due to significant increase in small HDL-P). This is explained by a fibrates ability to increase apoA-I production and to increase hepatic scavenger receptors B1 (SR-B1) which

delipidate large HDLs (reducing their size) facilitating hepatic excretion of cholesterol in to the bile for excretion on the stool. There is really no published data on HDL-P using fenofibrate or fenofibric acid so we really do not know if it behaves like gemfibrozil on these parameters. In one substudy analysis of FIELD (Arterioscler Thromb Vasc Biol. 2009;29:950-955.) there was no major increase in apoA-I (2%) or HDL-C (2.2%) and it was attenuated in those who experienced a rise in homocysteine. Also see Diabetologia 2007;50(10):2067-75, a different analysis of apoA-I in FIELD which showed no rise in apoA-I but a shift in large HDLs to smaller species (as seen in VA-HIT). In this analysis fenofibrate also dramatically reduced large VLDL-P. Since one cannot necessarily correlate apoA-I changes with HDL-P (there are 2-4 molecules of apoA-I per HDL particle), so we really need NMR HDL-P analysis from FIELD and the statin/Trilipix studies to better understand its true effects all HDL parameters.

But this man had a dramatic increase in LDL-P after the Trilipix was added. Anecdotally, this paradoxical response is occasionally seen with fenofibrate, fenofibric acid and N-3 fatty acid administration. There is no published data on LDL-P with fenofibric acid or N3-FA but there is apoB data which is neutral (no change) over the short term (3 months) and decreased over the long term (12 months). Some patients get the opposite or paradoxical response as did this man. The easiest way to explain it is that, the fenofibric acid induced PPAR alpha agonism significantly upregulated lipolytic forces like lipoprotein lipase activity inducing increased TG-hydrolysis of the increased numbers of large VLDL-P, causing a rapid conversion of VLDLs into IDLs and LDLs: even though the LDLs are larger there are too many compared to the number of LDL receptors present and LDL-P accumulates. When this is seen, the fibrate or N3-FA should be stopped or LDL-C up-regulating drugs increased.

So what next: can retry Niaspan as already discussed. Patient will probably object - but further counseling is indicated. However we should not forget the standard therapy for hyperbetalipoproteinemia (familial hypercholesterolemia): we really need to maximize LDLr upregulation. So why not continue the Crestor (at 40 mg) with Zetia 10 mg and add the bile acid sequestrant Welchol at full dose (6 tabs daily). This fall it is expected that Welchol will also be available as a palatable powder that can be mixed with a beverage and more easily swallowed. For those interested in a more complex discussion of bile acids and the effect of sequestrants on LDL receptors please visit Dr Michael Richman's and my web site: www.lipidcenter.com - click on professionals and scroll down and read the pdf and PP slides on this topic. Thus I have answered the provider's final question. I believe Welchol will help. May ultimately also need Niaspan, but go with the Welchol first.

LIPID CASE 239 Unusual Response to Statin

A clinician asked me about a 70 year old male, with hypertension, Type 2 DM, and obesity (BMI = 37) who had an on-therapy LDL-C of 26 and a non-HDL was of 55. In an attempt to save him some money and because of the very low LDL-C he was taken off of the simvastatin, but remained on OTC, Slo-Niacin 750 mg BID.

His lipid panel on Slo-Niacin alone was:

TC = 159, TG = 206, HDL-C = 32, VLDL-C = 41, LDL-C = 86, and non-HDL-C = 127 (all in mg/dL)

Soon thereafter, he was found to have moderate coronary disease per angiography, so his cardiologist placed him back on simvastatin 20 mg nightly.

His lipid panel on Slo-Niacin with simvastatin 20 mg:

TC = 83, TG = 217, HDL-C = 24, VLDL-C = 43, LDL-C = 16, and non-HDL-C = 59.

The clinician had questions: Does it matter that the LDL-C is only 16 mg/dL? Is there an LDL level that's too low? (Do not we need some cholesterol to make cell walls?). Is there any reason why the triglycerides increased and the HDL-C decreased after re-adding simvastatin? (Note: he did not stop niacin). Finally would niacin + a fibrate be a better combo for him? (His GFR is normal).

DAYSRING ANALYSIS:

By now all of you know that my first approach is to do an accurate risk assessment. As originally presented many would classify the man as high risk because of the T2DM. Once the CAD was documented, NCEP and almost everyone else would agree he is indeed in the very high risk category. The reason why proper risk assessment is crucial is with each higher risk category, there is a more aggressive goal of therapy needed to properly reduce that risk. NCEP Goals for the high risk category are an LDL-C less than 100 mg/dL and if TG are > 200 mg/dL, a non-HDL-C < 130 mg/dL. The very high risk goals for LDL-C and non-HDL-C would be < 70 mg/dL and 100 mg/dL respectively. Of course we all must recognize, since first stated in the NEJM classic, Fredrickson, Levy and Lees in 1967, that lipid concentrations are simply surrogates of lipoprotein concentrations. Indeed it is the lipoproteins that traffic the sterols into the arterial wall causing atherogenesis.

Well let's look at the above on-treatment lipid concentrations. On the Slo-Niacin, his LDL-C was 86 mg/dL. His TG were > 200 mg/dl and thus NCEP puts non-HDL-C into play. His non-HDL-C level of 127 mg/dL is also above the desirable 100 mg/dL. Accordingly, we should assume he has too many atherogenic particles in his plasma despite the 1500 mg of niacin. NCEP would demand more aggressive lifestyle therapy or additional drug-therapy. NCEP in 2001, suggested that when on a statin and non-HDL-C is still elevated, improve lifestyle, one should increase the statin dose or add a fibrate or niacin. Since that time statin/ezetimibe (Vytorin) has also received a non-HDL-C FDA indication. Although they lack the indication, there is good evidence that statin/4000 mg N3FA (Lovaza) can also help achieve non-HDL-C goals when TG are between 200-400 mg/dL).

The cardiologist simply re-added the simvastatin at 20 mg in an attempt to no doubt get the LDL-C < 70 mg/dL. Of course being a cardiologist he likely has no clue what non-HDL-C or apoB is (JUST A JOKE FROM A JERSEY BOY TO TEASE MY MANY

CARDIOLOGIST READERS). The actual tragedy is that > 70 % of providers (not doing apoB or LDL-P determinations) do not calculate, enter into the medical record or act upon non-HDL-C. What happened to the lipid profile after resumption of the statin/niacin combination? The LDL-C was blown away, but HDL-C by dropping 8 mg/dL and TG levels by increasing 9 mg/dL) seemingly worsened. Yet why should anyone be worried as his important lipid concentrations (LDL-C and non-HDL-C) are well under NCEP goal?

Diabetologists may state that unlike NCEP, the ADA Lipid Guidelines does have an HDL-C and a TG goal of therapy: (HDL-C >40 in men, 50 in women and TG < 150 mg/dL in all). This is a perfect case to show the absurdity of those non-evidenced based guidelines. I am still waiting for the trial to show me a low HDL-C still predicts risk when apoB or LDL-P are at desired goal. In this man with an on-treatment TC of 83 and an LDL-C of 16 at any risk because the HDL-C is still so low? I cannot imagine that he still has any excess of atherogenic apoB particles. I wonder what else the ADA would want a clinician to prescribe in a man already on niacin to raise the HDL-C from 24 to 40 mg/dL?

The low level of LDL-C is not a cause for concern. Cells make all the cholesterol they need for their cell membranes via endogenous cholesterol production (fatty acid is the substrate): most cells do not require lipoprotein delivery of cholesterol. Those cells that do (steroidogenic cells and adipocytes) get most of their cholesterol delivery from HDL particles (which for the most part are lipidated or acquire their cholesterol from hepatocytes and jejunal enterocytes). Although LDLs can deliver cholesterol to peripheral cells, that is not their primary function. LDLs, which are basically a waste product of a VLDL or IDL that has lost its TG, primarily traffic cholesterol back to the liver (indirect reverse cholesterol transport). Many mammalian species as well as hunter-gatherer human populations have LDL-C levels of 20-30 mg/dL and suffer no cholesterol deficiency problems. Lipidologists know there is actually a human condition called hypobetalipoproteinemia where apoB production is limited. Patients, especially those with complex hypobetalipoproteinemia, have LDL-C of 5-30 mg/dL and they have longevity as they suffer neither atherosclerosis nor consequences of their low cholesterol.

What about the TG rise on simvastatin? Please realize TG concentrations are very labile especially in insulin resistant patients with hypertriglyceridemia. Even in normal people TG levels have significant inter-individual variations. In insulin-resistant patients, values between tests can vary by 100 mg/dL, never mind 9 mg/dL. Thus a TG rise of 9 mg/dL has no clinical meaning. There is absolutely no different clinical meaning between a TG of 206 and 217 mg/dL. Both pre and post statin values are high in this patient - but again if there are no atherogenic apoB particles in this man's plasma, who cares about a TG level in the 200 range. Back to NCEP: in patients with high TG (between 200 and 500 mg/dL) the NCEP goal of therapy is LDL-C and non-HDL-C; NCEP would state CASE CLOSED despite the still low HDL-C and high TG!

The HDL-C decrease also has no meaning of clinical significance in this case. The cause of the low HDL-C is directly related to the elevated TG. In IR patients with high TG the HDLs are carrying lots of TG instead of cholesterol. IR patients with high TG

(somewhere above 120-130 mg/dL, or perhaps even lower) there is a cholesteryl ester transfer protein (CETP) mediated exchange of TG for cholesteryl ester (CE) between HDLs and apoB particles. The TG from TG-rich VLDLs and IDLs enters the HDLs - in exchange the HDL sends its CE back to the VLDLs and IDLs. Obviously in these patients the HDLs will be carrying TG instead CE and HDL-C will be accordingly low. The TG-rich, CE-poor HDL upon exposure to hepatic lipase shrinks and breaks up releasing its surface proteins (apoA-I) which are cleared by the kidney - further reducing HDL-P and HDL-C. It is impossible to predict CETP mediated lipoprotein changes by looking solely at TG levels (lots of other factors are at play including apoF or lipid inhibiting transfer protein). There is one other possible contributory factor. Large HDLs (typically seen in patients on niacin) can carry multiple copies of apoE. In this man, the simvastatin would have upregulated hepatic LDL receptors – they may simply have endocytosed apoE-rich HDL particles (improving indirect reverse cholesterol transport) . This would cause a decrease on HDL-C.

Also patients with extremely low levels of TC, tend to likewise have very low levels of LDL-C and HDL-C. There is not very much cholesterol left in this man's plasma - more than enough to support cellular functions (including delivery to steroidogenic tissues) but not enough to result in lipoprotein-mediated atherosclerosis. In the famous Dean Ornish severe fat restriction, angiographic study, plaque disappeared, but the drastic reduction in fat intake reduced both TC and HDL-C. These patients were helped, not hurt by reducing HDL-C. Almost certainly the HDL-C reduction in this man is related to the significant drop in TC.

Why was the drop on LDL-C so dramatic with the simvastatin 20 mg? As mentioned, on the Slo-niacin monotherapy both the LDL-C and non-HDL-C were still too high (above goal). The very high TG/HDL-C ratio certainly suggests way too many small LDL particles (high apoB and total LDL-P). This man's LDLs are predominantly small and may still be carrying excess TG instead of cholesterol (meaning his LDLs are very cholesterol depleted) and thus he will need a lot of them to carry his 86 mg/dL of cholesterol. Tim Russert reportedly had a TC in the 150s and LDL-C in the 60s and died a CHD death because he almost certainly had too many apoB (LDL particles). Here is my possible explanation for the dramatic LDL-C response. It is well established that people whose systemic cholesterol excess is due to overproduction of cholesterol rather than over absorption have hyper-responses to statins. Likewise, hyperabsorbers of cholesterol have hyporesponses to statins. In anyone overproducing cholesterol, there will be an excess of cellular HMG-CoA reductase, the enzyme inhibited by statins: thus they respond very well to statins. The statin-inhibition of excess HMGCoA reductase activity in an overproducer will greatly deplete hepatic cholesterol stores, causing a substantial upregulation of hepatic LDL receptors: which will lead to dramatic reductions in LDL-C, non-HDL-C, apoB and LDL-P. Au contraire hyperabsorbers of cholesterol have suppressed cholesterol synthesis and low cellular levels of HMG CoA reductase and typically are poor (hypo) responders to statins. So if this man was an overproducer of cholesterol, one might expect the tremendous response to the simvastatin. There is very old data on niacin suggesting increase cholesterol excretion in the stool - theoretically this could cause an increase HMGCoA reductase activity and cholesterol synthesis.

Hypothetically the niacin monotherapy in this patient increased cholesterol synthesis making it very likely there would be an exaggerated response to the statin.

Lastly, never forget non-HDL-C (the poor man's apoB) is far more concordant with apoB or LDL-P than is LDL-C, but there is still 30 % discordance between non-HDL-C and LDL-P. Therefore in unusual cases like this very high risk patient, the best way to know what the actual risk is and what therapy is needed is to measure LDL-P. (see www.lipoprofile.com). It is too dangerous to bet one's life on lipid concentrations in those with high or very high CV risk. There is a great review of apoB vs. non-HDL-C by Allan Sniderman in the just released issue of Current Opinions in Lipidology. In it he has a nice table showing what little meaning the LDL-C had in the JUPITER trial. These were indeed seriously at risk patients and their risk was certainly not identifiable by looking at LDL-C. Of course they all had very serious apoB elevations. Sniderman concludes and I wholeheartedly agree: "that apoB should be measured in any patient in whom fasting routine lipids are abnormal or in any patient at moderate or high risk for vascular disease to establish the true risk due to atherogenic lipoproteins. (Current Opinion in Lipidology 2009, 20:282–287).

For sure the first line therapy for elevated LDL-P (apoB) should always be a statin: one should not use niacin, fibrates, sequestrants or ezetimibe as a standalone first line drug unless TG are > 500 (fibrates). If the statin does not get the patient to LDL-P goal, then second and third drugs will be needed. In very high apoB (LDL-P) patients, starting two drugs is quite appropriate.

For the most part, when apoB, LDL-P are fine, persistent, elevated TG levels (as long as they are under 400) have little clinical meaning. The current on-therapy lipid values in this patient are fine and there is virtually no chance that apoB would still be high. It would be informative to know what the total HDL-P is, but that is a story for another newsletter. Lastly the clinician asks about using a fibrate and niacin together. There actually is a very positive clinical outcome trial where a fibrate (clofibrate) and immediate release niacin improved CHD mortality and non-fatal MI. (Acta Med Scand 1988;223:405-418). I certainly prefer the statin to be on board, but if a patient is statin intolerant, fibrate/niacin remains an option.

LIPID CASE 240 PCOS Choosing Combination Therapies

I want to discuss a 36 year old lady with Polycystic Ovarian Syndrome (PCOS) with insulin resistance (IR) on metformin XR 2000 mg at dinner along with oral contraceptives. She has lost 18 pounds since over the last year on metformin & with TLC. Currently she weighs 187 pounds & has a BMI of 31. Her gynecologist started her on treatment in 6-2006 with simvastatin (Zocor) 20 mg daily after a review of her abnormal lipids & then added meds over time as noted in the chart below.

After 5-07, because of the elevated TG, he added 48 mg of fenofibrate (using the TriCor brand) to get closer to goal. After 10-2007, because of the elevated LDL-P results he switched from simvastatin to rosuvastatin (Crestor) 20 mg & also added Omega FA at 2000 mg per day at the same time because of the still elevated TG. The lipid levels all improved very nicely and finally

in 4-2008 the clinician believed her non-HDL-C was at goal. However he was not happy with the improved but still elevated LDL-P so he added ezetimibe (Zetia) 10 mg. There was no further improvement in the LDL-P value in 12-2008 her Zetia was stopped since the doc didn't feel it had added any benefit. On treatment, this patient also had a mid-normal hs-CRP. Her Coronary Calcium score was 7, meaning 75% of women her age had a lower score than she. The gynecologist felt that the LDL-P is stuck were it is despite ezetimibe because of her IR and wanted my opinion. He of course urged her to lose more weight

	6-06	8-06	5-07	10-07	4-08	12-08
TC	230	170	183	184	138	115
HDL	37	40	54	64	48	43
LDL	165	108	77	83	61	49
TG	139	109	282	187	143	115
Non-HDL-C	193	130	129	120	90	72
Small LDL-P			1708	1665	904	1097
LDL-P			2178	2158	1388	1342
Current Rx	none	Zocor 20	Zocor 20	Zocor 20 Tricor 48	Crestor 10 Tricor 48 Omega 2 g bid	Crestor 10 Tricor 48 Zetia 10

DAYSRING DISCUSSION:

Remember my rule: perform accurate risk assessment first, then appropriate treatment next. At first glance one might suspect moderate risk because of the insulin resistance and metabolic syndrome. Technically, we do not have enough information to diagnose the metabolic syndrome (we lack glucose and BP parameters). She is obese with a low HDL-C but the TG are < 150 mg/dL. I am guessing her glucose was elevated as she was prescribed metformin and that would be the necessary third criteria. Once the positive calcium score is known, she has subclinical atherosclerosis and is considered high risk. The score is low but most 36 year old women would be zero. I do not think she meets criteria for very high risk and using NCEP-ATP-III recommendations the lipid goal of therapy is an LDL-C of less than 100 mg/dL. Because her TG are < 200 mg/dL non-HDL-C is not an ATP-III goal of therapy. If TG were > 200 mg/dL, the non-HDL-C would be 30 mg/dL above the desired LDL-C. (30 mg/dL is actually what NCEP considered a normal VLDL-C to be in 2001). Of course we now know that non-HDL-C is always as good and most of the time better than is LDL-C as a measure of atherogenic particles and risk assessment (Am J Cardiol 2006;98:1363–1368). Hopefully next year's ATP-IV will update non-HDL-C use criteria. In many people's opinion non-HDL-C should replace LDL-C as the main goal of therapy (never forget it does include LDL-C). Those of us who live in a lipoprotein world recognize that both LDL-C and non-HDL-C are simply apoB or LDL-P surrogates (with non-HDL-C being a better apoB surrogate than LDL-C). VLDL-P contributes very little to total apoB.

Let's go back and look at the above table. On simvastatin 20 mg, the LDL-C was 108 mg/dL and the non-HDL-C was 130 mg/dL. For practical purposes the patient is at NCEP ATP-III goal. Further lifestyle would be advised. The NMR (Nuclear Magnetic resonance Spectroscopy) LDL-P was not done. Her HDL-C was still low at 40 mg/dL (but there is no specific HDL-C goal of therapy), but the TG seem fine at 109 mg/dL (VLDL-C = TG/5 = 109/5 = 21). So we should be happy, right? Anyone who has heard me lecture knows I really want to know atherogenic particle numbers in high and very high risk patients. My advice to those using lipid profiles, is once you get non-HDL-C to goal, you really need to check apoB or better yet LDL-P. As good as non-HDL-

C there is a least a 30% discordance between non-HDL-C and atherogenic particle, number. That is too high to leave to chance. In this case the simvastatin 20 mg was continued.

The patient was next seen 9 months later and a glance at the lipid profile shows a substantial drop in LDL-C, rise in HDL-C but a drastic increase in TG (from 109 to 282). The non-HDL-C of 129 remained at goal (< 130 mg/dL). Look at the TG/HDL-C ratio of 282/54 or 5.2. A value of > 3.8 indicates an 80% likelihood of small LDL (Phenotype or Pattern B). The real danger is that the majority of folks with small LDLs have very high LDL-P (apoB) and of course it is particle number, not particle cholesterol that causes the apoB particle to enter the arterial wall. Well we do not have to guess, as an NMR LipoProfile was performed and the total LDL-P was extremely high at 2178 (even with an LDL-C in the 70s). Studies reveal: 74% of T2DM with LDL-C between 70 and 100 have an LDL-P > 1000 nmol/L. The reason for the drastic elevation of her LDL-P (most of which but not all are small -- her LDLs are cholesterol-depleted. It takes many more cholesterol depleted LDLs than cholesterol-rich LDLs to traffic a given level of LDL-cholesterol. With a TG of 280, there has to be high cholesteryl ester transfer protein (CETP) activity. TG are moving from VLDLs to the LDLs - making them TG-rich and cholesterol-poor: some of those LDLs are converted to small LDLs when the LDL core TG and surface phospholipids are hydrolyzed by hepatic lipase - in essence the particle shrinks and is not capable of holding a lot of cholesterol. The small LDLs are not so readily recognized and internalized by the simvastatin upregulated LDL receptors (LDLr) raising the LDL-P. The LDLs that are large, have to be carrying more TG than cholesteryl ester (CE) and thus even though they are large they are CE depleted. It takes a lot of large, CE-poor LDLs to traffic even low levels of LDL-C: hence there should be no shock that LDL-P is so high even with an at goal LDL-C!

The provider, no doubt because of the high TG and small LDLs elected to add fenofibrate at a 48 mg dose. Too bad, as that is a dose to be used in patients with renal impairment and a clearance well under 60 cc/min. It is likely a placebo at such a low dose in a woman with normal renal function. It should have been prescribed at its full and proper dose of 145 mg. As you can see 5 months later there was virtually no change in the lipid profile or more importantly the LDL-P. One might say there was a drop in TG of 282 to 187, but never forget there is no TG goal of therapy. Non-HDL-C is the ATP-III goal as mentioned above when TG are > 200 mg/dL. Despite the great TG drop, the non-HDL-C barely changed and remained at goal. Epidemiological trials show there is elevated risk with TG of 190 and elevated risk with TG of 280 - and the risk is virtually the same for both (Castelli W AJC 1992;70:3H-9H). I'll bet most physicians think a TG of 280 is associated with considerably more risk than a level of 190 mg/dL -- truth is they are both high risk TG.

The provider's next move was to drop the simvastatin and start rosuvastatin (Crestor) at 10 mg and add two grams of N-3 Fatty acids (I presume Lovaza). The "baby" TriCor was continued. The LDL-P is still extremely high. Switching from simvastatin 20 to rosuvastatin 10 is usually a lateral move, not a more aggressive move. One could have increased the fenofibrate to 148 mg, as it might further shift LDL size upwards making it easier for upregulated LDLr to remove them but even that is unlikely to normalize the LDL-P. It would certainly help with the VLDL-C and remnants. If you want to use N-3 FA for TG treatment, the dosage should be 4000 mg (2000 mg would not be expected to have any effect). With such a high LDL-P, I would have used Crestor 40 mg, not 10 mg and would have increased the fenofibrate to full dose and even at this point might have considered ezetimibe 10 mg. Note: although there are no efficacy differences between fenofibrate (a prodrug) and the active drug fenofibric acid (Trilipix), it might be wiser for a gynecologist to use the fenofibric acid with the statin as it is FDA approved to combine with a statin. Instead of ezetimibe others might want to consider colesevelam (Welchol) as it would help reduce LDL-P and would also help improve any glycemic issues.

Well what do I know? On the low dose Crestor, baby feno and low dose N-3 FA there was a substantial LDL-P response (improvement). All of the lipid parameters are at goal and even well below goal. The gynecologist correctly states he is not happy with the LDL-P of 1388 (40th percentile population cut point) in a high risk patient. For those interested in Framingham population cutpoints: see www.lipidcenter.com Click on Professionals and scroll down till you see

the pdf. So Zetia was added and low and behold - nothing at all happened. My regular readers likely have already figured out the reason.

I suspect if somewhere early in the game we had measured markers of cholesterol synthesis (lathosterol) and markers of absorption (sitosterol and campesterol) at Boston Heart Lab we would have identified her as an over-producer, not an over-absorber of cholesterol. In such patients there is usually (as in this case) a hyper response to statins and a hypo response to ezetimibe. In this woman, the rosuvastatin has better binding to HMGCoA reductase than did the simvastatin and the rosuvastatin inhibited cholesterol synthesis way more than did the simvastatin. One other possibility: Both fenofibrate and omega-3 fatty acids via a PPAR alpha agonistic effect reduce intestinal upregulation of the Niemann Pick C1 Like 1 protein (NPC1L1). So they have the ability to reduce cholesterol absorption and maybe this also helped minimize the effect of ezetimibe. Normally in folks with lots of NPC1L1, fenofibrate and ezetimibe are incredibly synergistic and FDA has approved them to be used together. In patients with no response to the Zetia, it should be abandoned and the Crestor dose increased to 20 and if needed to 40 mg. Again: if there are glycemic issues not covered by metformin, Welchol would be an excellent add-on choice and would allow a lower dose of statin to be used.

Last note: Yesterday the FDA approved a new statin: pitavastatin to be sold as Livalo. It will be available at 1, 2 and 4 mg dosages which will have the same potency as Crestor 10, 20 and 40 mg respectively. It powerfully binds to HMGCoA reductase far more than any other statin explaining why such low doses can be used. Unlike the hydrophilic pravastatin and rosuvastatin, pitavastatin is lipophilic, but is by far the least lipophilic statin and thus will have no major P450 interactions. It has been used in Japan for several years. It is produced by Kowa Pharmaceuticals.

LIPID CASE 241 Statins and Sterols

Long time readers of this newsletter know my career has been built upon the belief that the more clinicians understand lipid biochemistry, biology and pathology, the better they will be at assessing atherothrombotic risk and at reducing that risk with specific therapies. This newsletter will tackle sterol homeostasis. It is crucial for human existence that all cells tightly control their cholesterol content as some is needed for cellular membrane integrity and signaling. However too much cholesterol will crystallize and destroy the cell. Thus all cells in the body have the ability to both acquire (synthesis or delivery) and export cholesterol (active or passive diffusion to HDLs). In the big scheme of things, two master organs regulate total body sterols - the liver and the proximal small intestine (duodenum and jejunum). Although all cells regulate their own sterol homeostasis, hepatocytes and enterocytes have more methods to do so. Ultimately the only way the body gets rid of excess cholesterol or noncholesterol sterols is to excrete them in the stool. If we are to correct abnormal cholesterol homeostasis in our patients with lipid disorders we have to totally understand how cells, especially hepatocytes and enterocytes regulate sterols. I am fascinated by this topic and as many of you know my chapter in the textbook, Therapeutic Lipidology deals with regulation of cholesterol and noncholesterol sterols and Phytosterolemia (a severe premature CHD disease state where patients have high levels of noncholesterol sterols).

Some nomenclature: Sterols are steroid alcohols which are basically steranes (4-cyclic ring compounds) with a hydroxy (-OH) group at the number 3 position of the A (first) ring. They are grouped into two categories: phytosterols or zoosterols. Cholesterol is the animal produced sterol, sitosterol, campesterol, stigmasterol and others are plant produced and ergosterol is fungal produced. Because the structure of all of these molecules is quite similar, sterols that are not cholesterol are referred to as noncholesterol sterols. Thus sitosterol becomes sitostanol. Zoosterols and phytosterols are ubiquitous in the human diet. Noncholesterol sterols serve no

functions whatsoever in humans whereas cholesterol is critical for human existence. A stanol is simply a sterol that has lost its double bonds (become saturated).

Cholesterol can be synthesized de novo in virtually every cell in the human body. Thus under normal conditions very few cells need delivery of cholesterol. The substrate from which cholesterol is made is acetyl-CoA (a metabolic derivative from fatty acid oxidation and glucose metabolic pathways). Since our current diet is full of the latter, it is no wonder so many patients have pathological cholesterol homeostasis. Cholesterol synthesis is quite complex and is a 37 step process that changes acetyl CoA into cholesterol utilizing numerous enzymes. Since cholesterol can be both synthesized and absorbed it by itself is not useful as a marker of synthesis or absorption. Fortunately, there are many intermediary synthesis noncholesterol sterols some of which can be useful in our diagnostic workups. Desmosterol and lathosterol levels can be measured and they serve as markers of cholesterol synthesis - they would be elevated in those overproducing cholesterol and reduced in those not producing it. Their measurements are reported in absolute values as mg/dL. Since plasma sterols are mainly carried in the LDL particles, it is common practice to adjust sterol concentrations for the total plasma cholesterol level by reporting them as ratios dividing them by cholesterol (e.g. lathosterol/cholesterol ratio). To measure sterol absorption, one has to measure noncholesterol sterols that are not usually absorbed - like sitosterol, campesterol. Their levels would, be elevated in patients who are cholesterol hyperabsorbers. All of these tests are readily available at Boston Heart Lab (www.bostonheartlab.com)

Let's see how these tests can apply to real world lipidology using a patient from my own practice. A 61 year old man was referred to me by someone familiar with my lipid expertise. The patient has known of hyperlipidemia for over a decade and has used lifestyle and a statin (predominantly low dose atorvastatin (Lipitor) 20 mg. For a short while he also used ezetimibe (Zetia) but stopped it when all of the hysterical reports made TV appeared after ENHANCE. After having angina like symptoms a coronary angiogram in January of 2008 revealed two lesions and the right coronary artery (RCA) was stented. The left anterior descending (LAD) was not. Follow up stress tests were not perfect and a second angiogram in June 2008 led to a stent placed in the LAD. There has been no angina since the first stent. Over the last 8 months the Lipitor was increased to 40 and ultimately to 80 mg daily. He tolerates the drug very well. He was also using Plavix, allopurinol, omega-3 FA a lot of OTC nutraceuticals including antioxidants and plant sterols. Past history also includes gout. Family history reveals his mother had hypercholesterolemia and died at age 78 of MI; His father had 3 MIs starting age 55 and died at 82; 4S are well and a younger brother has 4 coronary stents.

On the initial visit the Lipid profile and lipoprotein analysis were wonderful: TC = 146, LDL-C = 83, HDL-C = 51, TG = 62. The total LDL-P was perfect at 767 (bottom 5th percentile of the population). Total HDL-P was in the high range and Vitamin D was normal. I encouraged him to continue the Lipitor 80 mg (I could care less that his LDL-C was above 70, in the face of a perfect LDL-P). It seemed that the statin, by significantly inhibiting cholesterol synthesis was upregulating plenty of hepatic LDL receptors which were removing the apoB particles very nicely. Few of us think there could be a downside to that. **STAY TUNED.**

I insisted that he stop the noncholesterol sterol supplements as they do nothing beneficial to the CV system that I am aware of and there is plenty of data on their potential harm (please see Vascular Effects of Diet Supplementation With Plant Sterols Oliver Weingärtner et al (J Am Coll Cardiol 2008;51:1553-61) where they conclude that "food supplementation with phytosterols impairs endothelial function, aggravates ischemic brain injury, effects atherogenesis in mice, and leads to increased tissue sterol concentrations in humans."

After that visit several major studies (including new data from STELLAR and Framingham Offspring Study or FOS) became available that should change the way we evaluate risk and make major therapeutic decisions. The data influenced me on the next follow up visit. First let's get back to the sterol homeostasis story which we will ultimately apply to this patient. Let's look at

how hepatocytes and enterocytes obtain cholesterol and how they get rid of it any excess and let's also see how those cells handle noncholesterol sterols.

STEROL ACQUISITION:

Enterocytes: [1] absorb unesterified or free cholesterol as well as noncholesterol sterols (ingested) from the gut lumen via the Niemann Pick C1 Like 1 protein. The vast majority (85%) of the FC was put there by the biliary tract, the rest by oral ingestion. Human cholesterol absorption varies from a mean of 55% to hyperabsorbers (70-80%) to hypoabsorbers (<30%). We can test for sterol absorption status by ordering sitosterol and campesterol levels (you will also receive sitosterol/C and campesterol/C ratios). [2] Delipidation of mature HDL particles using enterocyte scavenger receptors B1 (SR-B1): thus the jejunum is part of the direct reverse cholesterol transport system. [3] Denovo synthesis of cholesterol

Hepatocytes: [1] Denovo synthesis. 15% of total body cholesterol is made in the liver. We can monitor this by looking at cholesterol synthetic precursors such as desmosterol and lathosterol levels or their /C ratios. [2] Back-flux of FC from the bile into the hepatocyte via the NPC1L1 protein which is significantly expressed at the hepatobiliary interface. This is a potential significant source of cholesterol for the liver. [3] Delipidation of mature HDLs via hepatic SR-B1 or endocytosis of mature HDLs using the holoparticle receptor or LDL receptors (LDLr) which recognize and internalize apoE enriched HDL particles: HDLs returning to the liver is also part of direct RCT pathway. [4] Internalization of chylomicrons (carrying gut-derived cholesterol) via the LDL receptor related protein (LRP), and VLDLs, IDLs and LDLs via LDLr. Internalization of these apoB particles and their cholesterol content is termed indirect RCT.

STEROL EXPORT

Enterocyte: [1] esterifies the FC (replace the -OH group at the #3 position of the A ring with a long chain fatty acid, typically oleic acid) using ACAT (acylcholesterol acyl-transferase) forming cholesteryl ester (CE) which along with TG is incorporated into chylomicron particle synthesis. The chylomicrons and their sterols are released into the lymphatic system. [2] Export of FC into lipid-poor smaller HDL species, unlipidated apoA-I or onto unlipidated apoE using the ATP Binding Cassette Transporter A1 (ABCA1). 30% of plasma HDL-C is obtained in the jejunum. PEARL: when you see patients with high LDL-C and high HDL-C think hyperabsorption of cholesterol. [3] Re-excretion to gut lumen using the ABCG5,G8 transporters (sterol export transporters).

Hepatocytes: [1] Convert cholesterol into a bile acid using the enzyme cholesterol 7-alpha hydroxylase. Export bile acids into the bile using the bile export transporter (ABCB11). Once in the intestine via the biliary system, bile acids can be reabsorbed in the ileum or excreted in the stool. This is the body's number one pathway to get rid of cholesterol. [2] Esterify the cholesterol using ACAT to CE and incorporate it with TG into VLDL particles and secrete then into plasma. [3] Lipidate immature HDL particles using ABCA1 transporters. Upwards of 70% of the cholesterol within the HDLs is hepatic acquired. [4] Excrete FC into the bile using ABCG5,G8 which are expressed at the hepatobiliary interface.

With respect to noncholesterol sterols: Theoretically those that are absorbed from biliary micelles into the enterocyte are immediately re-excreted back into the gut lumen via the ABCG5 and G8 transporters. Unlike cholesterol, noncholesterol sterols are very poor substrates and are not readily esterified by ACAT and thus do not enter chylomicrons. Should any noncholesterol sterols make it to the liver as passengers inside of chylomicra, they are immediately excreted into the bile via hepatic ABCG5,G8. Persons with homozygous absence of G5 or G8 absorb very large amounts of noncholesterol sterols and develop the disease formerly called sitosterolemia and now called phytosterolemia (see my book chapter). Because these sterols cannot be esterified, if they make it into a VLDL and LDL they are readily prone to oxidation and it is oxysterols and oxidized LDLs that drive atherogenesis.

If everything (all homeostatic mechanisms) are in balance human absorption and excretion of sterols is in balance: cellular cholesterol levels are perfect and no noncholesterol sterols are in the plasma, peripheral tissues or artery walls. Of course in most of our patients these mechanisms are out of synch, because humans are making way more cholesterol than they can excrete. Unfortunately because of variable expression and polymorphisms of ABCG5 and G8 many patients do have high levels of potentially very atherogenic noncholesterol sterols in their plasma. Because absorptive markers are rarely measured, in reality clinicians ignore it perhaps occasionally to their patients peril.

In new data from the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial J. Lipid Res. 2009;50:730–739) the authors conclude rosuvastatin and atorvastatin decreased markers of cholesterol synthesis and increased markers of fractional cholesterol absorption, with rosuvastatin having significantly less effect on the latter parameter than atorvastatin. In addition, alterations in absolute values of plasma sterols correlated with the cholesterol lowering response. Simply put, although rosuvastatin is better than atorvastatin 80% of the patients using statins will be hyperabsorbers of cholesterol. Both drugs (at max dose) inhibited lathosterol/C (marker of synthesis) the same (atorva 64% and rosuva 68%) Both drugs increased absorption: campesterol/C (rosuva 52% and atorva 72%) sitosterol/C (rosuva 67% and atorva 96%). So if we average the two markers of absorption there seems to be a 25% difference

The author's state: "We noted a significant difference between these two statins with rosuvastatin not raising the relative amounts of campesterol or sitosterol as much as atorvastatin. Therefore rosuvastatin caused less of an up-regulation in markers of fractional cholesterol absorption than atorvastatin, indicating that this statin may have less of an effect on the intestine than atorvastatin." ----- Thus with regard to the absorption markers, both statins have different pharmacokinetic properties, which may account for the somewhat greater efficacy in LDL-C lowering and HDL-C increasing for rosuvastatin than atorvastatin." Please also note that statins do this by depleting hepatic and enterocyte cholesterol synthesis. This downregulates the Liver X Receptors (LXR) and upregulates SREBP (sterol regulatory element binding protein): this leads to upregulation of the NPC1L1 proteins and downregulation of ABCG5,G8: the effect of that is increased sterol absorption in the gut and increased hepatic reacquisition of cholesterol from the biliary tract and decreased excretion of the noncholesterol sterols back to the bile or gut lumen (both NPC1L1 and ABCG5,G8 are expressed at the hepatobiliary interface). So even though statins reduce cholesterol synthesis, homeostatic mechanisms go into play that make tissues replace that cholesterol via other means: in effect body cholesterol homeostatic mechanisms work hard to combat statin effectiveness.

Is all of this meaningless biochemistry or is there real clinical meaning? Just published but previously available on line is sterol data from FOS. The manuscript entitled "Alterations in cholesterol absorption/synthesis markers characterize Framingham Offspring Study participants with CHD" by Nirupa R. Matthan et al (J. Lipid Res. 2009. 50: 1927–1935) concludes "impaired cholesterol homeostasis, reflected by lower synthesis and higher absorption marker concentrations, are highly significant independent predictors of prevalent CVD in this study population." What explains hyperabsorption? Increased expression of NPC1L1 and decreased expression of ABCG5 and G8. Final conclusion is "Additionally, the cholesterol homeostasis markers appear to be better predictors of disease than traditional lipid risk factors in this study population." In hyperabsorbers there would be increased levels of sitosterol, campesterol and decreased levels of the synthesis markers lathosterol and desmosterol. Since many diabetics are hyperabsorbers of cholesterol it should not be such a surprise why they have such a high incidence of CHD. In post-hoc analysis of 4S data (first RBCT that proved statins do reduce CHD outcomes), the benefit of the simvastatin was limited to the hypoabsorbers of cholesterol. There was no event reduction in hyperabsorbers of cholesterol. The reason should be obvious: hyperabsorption of cholesterol overloads the liver with cholesterol and causing a suppression of cholesterol synthesis. These patients have high LDL-C because of over absorption and not

overproduction. These patients have reduced levels of hepatic HMGCoA reductase and thus would be statin hyporesponders. So if you prescribe a statin to a hyperabsorber of cholesterol, there will be no benefit! Finally in a study by Tatu A. Miettinen et al entitled Plant Sterols in Serum and in Atherosclerotic Plaques of Patients Undergoing Carotid Endarterectomy (J Am Coll Cardiol 2005;45:1794–801) the conclusion was: the higher the absorption of cholesterol, the higher are the plant sterol contents in serum resulting also in their higher contents in atherosclerotic plaque. Simply put in patients taking statins, cholesterol in the plaque was reduced but it was in part being replaced by campesterol and sitosterol. The greater the statin-induced suppression of lathosterol (synthesis marker), the greater the amount of campesterol in the plaque!!!!

How about one more study: Michael E. Greenberg et al in a new study entitled Moderately Decreased Cholesterol Absorption Rates Are Associated With a Large Atheroprotective Effect show that moderately decreased cholesterol absorption rates (on ezetimibe) result in a large atheroprotective effect attributable to a decrease in plasma cholesterol levels and an increase in RCT from peripheral tissue macrophages. (Arterioscler Thromb Vasc Biol. 2009;29: in print - available on line.)

So, being suspicious of a patient who has been on long-term high dose atorvastatin, I sent off serum to the Boston Heart Lab on the patient under discussion and was simply stunned by the results. This patient's results were in total agreement with the STELLAR data discussed above. He had virtually absent markers of cholesterol synthesis and significantly elevated levels of absorption markers:

Absorption markers:

Sitosterol = 502 mg/dL (n < 233) Campesterol = 922 mg/dL (n < 200)

Synthesis markers

Lathosterol = < 89 mg/dL (n < 205) Desmosterol = not detected

One has to wonder is this man's marked phytosterolemia purely statin induced or was he actually a ABCG5,G8 heterozygote made considerably worse by high dose atorvastatin use which massively increased sterol absorption. How much of his arterial plaque is cholesterol and how much is noncholesterol sterols? Lastly what can a clinician do about this? We need to therapeutically reduce the marked sterol over absorption. Theoretically we need to suppress sterol absorption and increase sterol excretion. That means we must both decrease the expression of NPC1L1 or hinder its function and we need to increase the expression of ABCG5,G8. Here is my approach:

1) Stop the high dose atorvastatin: by not over suppressing cholesterol synthesis (HMGCoA reductase inhibition) cholesterol synthesis markers will improve and sterol absorption from the gut lumen to gut and bile back to liver will reduce

2) Block the ability of NPC1L1 to pull sterols from the gut lumen into the enterocyte and hepatocyte (from bile). Of course ezetimibe is FDA indicated to do this in patients with marked elevations of phytosterols. The authors of STELLAR comment: "In summary, both rosuva and atorva significantly decreased cholesterol synthesis and increased markers of fractional cholesterol absorption. This study **strengthens the hypothesis that successful lipid-lowering depends on the synthesis/absorption status of the patient.** ----- Because ezetimibe very significantly reduces intestinal cholesterol absorption, but increases synthesis, and because statins have the opposite effect, it would appear that combination therapy would be ideal. In addition, because statin therapy is often long term, measuring sterols may prove to be a useful tool for optimizing therapy and reducing CHD risk." Since low dose statin + ezetimibe is as powerful as high dose statin in reducing apoB (LDL-P) and you would eliminate the statin induced over absorption of noncholesterol sterols, it is bizarre that most choose the high dose statin by itself. If you use a high dose statin, as per the authors, please use ezetimibe with it!

3) Few realize that PPAR-alpha plays a major role in the regulation of NPC1L1. PPAR-alpha agonists like fenofibrate and its active form fenofibric acid suppress NPC1L1 and reduce absorption of sterols. Fibrates have long been used to treat phytosterolemia and now we know why it works. (J. Lipid Res. 2007. 48: 2725–2735). The FDA has approved the combined use of ezetimibe/fenofibrate (gemfibrozil is contraindicated). The fibrate/ezetimibe combo will not only drastically reduce non-HDL-C (as powerful as statin therapy) but also synergistically reduce sterol absorption.

I stopped the Lipitor 80 mg and changed to Vytorin 40/10 mg daily. If the sterol parameters do not normalize I will add fenofibric acid (Trilipix), If LDL-P goes up I would then go to Crestor/Zetia. I should mention that bile acid sequestrants have also been used to treat folks with phytosterolemia, but they have taken a back seat since ezetimibe became available. My new approach will be in high and very high risk patients using statins monotherapy (especially high dose), to check absorption/synthesis markers and adjust therapies. Since I have always been an advocate of low dose statin/ezetimibe (or low dose statin/feno or low dose statin/Niaspan) rather than high dose statin, I probably minimize this problem. My error in this patient was simply assuming since the atorva 80 did such a great job on LDL-P, that all was well! Lastly it is very disturbing that 95% of practicing clinicians and even a high percentage of certified lipidologists have little knowledge of cholesterol and noncholesterol sterol homeostasis. It is even more frightening that many advocate plant sterols rather than stanols to their patients as an adjunctive LDL-C lowering therapy. IF YOU RECOMMEND PLANT STEROLS, I BEG YOU TO MONITOR STEROL ABSORPTION MARKERS. Again please visit www.bostonheartlab.com. **Lastly never forget controlling LDL-P (apoB) is still the # 1 therapeutic priority.**

LIPID CASE 242 Terrible Lipids Normal LDL-P (apoB)

I was asked by an internist about a confusing lipid/lipoprotein analysis in a 52 year old African-American woman. Pt had been under the care of an endocrinologist for at first metabolic syndrome with combined hyperlipidemia and afterwards Type 2 diabetes. Her height is 64.5 inches and weight is 201 pounds giving a BMI of 34. Blood pressure is 110/80. She had been on TriCor and Lipitor 10mg for years and her numbers had not been that bad until recently. She then saw the internist who got me involved. He tried increasing her Lipitor (atorvastatin) then switching her to Crestor (rosuvastatin) 20 mg. She also uses Lovaza at 2000 mg daily. Pt states she is taking her medication daily.

First set of labs on her (4/1999) before medication & before seeing the endocrinologist:
Total cholesterol = 273 TG = 387 VLDL-C = 77 HDL-C = 20 LDL-C = 176 (all in mg/dL)
Non-HDL-C = 253 (nightmarish??)

Most recently (2009) a lipid panel was done at the local lab and not much has changed. An NMR (nuclear magnetic resonance spectroscopy) LipoProfile was also done at LipoScience

TC = 377 TG = 466 HDL-C = 33 LDL-C (direct) = 167 (all in mg/dL)

Total LDL-P = 722 Small LDL-P = 231 (both perfect: the 20th% cutpoint is < 1000 nmol/L)
Large HDL-P = 0.9 (usually > 8 in drug naïve patients) This level is quite low
Large VLDL-P = 3.9 (normal < 0.5) This is an intermediate elevation

The provider was perplexed as there seemed to be a major disconnect between the Lipid Concentrations and the Lipoprotein concentrations. How could LDL-P (and remember 90% or more of apoB is LDL-P) be perfect with such grossly abnormal lipid concentrations including non-HDL-C. I was asked if I had ever seen anything like this before and for an explanation of what was "throwing off the results?" Should we believe the lipid or lipoprotein concentrations?

DAYSRING DISCUSSION

So Lipidaholics: did you look at the above very closely at all of the information above? How many are now thinking a major lab error was made or how many are thinking both reports are accurate and there is a very good explanation for the "disconnect?" **PLACE YOUR BETS!** Are there any other lab tests that might help clear this up? Since atherosclerosis is a lipoprotein mediated disease (the particles are the culprits that deliver the sterols to the intima), when you look solely at the lipid profile you have to be asking yourself using lipid numbers what **lipoproteins** are trafficking the TG and cholesterol. Of course only atherogenic particles (apoB-containing) serve as illegal sterol dumpers and result in atherosclerosis and as you all know it is usually particle number (especially LDL-P) that drives the apoB particles into the arterial wall. As my readers know often there are folks with ugly (abnormal) lipid concentrations but normal lipoprotein (apoB and LDL-P) concentrations and have little CHD risk. Is this woman one of them? If you are an LDL-P believer you will likely say I do not care if the LDL-C is high in the face of an absolutely perfect LDL-P. If you are a provider stuck in the last millennium you would dismiss the NMR LDL-P report and bet the patient's life on the lipid profile. Unless there is some condition that would easily explain the marked discordance. Finally, would there be any value in ordering an apoB (in the face of a normal LDL-P)? Can apoB ever be high in the face of a normal LDL-P?

Theoretically the liver produces apoB-containing TG-rich particles also carrying cholesterol, cholesteryl ester (CE) and phospholipids that upon lipolysis [hydrolysis of TG by lipoprotein lipase (LPL)] reduce in size and become smaller VLDLs and even IDLs. The apolipoprotein on a VLDL and chylomicron (another large TG-rich particle) that serves as a ligand for LPL is apoC-II. ApoC-II deficiency (very rare) is associated with no lipolysis and the patients have massive hypertriglyceridemia (HTG) as their chylomicrons and VLDL cannot empty. As lipolysis proceeds, the resulting particles, which have lost some TG and surface phospholipids are smaller than their VLDL or chylomicron parent and they are called remnant lipoproteins. Once they have delivered their TG, their function is complete and they, because of their surface apoB 100 and/or multiple copies of apoE are cleared by hepatic LDL receptors (LDLr). Of course chylomicra have no apoB100 and are cleared because of their high apoE content. In hepatic sinusoids some of the smaller VLDLs and the IDLs as they are about to be endocytosed are exposed to hepatic lipase – those particles undergo additional hydrolysis of surface phospholipids and core TG and become even smaller in size - they are of course now called LDLs. Only apoB-100 remains on the LDL particle - all of the other surface apolipoproteins including E should be gone. One reason the LDLs have a much longer half-life than IDLs and VLDLs (days compared to hours) is they have no apoE for the LDLr to grab. LDLs only have a single apoB100 for the LDLr to recognize. Of course the longer TG-rich VLDLs hang around (the longer their plasma residence time – conditions where delayed lipolysis is present – such as insulin resistance) cholesteryl ester transfer protein (CETP) swaps CE for TG with HDLs and LDLs. Thus if VLDLs are allowed to hang around (insulin -resistant states, VLDL-C will go up and up (as they in effect steal the CE from HDLs and LDLs) – of course LDL-C and HDL-C might go down as their CE now resides in the VLDLs and chylomicra. Please note that as VLDL-C goes up, HDL-C and LDL-C goes down, non-HDL-C (the ultimate NCEP goal of therapy) also rises

As you know the NCEP way to evaluate VLDLs and chylomicra and especially their remnants is to look at VLDL-C.. Using the Friedewald formula, VLDL-C is calculated as TG/5 (if TG are 150 mg/dL then the VLDL-C is 30 and that was considered OK by NCEP ATP-III. In this person the baseline VLDL-C was very high at 77 mg/dL. What if there was a condition where smaller VLDL remnants and IDLs were not converted to LDLs or were not rapidly cleared by LDLr – such patients would accumulate these particles. One could hypothesize that a defective type of apoE would prevent those particles from being recognized by LDLr thereby delaying rapid plasma removal. Also lots of abnormal apoE might knock off or interfere with apoC-II and other surface apolipoproteins from thereby preventing TG-rich particles from attaching to and activating LPL, drastically slowing conversion of the apoB100 remnants and IDLs to LDLs. Such patients would have increased levels of remnants and IDLs but very few LDLs. Lots of IDLs and VLDLs would obviously be carrying lots of cholesterol and lots of TG. Such patients therefore would have both very high TC, LDL-C and VLDL-C levels. However, why would such folks not making LDLs and

having normal or subnormal LDL-P have a very high LDL-C???? The answer is in totally understanding the following formula:

TC is simply the cholesterol that is trafficked in all of the lipoproteins that exist in a dL of plasma:
 $TC = HDL-C + VLDL-C + chylomicron-C + IDL-C + LDL-C + Lp(a)-C$

Of course no regular labs spin (centrifuge) out the lipoprotein particles or directly assay any of the above lipid measurements except for TC and HDL-C. Labs separate the apoB and apoA-I particles by precipitating the apoB particles. They then assay the cholesterol in the remaining particles (apoA-I particles) and that is the HDL-C value. VLDL-C is calculated using the Friedewald formula of $TG/5$. VLDL-C is actually VLDL-C + chylomicron-C. Dr. Friedewald assumed that all of the TGs are in VLDLs and normal VLDL lipid composition is 80% TG and 20% cholesterol. Next is realizing how labs deal with or report:

$IDL-C + LDL-C + LP(a)-C$ This is what VAP calls your real LDL-C. Most practitioners look at LDL-C and simply assume it is the cholesterol trafficked in all of the LDLs that exist in a dL of plasma. To be accurate it is the cholesterol trafficked in all of the IDLs, LDLs and Lp(a) particles that exist in a dL of plasma. The point I am making is that when you look at LDL-C you are really looking at all of the above 3 cholesterol-trafficking particles. However most folks have no Lp(a)-C and most folks have extremely few IDL particles (normal half-life 1-2 hours). In most people IDL-C and Lp(a)-C contribute almost nothing to LDL-C. Of course guidelines want us to assume if LDL-C is high, apoB or LDL-P is high and treatment is needed and LDL-C will serve as the goal of therapy. I wish it were that simple.

So what if you just happen to have a patient with a very high LDL-C and perfect LDL-P (as is present in the case under discussion). Before I would assume there is no CHD risk based on the normal LDL-P (apoB), I would want to know what is the IDL-P and total VLDL-P. If you have too many IDLs carrying a lot of cholesterol and cholesteryl ester as well as some TG and had lots of VLDLs carrying lots of TG and CE you might have a very high LDL-C and Non-HDL-C even though your LDL-P and apoB are fine. The very high LDL-C $[(LDL-C + IDL-C + Lp(a)-C)]$ is driven by the IDL-C, not the cholesterol that is in the LDL particles. In this case the high LDL-C is caused by a normal LDL-C with a high IDL-C.

Let' kill the suspense: You now all realize that the above description (defective apoE, lots of remnants and few LDLs) defines patients with Fredrickson Type III hyperlipoproteinemia: the one lipoprotein disorder apoB and LDL-P lets you down! The incidence of Type III is 1 per 10,000-20,000 people. It is almost never present in childhood and rarely before menopause in women. These patients often have the apoE2/e2 alleles and when obesity or T2DM or hypothyroidism occurs they have overproduction and impaired clearance of their remnants (small VLDLs and IDLs): the Type III patients have high VLDL-P, IDL-P but normal LDL-P: lipid-wise, TC, VLDL-C and LDL-C are all high (but the high LDL-C is explained because of the elevated IDL-C and high IDL-P with a normal LDL-P). Screening folks with apoE testing is of no help because only an extreme minority of patients with e2/e2 isoforms ever develops lipid abnormalities and of course treatment is based on the lipid/lipoprotein numbers not the Fredrickson classification. On the NMR when I see extremely high IDL-P and normal LDL-P, I have my diagnosis. Very recent data from the very large EPIC Norfolk epidemiological trial was just published and the conclusion is: "Despite the availability of extensive lifestyle data, the results from the present analysis of the largest prospective cohort study to date with ApoE genotype information indicated that CHD risk was not associated with ApoE genotype after controlling for a variety of cardiovascular risk factors (Arch Intern Med. 2009;169(15):1424-1429).

So I asked to see the rest of the NMR LipoProfile: and the results confirm my suspicion:

IDL-P = 269 nmol/L Extremely high value [normal is very low (5) or even zero when fasting]

Large VLDL-P = 3.9 Medium elevation: $n < 0.5$) VLDL-P = 63.2 (very high) Small VLDL-P = 70.5 (very high) Total VLDL-P ~ 134 (very high).

Of course medium and small VLDLs reported by NMR analysis are actually VLDL and chylomicron remnants. This person has almost all of his cholesterol in VLDLs (especially in the smaller, remnant species) and IDLs. Since these particles exist in significantly excess numbers (due to their delayed lipolysis and LDLr removal, they enter the arterial wall and atherogenesis occurs.

Most lipidologists are taught then Type III should be thought of in patients with combined hyperlipidemia when TC is similar to or no more than twice the TG level. In other high TG conditions (most commonly diabetes) the TG is > than the TC and in the rarer Type I and V the TG is way more than the TC. Notice in this patient the baseline and on therapy elevated TG and elevated TC are within a hundred points of one another. In reality, this method of making the diagnosis of Type III is quite crude and is obviously not the definitive test because of the readily available particle quantification tests.

Dr apoB better known as Alan Sniderman (see Journal of Clinical Lipidology (2007) 1, 256–263 for a thorough discussion of diagnosing Type III: although being Canadians they use molar concentrations in the paper) suggests the following algorithm to spot Type III patients (personal communication from Dr S): If TG are > 130 mg/dL, divide TG by apoB (both in mg/dL). If that number is < 8.8, then look at the TC/apoB ratio and if it is > 2.4 you likely have a Type III. If < 2.4 you have familial hypertriglyceridemia. If the TG/apoB ratio is > 8.8 you are dealing with a Type I or V. In another paper by different authors, an apoB/TC ratio in mg/dL of < .38 is a valuable tool (Clin Chem 2005;51:904-907).

Remember above I asked the question: Can apoB ever be high in the face of a normal LDL-P? Type III is one of the conditions. Familial hypertriglyceridemia is another. You may be thinking: if the patient has lots of remnants and IDLs, even though IDL-P is fine why is not apoB high? This is very important: Greater than 90-95% of apoB particles are LDLs. Thus even in a circumstance where VLDL-P and IDL-P are high, but LDL-P is normal, apoB will not be high. Notice on the NMR report total VLDL-P is usually in the 10-30 nmol/L range and IDLs in the 0-10 nmol/L range: whereas normal LDL-P is in the 1000-1300 nmol/L range. Thus apoB is another way of looking at LDL-P. When you look at non-HDL-C please remember it like LDL-C is simply a surrogate for LDL-P (non-HDL-C is simply a better surrogate). Unfortunately there are many patients where discordance exists between non-HDL-C and LDL-P (apoB).

The NMR LipoProfile report in this patient also gives us the following breakdown of on-treatment HDL-P: (all in umol/L)

Large HDL-P = 0.9 (low),
Medium HDL-P = 0 (low)
Small HDL-P = 34.3 (high)
Total HDL-P = 35.2 (normal).

Thus although this woman has more than enough HDL particles her on-treatment HDL-C is low at 33 mg/dL. The explanation for this discordance is that she has very few large and lots of small HDLs. About 80% of total HDL-C is trafficked in the larger HDL species. The disconnect between HDL-C and HDL-P is typical of someone on a fibrate or fibric acid. Thus looking at the low HDL-C one might be worried, but by utilizing and looking at total HDL-P maybe there is no HDL-related worry in such patients? With respect to HDL parameters, never judge a fibrate by what it does to total HDL-C but rather total HDL-P. This phenomenon was well described in the VA HIT trial where gemfibrozil did very little to HDL-C but dramatically raised HDL-P (most of the small variety). Fibrates induce apoA-I and apoA-II production (increasing HDL-P) but because they

induce hepatic scavenger receptors B1 (SR-B1) the large HDLs are delipidated and converted to smaller HDL species. The HDL-P increase is usually superior to the HDL-C increase.

Standard therapy for Type III is a potent statin plus fibrate or fibric acid. In this case, I would raise the Crestor to 40 mg daily, continue the fibrate (some would switch to fenofibric acid or Trilipix to be on FDA label - but Trilipix has not been tested with the largest statin doses). If the FDA approves the rosuvastatin/fenofibric acid combination tab I do not believe 40 mg rosuvastatin will be one of the available strengths. I would also add 4000 mg of Lovaza to this patient as there are still a lot of TG and TG-rich lipoproteins floating around. 2000 mg of N-3 FA (Lovaza) does nothing to TG levels. There is a threshold effect to reduce TG and 4000 mg are needed to impact TG. Using less Lovaza to treat TG-rich lipoproteins is silly. Lots of providers do not realize this. Lastly if this proposed regimen does not correct everything, there is solid data that ezetimibe also reduces both chylomicron and VLDL remnants (presumably by upregulating further LDL receptors and reducing chylomicron synthesis).

LIPID CASE 243 Unusual TG elevation

Lipidaholics: Welcome! What a case I have for you this week. It is a disease that until you know it exists you will miss it every time. However once you are taught it or have a case yourself, you will never miss it again. I've presented this to a bunch of smart lipid buddies and all struck out. Only one colleague got it and he is not an MD but rather a PhD. Lets see how you do. Please read the history carefully and scrutinize the laboratory findings for some obvious clues.

I received this case from a clinician in San Antonio who did make the diagnosis and sent it my way to see if I could also do so: fortune was with me and I correctly nailed it. Here we go: a 58 year old white male, hypertensive, frequent blood donor with a long history of elevated TG. He uses alcohol 2-3 times a week. Weight 164, Height 66 inches, BMI is 26.5. Only current medications are Crestor 10mg daily, lisinopril 10mg daily and aspirin 81 mg. This patient has been treated for years by cardiologists for "high triglycerides." Statins did not help. Niacin, fibrates, Omega-3s, etc also failed to reduce the high TG. Even on a low carbohydrate diet his TG actually went up. None of his triglyceride treatments had any effect on his triglyceride levels! Over the last several years only once did the TG ever come back as perfect with a reading of 55 mg/dL: that assay was done by Berkeley Heart Labs. That excellent level was looked at very skeptically as multiple tests from other conventional labs and LipoScience always revealed a very high TG.

Lab analysis:

(Fasting) TC = 127 LDL-C = 10 TG = 381 HDL-C = 41 Non-HDL-C = 86

Total LDL-P = 1064 nmol/L (perfect – at the 20th percentile population cutpoint)

Small LDL-P = 927 nmol/L (~ 60th percentile)

Large LDL-P = 132 nmol/L (low)

Large VLDL-P = 0 nmol/L (perfect)

Medium VLDL-P = 3.3 nmol/L (low)

Small VLDL-P = 29.1 nmol/L (low)

IDL-P = 5 nmol/L (normal)

Total HDL-P = 41 umol/L (excellent)

Large HDL-P = 5.0 (slightly low 30th percentile)

Medium HDL-P = 3.8 (50th percentile)

Small HDL-P = 32.2 (high 95th percentile)

glucose 90, A1c 5.7 TSH 2.27 CPK 117 Urine Micro albumin negative

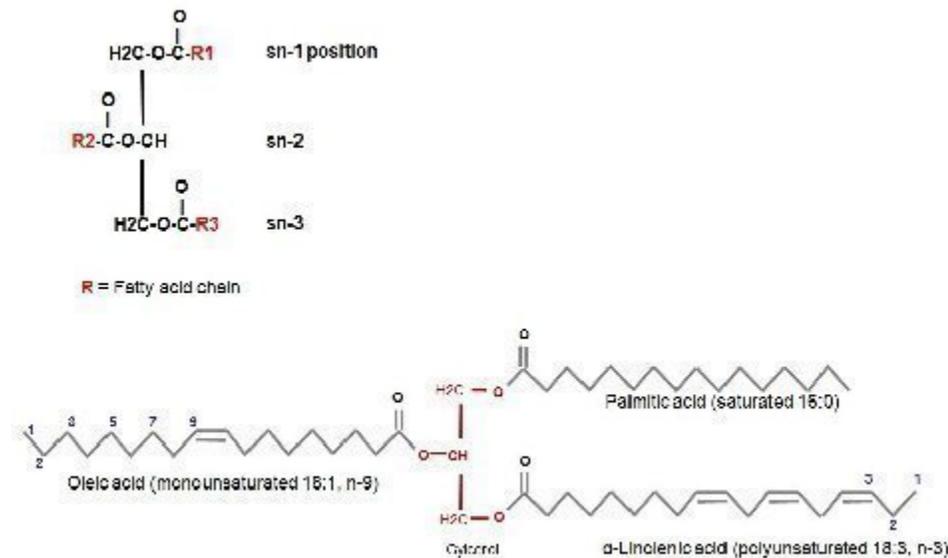
DAYSRING ANALYSIS

Pretty amazing case: With the information provided I'll assume he has moderate CHD risk and is seemingly well below his LDL-C and non-HDL-C goal. Likely his LDL-P was significantly higher prior to the Crestor Rx. He is also below his LDL-P goal for a moderate risk person (~1300 nmol/L). We cannot do Framingham Risk scoring as he is on medication and FRS is only a validated tool in drug naive patients. So what conclusions can one draw from the high TG level? Also it is interesting that he has never been able to find a physician using the standard TG-lowering therapies capable of reducing his TG.

First let's review a little TG biochemistry. Triglycerides (TG) should actually be called triacylglycerols (TAG). TG or TAG are molecules with a glycerol (a carbohydrate) backbone to which are attached three acyl groups. Phospholipids (PL) are also derived from glycerol. If glycerol is not used to synthesize TG or PL it enters gluconeogenesis or glycolysis pathways. It does that by being converted into glycerol-3-phosphate using an enzyme called glycerol kinase. Acyl groups are derived from hydrolyzed fatty acids (which are carboxylic acids or -COOH). When an acyl group is attached to an -OH on a glycerol, the process is called esterification. Esterification of glycerol will produce TG or PL. Glycerol with one acyl group is a monoacylglycerol (MAG), those with 2 acyl groups a diacylglycerol (DAG) and of course those with 3 a triacylglycerol or triglyceride molecule. There are very specific enzymes involved in each of the three esterification steps. The most well known is the enzyme that converts DAG to TAG and it is called diacyl-glycerol transferase (DGAT). Drugs that inhibit DGAT would reduce TG assembly (fibrates, niacin, N-3 fatty acids). Three FA acyl groups supply considerable energy and thus TG serve as an energy supplier for muscle or energy storage molecules in adipocytes. Enzymes capable of de-esterifying glycerol esters (TAG, DAG) are called lipases. The most potent triglyceridases (a lipase that hydrolyzes TG) that humans have are lipoprotein lipase (LPL) primarily expressed in adipocyte and muscular vascular beds and hormone sensitive lipase (now called triglyceride lipase) expressed in adipocytes. The lipases ultimately convert TG or TAG to FA and MAG. This de-esterification of the molecule is required as TG as a whole molecule cannot be absorbed into the enterocyte cell membranes or those of other cells throughout the body: of course FA can pass through membranes using fatty acid binding proteins. TG present in food are hydrolyzed almost immediately by salivary, gastric and ultimately pancreatic lipases. In the plasma LPL hydrolyzes the TG carried in the TG-rich lipoproteins (chylomicra and VLDLs). Please refer to the figure below showing TG structure. Each of the carbons in the glycerol molecule are numbered using the "stereospecific numbering (sn) system." Thus one FA acyl group is attached to the -sn1 position, the second (middle carbon) to the -sn2 position and the third to the -sn3 position. Believe it or not the positioning of the acyl groups to the various sn positions has great biologic importance but that is beyond this discussion. Providers are not taught to consider which FA acyl groups are in a given patient's TG. Do your TG carry 3 saturated fats (hope not), monounsaturated?, polyunsaturated? N-3FA? or combinations of all. As one might imagine there are thus multiple types of possible TG molecules. A TAG mixture with just five different fatty acids can therefore exist as 105 different TAG molecular species (TAG-MS) according to differences in positional composition. What would you call a TG that consists of a saturated fat (say palmitic acid: an 16 carbon fat with no double bonds), a monounsaturated fat (say oleic acid: an 18 carbon fat with one double bond at the n9 position) and a polyunsaturated fat (say linolenic acid: an 18 carbon fat with three double bonds, the first of which is at the 3 position)? That mouthful would be: 1-palmitoyl 2-oleoyl 3-linolenoylglycerol or in short-hand POL (where P is palmitic acid, O is oleic acid and L is linolenic acid).

Conventionally when describing at which carbon the first double bond exists we count backwards from the terminal methyl group (end) of the FA acyl chain - so if the first double bond is at the third carbon from the end it is called an omega-3 FA (omega being the last letter in the Greek alphabet) or as is now more correct an n3 FA. Omega-3 does not mean the FA has three double bonds (although it might - it means the first double bond is at the 3rd carbon). Oleic acid has its first double bond at the 9th carbon and is an omega-9 or N9 FA. Linoleic acid (not to be confused

with the n3 FA linolenic acid mentioned above) is an omega-6 or n6 FA. EVERYONE GOT ALL THAT???? (Nutrition Research Reviews 2009;22:3–17).



One may quickly assume because of the high TG, we may be dealing with insulin resistance, but he does not meet all of the metabolic syndrome criteria (has hypertension and seems to have high TG - but no other criteria. Other parameters that suggest IR is a mild reduction of large HDL-P and a slight increase in small LDL-P. VLDLs look great and usually with IR there is increased large VLDL-P. Glucose is 90 and A1C is above 5.

Note the LDL-P is perfect but then why is the LDL-C so very low? Is it possible to have ~1000 nmol/L of LDL-P with an LDL-C of 10 mg/dL. At first glance, the obvious answer seems to be that his LDLs are not only small they have an abnormal core composition and are carrying TGs. If LDLs are cholesterol-depleted it will take more LDLs to traffic a given level of LDL-C compared to LDL particles are not cholesterol depleted. The conditions that cause LDL particles to be cholesterol-depleted are small size, abnormal core composition with a preponderance of TG (normally an LDL has 80% cholesteryl ester and 20% TG) and we are also now finding out that statin therapy can in some folks deplete the LDL core of its CE creating a cholesterol depleted particle. One might surmise that all three may be at play in this patient. The patients with the most cholesterol depleted particles are those with small particles and increased TG in the core of those particles. However, the LDLs in this man would have to be EXTREMELY cholesterol-depleted LDL particles. I am becoming a “doubting Thomas.”

Let's take a close look at the LDL-C. What if the reported (calculated) LDL-C is a lab error? How could one make an error with LDL-C when using the classic Friedewald formula?

$$\text{LDL-C} = \text{TC} - [\text{HDL-C} + \text{VLDL-C}] \text{ where VLDL-C is also a calculation: } \text{TG}/5.$$

$$\text{In this case } \text{LDL-C} = 127 - [41 - 381/5] = 127 - [41 + 76] = 121 - 117 = 10 \text{ mg/dL}$$

Thus is LDL-C has to be 10 mg/dL!!!! Everyone agree? Direct LDL-C assays are totally non standardized with values all over the place and in general should never be relied on but in this case I suspect the direct LDL-C would not be 10 mg/dL. The LDL-C of 10 mg/dL (the 2nd percentile population cutpoint is discordant (does not agree with) with the LDL-P of 1000 nmol/L

(approaching the 20th percentile population cutpoint). To understand the concept of population cutpoint values see www.lipidcenter.com - click on professionals and scroll down to Lipid and Lipoprotein study materials.

The non-HDL-C of 86 (2nd percentile) is also discordant the LDL-P (20th percentile). Maybe in this case we should discard the LDL-C and the non-HDL-C or should we ignore the LDL-P. How do we explain this disconnect? However in a patient with this degree of risk both the lipid and lipoproteins concentrations are at goal so who really cares? One of the nice things about non-HDL-C is that TG do not figure into the calculation (TC – HDL-C) as they do with LDL-C.

Another warning signal that something bizarre is going on is why is the HDL-C normal in the face of such a high TG? Typically with such high TG, cholesteryl ester transfer protein (CETP) moves TG for cholesteryl ester (CE) from TG-rich lipoproteins like VLDLs to the typically CE-rich HDLs and LDLs. As HDLs lose their CE and instead fill with TG, HDL-C usually drops. One could theorize in this case the HDL-C originally was low but maybe the Crestor helped raise it -- yet with a TG of 381 mg/dL, HDL-C should still be low. So lipidologists should be getting suspicious that something very strange is at play: a totally not believable LDL-C and an unusually normal HDL-C in the face of very high TG. When labs tests do not make sense, maybe, just maybe the results are not correct.

When I first saw the case my first train of thought was the patient has TG-induced cholesterol depleted particles which can help explain high LDL-P in the face of a normal or even low LDL-P. Then, as always I carefully looked at every single NMR parameter. I always stress that you should look at VLDLs especially when TG are abnormal. As soon as I saw that the VLDL-P in this patient were extremely low I knew the hypertriglyceridemia was a false positive or as it is called pseudohypertriglyceridemia. As almost always coronary risk revolves around the lipoproteins that traffic the lipids. You must ask yourself, what particles are carrying the large amount of TG???? - Normally in someone with a TG of 381 mg/dL, we see either lots of VLDL particles or increased numbers of large VLDL-P. Yet in this case all of the VLDL-P, IDL-P and LDL-P numbers are very good and indeed with respect to the VLDLs the numbers are on the "very low" side -- so you have to figure out where the heck are the TG hiding???? They have to be somewhere? Yet, there are very few IDLs and there is no way normal numbers of LDLs and HDLs are trafficking 381 mg/dL of TG. Could this be a false positive TG level? If so what causes that? The answer is indeed a condition called pseudohypertriglyceridemia -- in other words the TG is reported by the lab as very high but in reality it is not. It seems like only a few lipidologists have heard of PSEUDOHYPERTRIGLYCERIDEMIA. (Clin Chem 1995;41:619-620 and Postgrad. Med. J. 2008;84:552-554 as well as the paper cited below).

Lipidologists should have some basic knowledge of how labs assay various lipid and lipoprotein concentrations. So when you send serum off to the lab how are TG analyzed? Lipoprotein lipase is added to the serum and the de-esterification process begins. Before you know it the TG are changed into collections of FA and glycerol molecules. The lab runs an assay on glycerol concentration and report the glycerol level as TG levels. Obviously the more TG molecules a patient has the more glycerol will be generated in the lab analysis. In essence labs measure the glycerol component not the FA of the TG molecule. Unfortunately there are a few patients out there who have very high glycerol levels. If you take their serum and analyze it for TG, the reported level will be extremely high and have no correlation with what their actual TG level is. If you have a patient with high glycerol levels who have perfect amounts of actual TG molecules in their plasma, the reported TG level will be very high and it is in effect a false positive TG level or pseudohypertriglyceridemia. Wow: **The lab test we use to measure TG is in fact a test that measures glycerol.** Here are the actual TG assay steps performed by Atherotech (almost all other labs do something similar). The glycerol is phosphorylated by ATP with glycerol kinase to produce glycerol-3-phosphate and ADP. Glycerol-3-phosphate is oxidized to dihydroxyacetone phosphate by glycerol phosphate oxidase producing hydrogen peroxide. In a color reaction

catalyzed by peroxidase, the H₂O₂ reacts with 4-aminoantipyrine to produce a red colored dye. The absorbance of this dye is proportional to the concentration of TG in the serum.

Guess what: there is a human condition resulting in high plasma glycerol levels and it is called glycerol kinase deficiency (GKD) which *is an X-linked recessive disorder. There are two types, an isolated form and a complex form. The clinical and biochemical phenotype of isolated GKD may vary from a life-threatening childhood metabolic crisis to asymptomatic adult 'pseudohypertriglyceridemia', resulting from hyperglycerolemia. The clinical manifestations such as an altered consciousness and seizures in isolated GKD patients can be classified as glucose deprivation symptoms precipitated by catabolic situations such as poor oral intake, intercurrent illness or exercise.* (italics are from J. Inherit. Metab. Dis. 23 (2000) 529-547). Normally as a substrate for gluconeogenesis, glycerol is converted into glycerol-3-phosphate by an enzyme called glycerol kinase. Patients who have a glycerol kinase deficiency have very high plasma glycerol levels and of course falsely reported high TG levels. To make the diagnosis glycerol can be assayed in the urine (glyceroluria) and it would be quite high.

The following labs do standard triglyceride assays (reporting total triglycerides, not using blanked triglycerides) using lipoprotein lipase as the first step to generate glycerol and free fatty acids: Quest, LabCorp, all office labs, and LipoScience and Atherotech (VAP). Interestingly, Berkeley does a "blank" in their assay, which controls for any free glycerol which is present before lipolysis. Remember in this case the patient's Berkeley Panel reported a TG level of only 55 mg/dl.

Let's go back and recalculate the LDL-C using the correct TG level reported by Berkeley Labs of 55 mg/dL instead of the one using the erroneous TG to calculate VLDL-C.

LDL-C = TC - [HDL-C + VLDL-C] Now let's plug in a TG of 55 instead of 381 mg/dL.
Wow the VLDL-C changes from 76 to 11. Look what happens to LDL-C!
LDL-C = 127 - [41 - 55/5] = 127 - [41 + 11] = 127 - 52 = 75 mg/dL.

Thus what seemed to be at first glance (LDL-C of 10) a case of hypobetalipoproteinemia is not because the LDL-C is actually 75, not 10 mg/dL. Of course the LDL-P was never at hypobetalipoproteinemia levels. The LDL-C and LDL-P are in reality are a lot less discordant than they were at first glance (but they are not perfectly concordant showing why we should always rely of LDL-P). Once you realize the TG in this case are in fact a lab error, which can be ignored, proper management returns to normalizing LDL-P. Well, the LDL-P is at goal on Crestor so nothing else is needed. Think of all the wasted time and effort over years in repeating lipid and lipoprotein levels and subjecting this man to every lipid drug on the planet likely in high doses. Talk about potential toxicity, cost and no benefit!!

So with respect to LDL-C and TG, not everything is as it may seem. IT IS THE PARTICLES!

To see several great slides depicting FA and TG structure go to www.lipidcenter.com Click on professionals. Scroll down to the lipid/lipoprotein section and open the pdf called FA and TG structure. Scroll down further and open the Power Point slide set on the same topic. These are excellent study resources.

LIPID CASE 244 Cannot Control the Triglycerides

A question: if you could only have one test to ascertain risk for CAD (in our insulin resistant society) would you rather have an LDL-C or LDL-TG concentration? Think long and hard before you answer and then keep reading. I was asked about the following case: a young man, age 33, with no cardiac history and no classical risk factors aside from family history. Notably his father had an MI and stent at age 59, but he was a

lifelong smoker with poor eating habits, diabetes and obesity which the patient is quick to point he does not have. Are patients always truthful with respect to reporting lifestyle? A standard lipid profile as part of a general physical was done in June, 2009:

6/9/2009: Wt 185 lbs (BMI 26.5), BP 114/70. Already exercising regularly, but patient admits could be better with diet (contradistinction to what he said above).

TC = 207, TG = 211, HDL-C = 29, VLDL-C = 42, LDL-C = 136 (all in mg/dL)
Non-HDL-C = 178 mg/dL TC/HDL 7.1 TG/HDL-C = 7.2

The provider instructed him on additional dietary change, and increased exercise, and had him come back in 3 months, for lipid panel and an NMR LipoProfile. To the patient's frustration (because he has worked very hard on the dietary and lifestyle changes), things actually look a little worse:

9/17/2009: Weight about 175 (10 lb drop - but this is self reported not measured on a scale)

TC 215, TG = 177, HDL-C = 29, LDL-C = 151 Non-HDL-C 186 (all in mg/dL)
Total LDL-P 2270 nmol/L (this is > 95th percentile population cutpoint)

For those who do not understand the concept of population percentiles please go to www.lipidcenter.com Click on professionals Scroll down to lipid and lipoprotein study materials and click on Framingham Offspring cutpoints

Small LDL-P 1882 nmol/L (thus most of the LDLs are Pattern B)

Large HDL-P = 0 umol/L (obviously very low)

The full report obtainable when results are done at LipoScience (not LabCorp) would also report medium and small HDL-P: The sum of small, medium and large would give us total HDL-P

Large VLDL-P 0 nmol/L

Likewise the LabCorp NMR version does not report small and medium VLDL-P (remnants)

The provider notes that since we don't know what his initial LDL-P was, we can't really say whether this second set of numbers is actually *worse* than the first set (meaning although the lipid values are no better it is conceivable the LDL-P is somewhat improved), but to the patient (and the provider) the lack of change is discouraging. The question is - how to treat him? The clinician notes that NCEP ATP- III would actually not even count his father's CHD as a risk factor, since by their definition, the age cutoff for premature heart disease is 55 for males; thus the patient has only 1 major risk factor with his low HDL-C. Being in the 0-1 risk factor category he does not qualify for Framingham Risk Scoring and he is low risk and thus already is 'at goal' for LDL-C (<160) and non-HDL-C (< 190 mg/dL).

Of course, the provider is perplexed because the patient's LDL-P is above the 95th percentile per Framingham Offspring, and regardless of the NCEP recommendations he is not terribly happy to "do nothing." He asks me where is the data that would support putting a 33 year old on a statin for the next 50 + years? And what, truly, is the best "lifestyle" to reduce the LDL-P?

DAYSRING DICSUSSION

Using NCEP the provider is right this man does not qualify for Framingham Risk Scoring. I for one hope NCEP dumps or radically improves this outdated way of evaluating risk. It was developed long before we became a very insulin resistant society. Family history, TG, non-HDL-C, apoB are all ignored by FRS. Even though he does not meet all of the needed criteria for the Metabolic Syndrome (or maybe he does as I was not provided actual waist size, glucose or BP), however I smell insulin resistance (IR) in this patient:

High TG, Low HDL-C, FH of T2DM, Increased Small LDL, Lack of Large HDL species (in a drug naive patient).

He was seemingly successful with lifestyle on the scale but not on the lipid profile: I have to wonder if the ten pounds is in his imagination or not. If you look closely at the history the patient was adamant he did not have his dad's poor nutrition but then admits he could be better with his diet. What does exercising regularly mean? Not using the remote controller or is he really doing aerobics or cross training? All we can do is continue the lifestyle advice and record weight.

Whatever - the clinician feels he has a dilemma as the extremely high LDL-P portends very high risk and would call for serious therapy despite 8 year old NCEP advice that lifestyle will suffice. First we must ask is the extreme LDL-P real? The man has a classic TG/HDL axis (high TG, low HDL-C) which is so characteristic of IR and T2DM and high CV risk as well as high LDL-P. (Szapary and Rader's classic paper: *Am Heart J* 2004;148:211-21). Those authors write despite the usually unremarkable LDL-C in these patients combination therapy is often required to reduce CV risk. The 2008 ADA/ACC consensus statement believes apoB or LDL-P is needed to make pharmacotherapeutic decisions in these patients. We do know that the more insulin resistant a patient is, the higher will be the LDL-P. As one goes from 2,3,4 and 5 components of the metabolic syndrome LDL-P raises significantly whereas LDL-C does not change. As hs-CRP (a marker of IR) rises (*Circulation* 2003;107:391-397), LDL size reduces (*Clin Lab* 2002;48:171-180) and LDL-P rises (*Circulation* 2006;113:20-29).

We have been though the multiple aspects of lipoprotein pathology in these TG/HDL axis cases before but this malady is so common it needs repeated review. A physiologic TG is 10-70 mg/dL with a mean of 30 mg/dL. Any IR person with TG greater than that is subject to the pathologic consequences of TG-rich lipoproteins. Rising TG are typically a result of a high glycemic diet in patients with the underlying genes for IR. Typically as the hepatic TG pools increase, there is increased lipidation of apoB and overproduction of

VLDL particles and/or increased TG content of the VLDLs (large VLDLs created). Interestingly this patient has no large VLDL-P which is typically increased in IR patients. Because this NMR was done at LabCorp it is a truncated report. Had the analysis been reported by LipoScience we would also have medium and small VLDL-P levels which I suspect would be increased with the TG of 211 and 177. His lifestyle may have eliminated large VLDL production. Thus his elevated TG must be in the medium and small VLDL species. When TG are high there is likely to be increased cholesteryl ester transfer protein (CETP) activity and the VLDLs will start exchanging their TG molecules on a one for one basis for cholesteryl ester (CE). The VLDL-C will rise (as the VLDL is in effect robbing the CE from both LDLs and HDLs) - even worse the CE is going from non-atherogenic HDL particles into apoB particles (VLDL-P). In effect, CE that was not atherogenic (because it was in an HDL) just became atherogenic by transferring to an apoB particle). Of course the CETP activity results in decreases the CE in the core of the LDLs and HDLs while at the same time increasing the core TG in HDLs and LDLs.

The now still large TG-rich, CE poor HDLs enter the hepatic circulation and are exposed to hepatic lipase: core TG and surface phospholipids are hydrolyzed and the HDL size shrinks dramatically. Some apoA-I invariably frees up and is prone to renal excretion, further worsening HDL-C and dramatically lowering apoA-I and HDL-P (powerful predictors of risk). If you read this paragraph slowly and thoroughly you now understand why in drug naive patients, the reduced large HDL-P is such an important predictor of risk: the excess TG sent over from the apoB VLDLs and LDLs lead to increased HDL catabolism. In reality IR patients who lack large HDL-P (almost all of their HDLs will be small) almost always have very high LDL-P and VLDL remnants which have the potential to crash the artery wall enabling atherogenesis. If you see the big picture, the risk related to a lack of large HDL is high apoB and proper way to reduce risk in IR patients with low HDL-C is to blow away apoB and LDL-P (exactly what the ADA/ACC consensus statement recommends for IR patients with low HDL-C). Patients with very low HDL-C who do not have high apoB tend not to be at CV risk. The high TG is a big warning sign of elevated apoB and LDL-P. **THUS THE LACK OF LARGE HDL IN DRUG NAÏVE PATIENTS IS A RISK FACTOR IN PATIENTS WITH ELEVATED TG BECAUSE OF THE HIGH APOB, NOT BECAUSE LARGE HDLS ARE SOMEHOW GOOD. YOUR THERAPEUTIC MISSION IS TO REDUCE APOB NOT INCREASE LARGE HDL.** Did I yell that loudly enough! All HDLs are good if they are functional and no HDLs are of value if they are dysfunctional. HDL functionality has nothing to do with LDL size.

MUST READING: A fascinating study published 5 years ago should be mandatory reading for those who deal with IR patients. It is called the Ludwigshafen Risk and Cardiovascular Health Study (Circulation. 2004;110:3068-3074). The conclusion is: "Alterations of LDL metabolism characterized by high LDL-TG are related to CAD, systemic low-grade inflammation, and vascular damage. High LDL-TGs are indicative of CE-depleted LDL, elevated IDL, and dense LDL." **LDL-TG (defined as > 54 mg/dL) may better reflect the atherogenic potential of LDL than LDL-C.** They studied 739 subjects with stable angiographic CAD and 570 matched control subjects in which CAD had been ruled out by angiography. The association of LDL triglycerides

(LDL-TGs) (odds ratio [OR], 1.30; 95% CI, 1.19 to 1.43; P <0.001) with CAD was stronger than that of LDL-C (OR, 1.10; 95% CI, 1.00 to 1.21; P = 0.047). **The predictive value of LDL-TG for CAD was independent of LDL-C.** LDL-TG correlated with apoB better than did LDL-C. In a few days slides on this study will be available on the web site: www.lipidcenter.com Professionals - Scroll down to Lipid and Lipoprotein Study materials

In this patient I guarantee you his LDL-TG is elevated and a big reason his LDL-P is so high. Anyone who has cholesterol depleted LDLs will need lots of them to traffic a given level of LDL-cholesterol. Of course it is typical for the TG-rich and CE-poor LDLs and HDLs (which this man had to have) to undergo further TG and surface phospholipid hydrolysis upon exposure to hepatic lipase (HL) in the hepatic sinusoids. The lipolytic action of HL reduces the size of the LDLs and HDLs. The altered particle surface in the small LDL often causes conformational changes in the apoB protein making it less recognizable and less removable to hepatic LDL receptors - the half life of the LDL particles increase as does the Total LDL-P level. The LDL-C is elevated in this man - if his LDLs are CE depleted because they are small as well as TG-rich, he will have an extreme LDL-P (it simply takes an awful lot of CE-depleted LDLs to traffic 151 mg of cholesterol per dL. What few recognize, even lipidologists, is that it is the increase in LDL core TG content and not necessarily the reduction in LDL size per se that causes the rise in LDL-P and the LDL-C/LDL-P disconnect.

Likewise: in patients with very high TG (> 500 mg/dL) both fibrates and fenofibric acid and high dose N-3 FA (like Lovaza) can reduce TG by 40-50%. Dropping TG from > 500 mg/dl to ~250 mg/dl with these drugs would do nothing to LDL size - but would drastically reduce the core TG and increase the CE within the LDLs. This is why powerful TG-modulating drugs like these can raise LDL-C. In many, many cases the rise in LDL-C has nothing to do with any change on LDL size but rather with changing the core TG/CE ratio. Interestingly, as seen in the Ludwigschafen Study the reduction in LDL-TG is likely far more meaningful for CV health and the rising LDL-C not as consequential.

One other thing about VLDL, and LDL particles and LDL particles with increased TG. In many IR patients these TG-rich particles carry copies of apolipoprotein C-III, especially the C-III-1 and C-III-2 isoforms which are associated with small LDL size and high LDL-P (J. Lipid Res. 2006;47:1212–1218). ApoC-III blocks the interaction of apoC-II with lipoprotein lipase (LPL) and may displace apoE (which is involved with VLDL attachment to VLDL receptors). This delays rapid VLDL lipolysis and increases VLDL residence time, allowing more time for CETP to pathologically alter LDL and HDL particle composition. ApoC-III also has inflammatory properties as it can stimulate nuclear factor kappa beta production. If apoC-III attaches to LDLs it can interfere with particle recognition and clearance by LDLr and lead to high LDL-TG and LDL-P. In the CARE trial, the second statin trial to demonstrate efficacy on outcomes, Sacks et al noted: “The plasma concentrations of VLDL particles and apoC-III in VLDL and LDL are more specific measures of coronary heart disease risk than plasma triglycerides perhaps because their known metabolic properties link them more closely to

atherosclerosis” (Circulation. 2000;102:1886-1892). I suspect many of our metabolic syndrome and T2DM patients who have variable TG elevations have serious elevations of apoC-III explaining a big part of their risk. Both fibrates and also statins (likely through their PPAR alpha effects) can reduce apoC-III.

Thus I have no doubt that the extreme LDL-P elevation in this patient is real and aggressive therapy will be needed to reduce his CV risk. First step is to get the patient out of his date of denial. Despite his comments that he is not, in reality the patient is a metabolic carbon copy of his father (younger readers of this newsletter have no clue what a carbon copy is). He has the genes and he has plenty of metabolic abnormalities typical of IR that we have discussed. Ultimately his PP glucose and the fasting glucose will elevate as his beta cells slowly fail. Hepatic steatosis will also slowly occur. Endothelial dysfunction will occur because of the TG-rich lipoproteins and apoB will remain nightmarish. Coagulation abnormalities are probably present or will follow (increased fibrinogen and PAI-1).

Therapeutic Pathway: Encourage him to be aggressive with therapeutic lifestyle: Lot's of proven diets: Mediterranean, South Beach, DASH - with serious daily exercise should all be of benefit. As per the ADA/ACC consensus statement, a statin must be the first drug therapy. The problem is elevated apoB (almost all of which are LDL-P). Although statin-monotherapy has almost no prayer of getting this man to goal, statins lower apoB and LDL-P more than any other monotherapy. The clinician did ask me where the data is supporting many years of statin therapy in “low risk” folks with lipid/lipoprotein abnormalities.

1) The second primary prevention trial ever done using a statin: AFCAPS-TexCAPS: over 6000 patients aged 45-67 (primary prevention setting). Lovastatin significantly reduced events (JAMA 1998;279:1615-22). Subsequent publications showed the benefit of the statin correlated better with apoB than LDL-C (Circulation 2000;101:477-484). And just published (see reference 2 below) is the patients with the best results had both lowered apoB and increased apoA-I. By the way the first primary prevention trial using a statin ever done was the West of Scotland Study (WOSCOPS) using pravastatin.

2) The METEOR Trial (JAMA. 2007;297:1344-1353) a CIMT study using Rosuvastatin 40 mg vs. placebo in relatively healthy middle-aged adults with an FRS of less than 10% and evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs. placebo.

With an LDL-P level in the 95th percentile I would start with two medications:

Statin-niacin: Simcor titrated over time to 40/2000 mg makes sense as it is an available fixed dose combo (save a copay) and may have less flushing than Niaspan use. Not sure simva as the statin can get that LDL-P down but with aggressive lifestyle and

extended-release niacin it might. Of course rosuvastatin or Crestor/Niaspan would be more potent. Beyond the statin, Niaspan would further reduce LDL-P, VLDL-P as well as reduce VLDL-TG and perhaps importantly raise HDL-P. Almost certainly Niaspan can help HDL functionality. Because niacin creates larger HDL species the increase in apoA-I is accompanied by substantial increases in HDL-C. If the Simcor or Crestor Niaspan did not get the patient to goal, ezetimibe would be the logical thirds line drug.

Statin-ezetimibe (Vytorin): You would upregulate additional of LDL receptors by adding ezetimibe to a statin (you would upregulate more with Crestor/Zetia but that is two co-pays). Statins can raise HDL-P a bit and ezetimibe can also improve macrophage RCT. In this patient with extreme LDL-P ultimately I think you would have to add Niaspan to the statin/ezetimibe combo ((J Am Coll Cardiol 2008;51:1564–72).

Statin-fibrate (as long as it is not gemfibrozil) or statin-fenofibric acid (FFA) are possibilities. The FFA + statin is FDA approved (and in a polypharmacy world that is of medicolegal importance) but we all know (and NCEP 2004 addendum states) fenofibrate is safe when used with moderate statin doses. The TG and any VLDL-P increase would be very improved as would LDL and HDL composition. HDL-P would rise significantly, but the rise in HDL-C would be minimal because unlike niacin fibrates increase small not large HDL-P. But who cares as there certainly is no specific HDL-C goal of therapy. In the VA-HIT trial the fibrate did nothing to HDL-C that was beneficial, but seriously raised HDL-P (most of it small HDL-P) which did correlate with benefit. Remember fibrates, by upregulating hepatic SR-B1, cause large HDLs to delipidate creating smaller HDL species - which return to plasma with great potential to reacquire more CE. If this man had T2DM, the fibrates move to the head of the class after statin use because of their ability to reduce microvascular disease (retinal disease, proteinuria and distal amputations of the feet).

Many might turn to statin/Lovaza 4000 mg daily to improve the profile. Patients feel very comfortable adding "fish oils" to their regimen. This would be off label use, but COMBOS and other studies have proven the effectiveness of this combination therapy. Like the fibrates there would be significant improvement (lessening) of TG-rich lipoproteins which would likely be very beneficial. Like fibrates, you do not get a lot of additional apoB or LDL-P lowering beyond what the statin does (5-6%), but I believe powerful drugs (fibrates and properly dosed N3-FA) that inhibit TG synthesis, or enhance clearance of TG-rich lipoproteins are very beneficial as they improve blood viscosity, reduce TG-related inflammatory factors, improve coagulation and likely do many other positive things. Because of the very, very high LDL-P, as discussed with niacin above, I think you would have to use Crestor + Zetia or Vytorin with fibrate/FFA or Lovaza. There is new evidence that N3 FA improve macrophage RCT. See reference 3 below

Likely every clinician would have their own preferred regimen and all are defensible. I would likely send this patient for coronary calcium scoring - others would do CIMT. If the CAC was significantly positive, I'd probably start with the Simcor and go from there. I like niacin on board when significant CAD is present in patients with low HDL-P (NOTE I DID NOT SAY LOW HDL-C --- it is HDL-P that drives my decision making).

He would also need ASA and at least 1 gram of N-3 FA (Lovaza). As I have recently stated, I am using the Omegaquant test (www.omegaquant.com) to assess N-3 FA status and adjust the Lovaza dose accordingly. I hope you have all visited that very informative web site and perhaps tried the test.

LIPID CASE 246 Statin Unresponsiveness

I recently received an interesting e-mail from an AstraZeneca rep who inquired: "Is there data on Crestor super metabolizes or patients who have an anomaly in HMG CoA reductase, etc that could explain why a patient would not see any reduction in LDL-C when taking Crestor as prescribed? Specifically, the patient, a male aged 44 years old had an LDL of 153 mg/dl, and was put on Crestor 10mg. Astonishingly 3 months later LDL was only down to 150 mg/dl. Crestor was titrated up to 20 mg and then 3 months later LDL was rechecked and was 152 mg/dL. The patient is 6 feet 200 lbs and works out daily, and takes allergy med - flonase. He does not drink alcohol."

DAYSRING DISCUSSION:

First an editorial from me: a real sticking point: When presenting a case it is meaningless to state that a patient has an LDL of whatever! As far as I know there is absolutely no laboratory test offered anywhere called LDL. LDL means low density lipoprotein. Of course LDL is the lipoprotein mediator of atherosclerosis and thus it behooves us to assay it in the laboratory to evaluate risk and treat. The following are the readily available LDL evaluation assays in the lab:

LDL-C The amount of cholesterol within all of the LDLs that exist in a deciliter of plasma

LDL-P The total numbers of LDL particles that exist in a liter of plasma

 In ,any patients LDL-C has no relationship to LDL-P

ApoB The number of apoB particles per deciliter (vast majority are LDL particles)

LDL size: The peak particle size in Angstroms or nanometers

LDL phenotype or pattern: The predominant LDL size (A - larger; V - smaller)

All serious about lipids must stop using the term LDL when talking about lab results. The same applies to HDL. In the case above the rep is reporting lipid concentrations (LDL-C, HDL-C) which may or may not have any concordance with lipoprotein concentrations.

So why did this patient not respond to the most powerful lipid-modulating statin, rosuvastatin (Crestor)? Of course the most obvious answer is noncompliance. Let's assume that is not the case - what else would explain this. Statins work by inhibiting cholesterol synthesis, specifically in the liver. When liver cholesterol pools are depleted by statins, genes (nuclear transcription factors) are activated and they set off the biologic routes of restoring hepatic cholesterol pools: remember the liver needs cholesterol to lipidate HDL particles and to synthesize bile acids. Under normal conditions the liver would simply upregulate HMGCoA reductase and other cholesterol synthetic genes and increase synthesis. There would also be upregulation of hepatic LDL receptors (LDLr) which would attach to and internalize lipoproteins with apoB100 (VLDLs, IDLs and LDLs) or apoE on their surface (VLDL and IDLs and HDLs). If LDLr are internalizing the apoB particles, there should be a reduction in apoB, LDL-P, non-HDL-C, TG, and LDL-C. There are other ways the liver could reacquire cholesterol: upregulation of the Niemann Pick C1 like1 (NPC1L1) protein at the hepatobiliary interface or upregulation of Scavenger Receptors B1 (SR B1) or apoA-I beta chain synthase (holoparticle or HDL catabolism receptor) which delipidate or internalize respectively large HDLs carrying cholesterol.

So if the Crestor did indeed inhibit HMGCoA reductase in this patient, why were no LDL receptors upregulated? There could be several possibilities:

1) Maybe LDL receptors were upregulated, but there is an LDL mutation which renders the receptor incapable of efficaciously attaching to LDL particles: Dysfunctional LDLr are a cause of familial hypercholesterolemia. This patient's LDL-C is not at the level one would see with heterozygous LDLr dysfunction (300-600 mg/dL)

2) Maybe there are upregulated LDL receptors, but the apoB particles carry a "defective" apoB molecule that is not recognized by the upregulated LDLr. This is called defective apoB. Several single nucleotide polymorphisms (SNPs) can cause this. Usually the LDL-C is higher than what is seen here (200-400 mg/dL).

3) What if the patient had extremely small LDL particles: the apoB might assume a confirmation that is not readily recognized by LDLr. This could be diagnosed by seeing a very high total and small LDL-P level. Normally TG are high and HDL-C low in such patients almost all of whom are insulin resistant. However when statins are prescribed to patients with small LDLs there is normally some LDL-C reduction response. I do not think that is occurring here.

4) LDLr half-life is regulated by a proteolytic enzyme called proprotein convertase subtilisin kexin type 9 (PCSK9). If one has increased PCSK9 activity, LDLr half-life will be dramatically lessened and there will be poor clearance of apoB particles including LDL-P. This is another cause of familial hypercholesterolemia. Again the LDL-C levels are not that high in this case. By the way low activity of PCSK9 extends LDLr half-life and is a cause of hypobetalipoproteinemia (very low LDL-C) and an absence of atherosclerosis.

5) What if the hydrophilic molecule rosuvastatin cannot enter the liver. Hydrophilic molecules cannot readily pass through lipid cell membranes. Normally such molecules gain entrance into cells via the Organic Anion Transporter Protein (OATP). If one did not have the specific OATP (C) needed to internalize hydrophilic statins, the rosuvastatin or pravastatin (both high affinity substrates for OATP-C) would not get into the liver and therefore would not work. Drugs like cyclosporine that also use the OATP-C to gain cell entry and compete with molecules like hydrophilic statins, leading to high serum statin levels but less hepatic statin levels. Obviously this is not the case in this patient. Since OATP-C is selective for the liver expression this is one reason rosuvastatin may have hepatic selectivity over other statins and avoid muscles (theoretically making it potentially safer than more lipophilic statins).

The new pitavastatin (Livalo) which has extremely low lipophilicity is transported by hepatically expressed OATP2 and also like rosuvastatin be hepatic selective. This gets even more complicated: individuals carrying one of the prevalent variants, T521C (Val174Ala, OATPC5), appeared to be associated with delayed hepatocellular uptake of pravastatin and, thereby, greater AUC values, compared with noncarriers. Recently, a new transporter designated OAT3 has been found to affect the disposition of fluvastatin, simvastatin, and pravastatin (Current Opinion in Lipidology 2005, 16:606–613).

6) Let's now deal with the most likely answer: One reason there would be little or hypo response to a statin would be if there was little HMGCoA reductase activity. Clearly a patient who had little HMGCoA reductase activity could not have much of a response to a statin. How could a patient with high LDL-C have little HMGCoA reductase activity? Easy: Hyperabsorbers of cholesterol (have high expressions of NPC1L1 in the brush border of enterocyte epithelium or hepatobiliary interface have increased hepatic pools of cholesterol due to excess delivery in chylomicrons (and their enterocyte obtained cholesterol supply) or refluxed cholesterol from bile back to hepatocyte. Many are unaware that bile cholesterol serves as a source of cholesterol the liver can use.

Hyperabsorbers of cholesterol also over absorb noncholesterol sterols and by measuring sitosterol and campesterol in plasma one could easily diagnose cholesterol over absorption. Very often these patients also have high HDL-C, as the enterocyte will efflux its extra cholesterol to premature HDL species via the upregulated enterocyte ATP binding cassette transporter A1 (ABCA1).

In patients with cholesterol hyperabsorption the liver obtains most of its cholesterol from delivery (chylous and biliary NPC1L1). Hepatocytes that acquire a lot of cholesterol through these mechanisms, will downregulate production of the cholesterolgenic enzymes needed for cholesterol synthesis, especially HMGCoA reductase. Livers with low level of HMGCoA reductase will obviously not respond well to a statin. If one wants a direct measurement of cholesterol synthesis, one cannot measure cholesterol, because high cholesterol could be a result of overproduction, over absorption or both. If one looks at the 37 steps involved with cholesterol synthesis, the far downstream sterols (immediate cholesterol precursors) are desmosterol and lathosterol. Both of these can be measured.

Boston Heart lab (www.bostonheartlab.com) provides a test called "Cholesterol Balance" where they provide sitosterol, campesterol and lathosterol levels and one will instantly know the source of the increased cholesterol and treatment can be much more appropriately made: statins reduce synthesis and ezetimibe (Zetia) to reduce absorption both at the intestine and the hepatobiliary interface. Few realize that ezetimibe thus has a dual mechanism of action: it denies the liver its intestinal and biliary supply of cholesterol. This will force the liver to upregulate LDLr (and of course lead to reductions in LDL-C, non-HDL-C, apoB and LDL-P). This also explains why statin plus ezetimibe will upregulate considerably more LDLr than either drug will by itself. (Paul Ziajka et al. Am J Cardiol 2004;93:779–780).

Since NPC1L1 expressions is in part regulated by PPARs alpha and beta (delta) fibrates can also reduce cholesterol absorption. Since niacin and high dose N-3 FA also activate PPARs they like also reduce cholesterol absorption to variable degrees (there is mice data with N-3 FA on this and one old study showed increased stool excretion of cholesterol in niacin users). The synergism between fenofibrate and ezetimibe is likely one reason combination use of the both are an FDA approved way of reducing non-HDL-C (perfect for statin intolerant patients with dyslipidemia).

As an aside: I have discussed many times that statin monotherapy will increase the intestinal absorption and hepatobiliary reabsorption of cholesterol, in part diminishing the efficacy of a statin. This is another use for the cholesterol balance test. If you have not read it yet please check out the article Comparison of the effects of maximal dose atorvastatin and rosuvastatin therapy on cholesterol synthesis and absorption markers J. Lipid Res. 2009. 50: 730–739. Also see reference 4 below under references of the week. Also please see Arterioscler Thromb Vasc Biol. 2009;29:1745-1750 to understand that reducing sterol absorption is very cardioprotective.

Finally back to the patient under discussion: Simplest thing to do is add ezetimibe (Zetia): or better yet measure sitosterol and campesterol and lathosterol at BHL. If over absorption is present, then simply add ezetimibe to the Crestor. If over absorption is not the problem, then we may be dealing with an OATP problem. Stop the Crestor and switch to a very lipophilic statin like simvastatin and see what happens. That can pass through the hepatic cell membrane without using OATP.

Plenty of great slides on the above physiology at www.lipidcenter.com -- click on professionals and scroll down and read about sterols. For check out the PP slide set entitled oxysterols.

LIPID CASE 247 LDL Analysis

I was contacted with the following dilemma. "I just got my Lipids and NMR LipoProfile results and I'm not sure what to make of it." I am a male with an age of 37, never smoked, BP 120/80, relatively sedentary lifestyle over past 2 years. Ht: 5'7" wt 164 (BMI 25.7). Only relevant family history is a grandfather who died of an MI at age 54.

Total Cholesterol = 228 LDL-C = 140 HDL-C = 62 TG = 129 VLDL-C = 26 Non-HDL-C = 166 (all mg/dL)

TC/HDL-C = 3.6 TG/HDL-C = 2.08

Total LDL-P 1967 nmol/L which is in the high risk range (> 80th population percentile)

Small LDL-P = 1199 nmol/L (elevated)

LDL particle size: 20.8 nm (Large pattern A): Large defined as > 20.5 nm (nanometers)

Large HDL-P = 14.9 umol/L (quite high)

Large VLDL-P 0.8 nmol/L (minimally elevated) perfect < 0.5 nmol/L

Cardiac-CRP 0.34 (<1.0 is low risk)

I was asked: "Does my high HDL-C and HDL-P offer me any protection from the very High LDL-P and small LDL-P number? Also I don't understand how my LDL-P is so high if my LDL particle size seems to be large. I thought that there usually was an inverse relationship between the two?"

DAYSRING DISCUSSION:

This case, not at all unusual allows me to discuss critically important concepts necessary to truly understand CVD lipid-related risk and especially the weaknesses of using LDL-C by itself or at all. Amazingly with respect to laboratory analysis the term LDL is totally misused by providers and even many lipidologists and thought leaders. There is absolutely no doubt that LDL particles mediate atherosclerosis: it is they who deposit the vast majority of sterols involved with atherogenesis. It is critical for risk analysis and for goals of therapy to have a laboratory assessment of LDLs: In the real world, practitioners can order any of the following to help assess LDL-related risk:

1) LDL-C The amount of cholesterol trafficked by all of the LDL particles that exist in 100 deciliters (dL) of plasma. That value can be determined by direct measurement (using nonstandardized testing methods) or calculation using the Friedewald Formula. It is a sad commentary that most clinicians use the term LDL-C and LDL (low density lipoprotein) interchangeably. LDL-C is simply one way (the least accurate) to make LDL-related decisions.

LDL-C = TC minus [HDL-C + VLDL-C] where VLDL-C = TG/5 (on the assumption that all TG are trafficked within VLDL particles and that the core TG/cholesterol composition of VLDLs is 5 (80% TG 20% chol). Because TG are used in the formula, fasting is required.

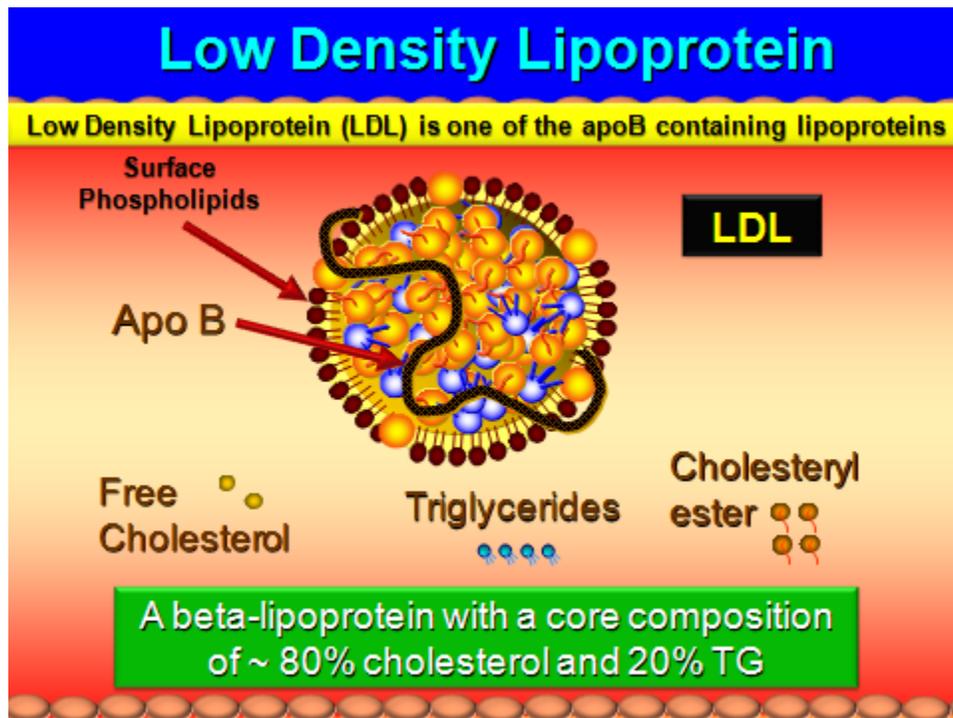
2) LDL-P: the number of LDL particles that exist in a liter of plasma. Typically this is done by LipoScience using nuclear magnetic resonance spectroscopy (NMR). This method has been validated in numerous epidemiological and therapeutic trials. LDL-P is also available from Spectracell using centrifugation and particle staining: this has not been validated against apoB or LDL-P by NMR using large clinical trials. An even newer methodology for determining LDL-P is ion mobility transfer (available at Quest). This method also has not been validated in the trials mentioned above.

3) Apolipoprotein B (apoB): Because of its much longer half life compared to chylomicrons, VLDLs, and IDLs, over 90% or more of apoB particles are LDLs. Thus in essence apoB measurements (the term used in the ADA/ACC statement on lipoprotein management, to differentiate apoB obtained via lab assay vs. calculation) are LDL-P measurements. Since apoB

is a protein immunoassay, where the paratopes on an antibody must recognize the epitopes on the apoB particle, anything that changes the shape (particle size variance) or the structure (oxidative and other inflammatory processes) might lessen the ability of the paratopes to attach to the epitopes, leading to false negative apoB levels. In general, using the WHO recognized Marcovina assay, apoB levels are reliable and reproducible.

4) Non-HDL-C: a calculation obtained by subtracting HDL-C (seemingly nonatherogenic cholesterol) from total cholesterol (the cholesterol within all of the lipoproteins that exists in 100 dL of plasma. Since 90% of apoB particle are LDLs, non-HDL-C is simply a surrogate of LDL-P. Many mistakenly think that non-HDL-C is better than LDL-C because it also includes VLDL-C. Since VLDL-C has little relationship to apoB, non-HDL-C is not a surrogate of VLDL-P + LDL-P, but rather LDL-P. This was clearly seen in particle analysis in the Framingham Offspring study, where adding VLDL-P to LDL-P added little prognostic value (Cromwell et al. Journal of Clinical Lipidology (2007) 1, 583–592).

5) LDL size: in nm (using NMR) or Angstroms using electrophoretic techniques (1 angstrom = 0.1 nanometers): Patients with predominantly small particle sizes are referred to as having Pattern or Phenotype B (no relationship to apoB) and those with larger particles as Pattern or Phenotype A. Note to those using the Vertical Auto-Profile (VAP testing) that phenotype but not actual particle sizes are reported. We now know, using data from several large epidemiological trials that once one adjusts for LDL-P, LDL size is not statistically significantly related to atherosclerotic risk. We have actually known this for a long time: remember when Hannia Campos and Frank Sacks stunned everyone by reporting CARE data: *"Large LDL size was an independent predictor of coronary events in a typical population with myocardial infarction, but the adverse effect was not present among patients who were treated with pravastatin. Identifying patients on the basis of LDL size may not be useful clinically, since effective treatment for elevated LDL cholesterol concentrations also effectively treats risk associated with large LDL"* (JAMA. 2001;286:1468-1474). For other confirmation see MESA data (Atherosclerosis 192 (2007) 211–217) and EPIC-Norfolk data (J Am Coll Cardiol 2007;49:547–53) the AACC statement (Clinical Chemistry 2009;55:407–419).



Note that the surface consists mostly of phospholipids and free or unesterified 3-hydroxy cholesterol. In the core are variable amounts of triacylglycerols (TG) and esterified cholesterol properly called cholesteryl ester (CE). Typical core composition is a 4:1 ratio of CE to TG. Depending on the size of the particle, each LDL (or any other lipoprotein) carries "X" amount of CE molecules and "X" amount of TG molecules. Typically, per molecule, a TG molecule will take up slightly more space than a CE molecule. TG and CE molecules are very lipophilic (hydrophobic) which explains why they are in the core of the particle. Both phospholipids and free cholesterol (with its -OH group) are amphipathic (one side hydrophilic and one side lipophilic) and thus exist on the surface interface with aqueous plasma.

To keep this as simple as possible: Two major factors play a role in the LDL-C to LDL-P relationship, one obvious and one rarely considered: Let's examine an LDL particle:

1) Particle size: Because the volume of a sphere is related to the 3rd power of the radius, it will take more small LDLs to traffic a given level of cholesterol than larger particles. Indeed, depending on LDL upwards of 70% more small than large LDLs will be needed to traffic a given level of LDL-C. Two patients with the exact same LDL-C can have very different LDL-P or apoB concentrations. For LDL particles differing by 3 nm in diameter, there is approximately 40% less core cholesteryl ester in the smaller particle.

2) The second factor also of critical importance is not taken into account by most providers. I am referring to particle composition. As mentioned, all lipoproteins including LDLs have core compositions of variable amounts of cholesteryl ester and TG. Normally an LDL has a 4:1 or greater ratio of CE to TG. However if one's LDLs carry more TG than normal, it means those LDLs will be carrying less CE per particle and they will have a much lower ratio of CE to TG. Or in other words patients who have cholesterol depleted LDL particles. It will obviously take considerably more CE-depleted LDLs to traffic a given level of cholesterol than CE-rich particles. The person with a high LDL-TG level will require more LDLs than a patient with a low LDL-TG value. I strongly recommend (indeed insist if you are a lipidologist) that all read the data from the The Ludwigshafen Risk and Cardiovascular Health Study (Circulation. 2004;110:3068-3074) where the conclusion was: ***Alterations of LDL metabolism characterized by high LDL-TG are related to CAD, systemic low-grade inflammation, and vascular damage. High LDL-TGs are indicative of CE-depleted LDL, elevated IDL, and dense LDL. LDL-TG may better reflect the atherogenic potential of LDL than LDL-C.***

When clinicians see large LDL phenotype or size, they (often erroneously) assume those are cholesterol laden LDL particles, but in some patients they could well be large CE-poor, TG-rich LDL particles. The activity of hepatic lipase (an enzyme that hydrolyzes LDL and HDL core TG and surface phospholipids) often (certainly not always) changes TG-rich, CE-poor LDLs and HDLs into smaller, denser LDL and HDL species. One should now be asking, how do LDLs (and HDLs for that matter) acquire TG? The answer is lipid transfer proteins: namely apolipoprotein D (or cholesteryl ester transfer protein or CETP) and apolipoprotein F (lipoprotein transfer protein inhibitor). CETP, which is made in the liver, arterial macrophages and adipocytes, traffics with HDL particles and mitigates the exchange of one molecule of TG for one molecule of CE between lipoproteins. CETP can be inhibited by apolipoprotein C-I (apoC-I). Thus the exchange of TG from TG-rich particles (VLDLs and chylomicrons) for CE in LDLs and HDLs is what determines the core CE/TG composition. Clinicians have no way of knowing the composition of their patients' lipoproteins or CETP mass or activity. In many patients, there is increased activity of cholesteryl ester transfer protein (CETP) which transfers TG from VLDLs to LDLs. In exchange for CE. The LDLs become TG-rich and CE poor. There are tremendous differences in CETP activity between people. In some people CETP activity increases at TG > 70 mg/dL. The CETP process is driven by plasma TG concentrations and may occur at what have been considered normal TG levels (70-150 mg/dL).

It's like to summarize an excellent article published in the Am J Cardiol 2002;90(suppl):22i–29i. There are 4 different types of LDL particles likely to be seen in individuals depending on their lipid metabolic circumstances: large LDL with a normal core lipid content, small LDL with normal lipid content, and large and small LDL with relatively cholesterol-deficient, triglyceride-rich lipid cores. For those of you who prescribe fibrates and high-dose N- fatty acids to reduce TG, **it should be noted that the reactions leading to the production of these different forms of LDL are fully reversible, so that a patient with high triglycerides and cholesterol-deficient LDL who is placed on successful triglyceride-lowering therapy may exhibit an LDL cholesterol increase even though the number of LDL particles has decreased, simply because the particles have become more cholesterol rich.**

3) The third factor influencing core CE content applies during statin therapy: Sniderman (Journal of Clinical Lipidology 2008;2:36–42) deduces the following: *"statins produce a similar directional shift in the balance between exchangeable ApoB-contained triglyceride and cholesterol by substantially reducing the LDL-C pool. In addition, very LDL, ApoB, and cholesterol are reduced relative to triglyceride-producing triglyceride-enriched VLDL, and this also promotes net triglyceride shift to LDL. Therefore, statin therapy results in triglyceride enrichment and cholesterol depletion of LDL particles. Because triglycerides persist within the particle core, LDL composition, but not LDL size, changes. Changes in core lipid composition of LDL can, therefore, be driven not only by VLDL triglyceride elevation, i.e., the usual model, but also by LDL-C reduction, i.e., the statin model."*

In the case under discussion, the key parameter that tells us what is happening, is that despite the fact that the peak particle size is large, there are considerable numbers of small LDL particles, which are the by-products of CETP induced TG-rich large LDLs undergoing subsequent lipolysis (TG removal) by hepatic lipase in hepatic sinusoids. Thus this patient has a likely mixture of large TG-rich, CE poor LDLs and small LDLs (many of them might, despite their small size still be TG-rich). The LDLs that are the most cholesterol depleted are small, TG-rich LDLs. One would expect extremely high LDL-P levels in such patients, with little correlation with their LDL-C. Indeed: with equal numbers of LDL particles, these individuals can easily have LDL cholesterol values that are 50 mg/dL lower than people who have large LDL particles of normal lipid composition (Am J Cardiol 2002;90(suppl):22i–29i).

If you really comprehend all that I have just elaborated on, isn't it obvious that we really have little prayer of accurately diagnosing atherogenic particles, especially in our insulin resistant epidemic, without apoB or LDL-P measurements? In data from healthy patients, (not IR patients) amazingly 21% of patients had LDL particles that were core cholesterol depleted (CE/TG ratio < 4). Even the most accurate LDL-C will underestimate by 10% to 25% the actual amounts of LDL particles these individuals have, compared with those with LDL particles containing normal core cholesterol. Measured or calculated LDL-C values, even for people with LDL particles of the same size, can easily vary by 10 to 40 mg/dL without there being any difference in LDL particle concentration (Am J Cardiol 2002;90(suppl):22i–29i).

Next I need to answer the question does the patient's high HDL-C and high HDL-P offer cardioprotection? In reality from the data provided, the patient has no idea whether he has a high HDL-P, as LabCorp only reports the number of large HDLs unlike the full report from LipoScience. Total HDL-P is really what matters most: total HDL-P is the sum of small + medium + large HDLs. This patient has more than adequate numbers of large HDLs but if small and medium HDL-P is low, the overall total HDL-P might not be perfect. As mentioned above, as of 11/23/09 total HDL-P will be reported henceforth on the Raleigh (but not the LabCorp) generated reports. We found out from the VA-HIT analysis that total HDL-P is a very important risk predictor as well as predictor of therapeutic response. In that study gemfibrozil (the precursor to gemfibric acid) barely raises HDL-C but very significantly, raised HDL-P.

Last but not least when you see patients like this with elevated LDL-C and HDL-C one should suspect over absorption of cholesterol which can easily be determined by running markers of

cholesterol absorption and synthesis at Boston heart Labs (www.bostonheartlab.com): see their cholesterol balance test. You need to use a statin/ezetimibe combo and hyperabsorbers and see what happens: In the case at hand some type of TG-lowering therapy (lifestyle, Lovaza, fenofibrate or fenofibric acid) might be needed to get LDL-P to goal:

LIPID CASE 248 Pancreatitis

A 21 year old Caucasian male was admitted to hospital with abdominal pain. Just prior he had visited his primary care physician for an annoying skin rash. He was told that it was folliculitis pilaris and therefore nothing to worry about. In the hospital he was found to have high triglycerides and acute pancreatitis. Patient had a history of "high cholesterol" treated with Vytorin which the patient discontinued a few months prior to admission because he "didn't want to take anymore." Family history was significant for DM and "typical high cholesterol." No family of premature coronary disease or xantheloma/xanthelasma. Social history was positive for tobacco, but negligible for alcohol use Examination revealed eruptive xanthomas all over his body.

Labs:

Admission labs: TC = 1046, TG = 20,803,
Amylase 28 (25-115), Lipase 182 (114-286), Note: these can be normal in 10% of pancreatitis cases
TSH 1.07,
HgbA1c 10.8%
Apolipoprotein B =225 mg/dL (extremely high 99th population percentile)
Lp(a) < 5

NMR LipoProfile done the same day:

Total LDL-P = 680 nmol/L (very low - the bottom first population percentile)
Small LDL-P = 121 nmol/L
LDL size 21.5 nm (large)
Large HDL-P = 0
Large VLDL-P 147.1 nmol/L Extremely high (perfect < 0.7)

Three days after admission and treatments: TG = 451 mg/dL
8 days later glucose was normal and TG 138 mg/dL

Current Therapeutic Regimen:

Lipitor 80 mg
Actos 45 mg
Niaspan 2000 mg
Lovaza 4 gm
Zetia 10 mg (because he was actually eating)
B12 shots weekly (1000 mcg)

The endocrinologist upon my questioning explained the nonuse of a fibrate in this case: she felt that in a dysmetabolic patient, her first choice is going to be pioglitazone (Actos) and then see what happens. For her diabetics she believes that with adding metformin and Byetta she rarely needs fibrates as the TG are frequently below 150 mg/dL. She mentions that in this case he already had him on the Niaspan and the Lovaza so she figured the fibrate would be a drop in the bucket. She pointed out that the TG normalized without using a fibrate. She noted that she could probably change the Zetia to Trilipix but honestly "his diet sucks so bad, he needs the Zetia."

DAYSRING DISCUSSION:

NOTE: IF YOU ARE A LIPODOLOGIST OR SCHOOLED IN RARE LIPID DISORDERS I WANT YOU TO STOP READING: GO BACK AND ANALYZE THE CLINICAL INFO (INCLUDING THE LABS) AND MAKE A SPECIFIC LIPOPROTEIN DIAGNOSIS - WRITE IT DOWN - NOW READ ON AND SEE IF YOU COME UP WITH THE SAME DIAGNOSIS I HAVE.

There is a lot to discuss here, including the treatment. Obviously there are many ways to "skin a duck" and although the approach used is not exactly out of NCEP recommendations, it obviously worked. Before we start, did you all notice the massive elevation of apoB with the low levels of NMR derived LDL-P (terrible discordance) - Is there a lab error here: if 90% of apoB particles are supposed to be LDLs, something is wrong. Or do you believe the two measurements are concordant. Before we answer that, let's start with some basic triglyceride biochemistry and take it from there.

Triacylglycerol (triglycerides) are molecules containing three acyl groups (oxoacids or COO) bound to a glycerol (a carbohydrate) molecule. Acyl groups are mostly derived from fatty acids (FA). In the synthetic process, one FA derived acyl group is added to the glycerol, creating in sequence monoacylglycerol, diacylglycerol and finally triacylglycerol. Obviously there are specific enzymes that catalyze each step. The final enzyme is diacyl glycerol acyl transferase or DGAT (as the name suggests the enzyme transfers an acyl group to the existing diacylglycerol molecule). At 9 kilocalories per gram TG provide a powerful supply of energy to cells. Because TG are very hydrophobic molecules they have to be trafficked in aqueous plasma as core lipids deep inside protein wrapped lipid transportation vehicles better known as lipoproteins. Of course there is one other passenger inside the core of all lipoproteins and that would be esterified cholesterol which is called cholesteryl ester (CE). CE is the storage form of cholesterol (technically to differentiate it from CE, cholesterol is termed free or unesterified cholesterol (FC or UC). FC can be converted into other molecules (oxysterols) like steroids or bile acids. CE has to be de-esterified, using cholesterol esterase) to become FC. Of course there are many FA that potentially make up our TG molecules: on your TG molecules, are they trafficking saturated FA, monounsaturated FA or polyunsaturated FA. As you know different FA have different atherogenic potential - so are all TG created equal, meaning of equal atherogenic potential? We as clinicians have no clue what FA might be attached to our patient's glycerol molecules. Thus some TG molecules are worse than others.

Most TG are synthesized in hepatocytes or jejunal enterocytes, organs that have large supplies of FA. Of course once synthesized, the TG have to be trafficked to energy-utilizing cells like muscles or to fat storage depots (adipocytes). Thus after hepatic or enterocyte synthesis, TG have to be incorporated into lipoproteins; Using microsomal TG transfer protein (MTP) the TG join CE and apolipoprotein B in the creation of large TG-rich lipoproteins called chylomicrons in the intestine and very low density lipoproteins in the liver. The liver uses apolipoprotein B 100 to bind the lipids and the enterocytes apolipoprotein B48 (a truncated apoB molecule having 48% of the molecular weight of the hepatic apoB). Typically chylomicra and VLDLs have a core composition of 80-90% TG and 10-20% CE. Chylomicra are much larger than VLDL particles and hence carry significantly more lipids. The former (chylos) are secreted into the lymphatic system (where they make their way to plasma) and the latter (VLDLs) into plasma. Once in lymph or plasma they acquire numerous other apolipoproteins that will be necessary for particle lipolysis (hydrolysis of lipids): specifically apoE, and the apoC family. Chylos but not VLDLs also initially traffic apoA-I (the HDL precursor protein).

Chylomicra and VLDLs have multiple copies of apoC-II (an apoprotein that binds to and activates the major human TG hydrolyzing enzyme called lipoprotein lipase or LPL (a triglyceridase) which is most heavily expressed in myocyte, adipocyte or placental endothelium. Because of their much larger size and more copies of apoC-II there is a "preferential" lipolysis of chylomicra which is why they have shorter half life's than do VLDLs. Indeed chylos undergo immediate lipolysis within minutes of entering plasma and have very short half life's (1-2 hours) under normal conditions. Of course severe impairments of lipolysis (as in this patient) would cause serious

hyperchylomicronemia and of course marked postprandial and fasting hypertriglyceridemia (HTGH). Once chylous concentrations are reduced, VLDLs undergo somewhat slower because of their smaller size VLDLs simply carry less apoC-II than do chylous) but still fairly rapid lipolysis (half life of 2-6 hours) (.).

As the TG-rich chylous and VLDLs lose TG, they reduce in size and in doing so also release large amounts of surface phospholipids which are immediately picked up by phospholipid transfer protein (PLTP). Of course there is another way chylous and VLDLs lose their core TG: a lipid transfer protein called cholesteryl ester transfer protein (CETP) swaps molecules of TG for molecules of CE (a one for one molecular swap) with lipoproteins that are not TG-rich, namely HDLs and LDLs (typical core lipids of a normally composed LDL is 80% CE and 20% TG and a normally composed HDL 90% CE and 10% TG).

As the chylous and VLDLs lose their core TG and surface phospholipids they become smaller particles called remnants (I guess if I got skinny and I lost my visceral adipocytes TG, you could call me a Dayspring remnant). Remnants are TG-poor and CE-rich particles. Normally they are rapidly cleared by hepatic LDL receptors (VLDLs) and remnant receptors (LDL receptor related proteins). These membrane internalization proteins attach to apoE or apoB 100 (not apoB 48). As these particles are cleared they supply the liver with whatever TG they still carry as well as their CE. In effect these apoB particles are returning cholesterol to the liver and are performing what is termed indirect reverse cholesterol transport. Once VLDLs shrink enough in size they are called intermediate density lipoproteins (IDLs). As very small VLDLs and IDLs enter hepatic sinusoids to be cleared by LDL receptors (LDLr), SOME are exposed to hepatic lipase (an enzyme with both triglyceridase and phospholipase properties) and further lipolysis results in the creation of LDL particles. Because it contains no apoE, LDLs are less rapidly cleared by LDLr than are the apoE rich VLDLs and IDLs: the typical LDL half-life is 1.5 to 3 days, explaining why under normal circumstances 90% of apoB 100 particles are LDLs.

With that knowledge let's get back to the case. This young man with a history of abnormal cholesterol suddenly developed massive elevations of both cholesterol and TG. Something sure turned on his lipogenic genes. That something is the fairly acute onset of type 2 diabetes mellitus. As the lipid levels became grossly pathological, the first manifestation was not the pancreatitis but rather the deposition of the TG into the dermis causing eruptive xanthomas. Tragically that diagnosis was missed and that could have had lethal consequences (pancreatitis can be fatal). When you see rapid onset of papulovesicular lesions on trunks and extremities, eruptive xanthomas have to be in the differential diagnosis. They are often quite pruritic. It takes 5 minutes to make the diagnosis: draw a red top tube, spin it and you will see "milk" not clear yellow serum. Or pick up and ophthalmoscope and glance at the retina where you might see white rather than red arterial vessels (lipemia retinalis). Both FA and cholesterol lipogenic genes (influenced by the nuclear transcription factors (NTF) sterol regulatory element binding proteins (SREBP) 2 and 1C can go crazy when the glycemia onset is sudden in insulin resistant and/or insulin deficient patients developing T2DM. These NTF or genes cause synthesis of enzymes (lipogenic) that create lipids: such as DGAT, HMGCoA reductase) The FA are rapidly converted to TG which utilizing MTP joins lots of newly synthesized FC, and CE forming chylomicra and VLDLs. As one would expect in someone with extreme hypercholesterolemia and hypertriglyceridemia, there is a massive increase in large TG-rich lipoproteins as evidenced by the VLDL-P (147 nmol/L). In this case they are both chylous and VLDLs. One cannot differentiate between chylomicra and VLDL using NMR -- they are simply both very large TG trafficking particles and reported as large VLDL-P.

The acute onset of T2DM (due to IR and insulin deficiency) is often accompanied by severe deficiency of lipoprotein lipase (LPL). So this man is not only synthesizing tremendous numbers of TG-rich lipoproteins, but they will also have markedly delayed lipolysis (catabolism). Obviously having extreme numbers of giant TG-rich "fat-balls" (lipoproteins) float around will cause severe HTGH. These particles drastically increase blood viscosity. In the setting of HTGH, CETP activity will be high and TG will be exchanged for CE from LDLs and HDLs. This will cause the VLDLs to

acquire even more CE, further raising the VLDL-C, but depleting the LDLs and HDLs of CE (this explains why LDL-C and HDL-C drop when TG rises). Of course LDL-TG and HDL-TG goes up. Note this man has extremely large LDL particles: they are large because they are carrying excess TG: a normal LDL particle has a CE/TG ratio of 4. I suspect this man's ratio is much higher. This change in core TG composition of HDLs ultimately leads to further HDL lipolysis by hepatic lipase creating a loss of large HDLs and an increase of small dense HDLs some of which break up leading to renal excretion of apoA-I. Note the large HDL-P of zero in this case.

However we still have to explain the gross disconnect between LDL-P (which is very low) and the extreme apoB elevation. You might think the apoB is explained by the big increase in VLDL-P. I think not. Note that even though they are drastically low, the total LDL-P of 680 nmol/L far exceeds the large VLDL-P of 147 nmol/L. But an LDL-P of 680 plus a large VLDL-P of 147 does not even come close to explaining the extreme apoB elevation. Thus we have to come up with something else. That something else is IDL-P. I strongly suspect this man has Fredrickson's Type III Hyperlipidemia (apo e2/e2). The vast majority of apoE2/e2 patients have normal lipids. But when a condition like uncontrolled diabetes develops these patients have massive lipogenesis and make extreme amounts of pre-beta VLDLs (IDLs) – they have a defective apoE that is not a good substrate for LDLr and hence they accumulate in plasma. These particles carry large amounts of TG and CE, but are not converted to LDL particles. Pancreatitis is a known complication of Type III when the HTGH is extreme. To confirm the diagnosis, I would love to see apoE testing in this man.

What caused the pancreatitis in this man? Well, severe HTGH (> 1000 mg/dL) causes 10% of all cases and even up to 50% of all cases in pregnancy (see a great review by Ewald et al, in Current Opinion in Lipidology 2009, 20:497–504). The most common causes of pancreatitis are gallstones and alcohol abuse. The latter, by reducing beta-oxidation of fatty acids can also exacerbate the HTG (note there was no alcohol abuse the patient under discussion). Ewald et al state: "excess amounts of circulating triglyceride-rich lipoproteins are hydrolyzed by high levels of pancreatic lipase released into the vascular bed of the pancreas. The very high concentration of FFA thus formed will exceed the binding capacity of plasma albumin. FFA will self-aggregate forming micellar structures with detergent properties. These FFA micelles will attack platelets, the vascular endothelium and, finally, acinar cells producing ischemia and pancreatic injury." The hyperviscosity also aggravates the situation.

Treatment of HTGH in the presence of acute pancreatitis is of course keep to the patient NPO and start hydration which I suspect was done in this man. In HTGH > 500 mg/dL, the cholesterol is to be ignored. The emergency mandate is to get the TG < 500 mg/dL and stop the FA induced pancreatitis. Thus TG, not cholesterol reduction becomes the primary focus. In an uncontrolled diabetic both TG and glucose reduction are the imperatives. After diagnosis and admission the first drug to consider and use is insulin. Insulin is a powerful stimulator of LPL and can dramatically reduce TG. Insulin is even more indicated in this patient because of the severe uncontrolled diabetes. It is tough to control TG without glycemic control. IV Heparin which frees up LPL as well as plasmapheresis can also be used in emergency conditions.

Of course this man will require major lifestyle changes, glycemic control and likely chronic lipid modulating therapy. If he is going to stop his meds again after surviving pancreatitis he is of course a moron (no law against that in the US). So after the NPO, hydration and insulin (and or heparin) are started chronic therapy also begins: Of course the two drugs most recommended by experts (and with FDA indication) to tackle severe HTGH are fibrates (fenofibrate or fenofibric acid) and N-3 fatty acids (Lovaza) used at doses of 4 grams or higher. High dose Niaspan is an effective long term treatment for HGTH but is not used in emergency situations as it usually requires a slow titration over weeks to get to the 1500 - 2000 mg necessary for TG reduction. TZDs like pioglitazone are not recommended to treat extreme HTGH and of course have no FDA indication to do so. Their ability to reduce TG is modest. Statins are not to be used in the emergency treatment of severe HTG: all statins do is upregulate LDLr, which pull TG-rich VLDLs and their load of fat back into the liver. Since statins do not increase beta-oxidation of FA, I do not

see how statins internalizing TG-rich VLDLs will solve anything. Statins should not be started until initial urgent therapy described above, the Lovaza and fibrates (and or Niaspan if needed) get the TG to below 500 mg/dL. The reason is statins do nothing to TG synthesis, but of course fibrates, N-3 FA and niacin do. All of the latter three do increase beta-oxidation of FA, reduce FA synthesis and inhibit DGAT. Of course once the TG are < 500 mg/dL

It seems like the rational to use Zetia was that the patient was "eating." All know that ezetimibe, by interfering with enterocyte and hepatobiliary expressed Niemann Pick C1 Like 1 proteins (NPC1L1) reduces both intestinal absorption of cholesterol and back flux of cholesterol from bile into the liver. Many do not realize that the vast majority (85%) of cholesterol present in the duodenum and jejunum has a biliary origin, not an exogenous eaten origin) origin. The vast majority of cholesterol that ezetimibe prevents from coming in was sent to the intestine via the bile. Thus Zetia's real MOA is to block biliary, not eaten cholesterol. Zetia works as well in vegetarians who eat no cholesterol as it does in meat eaters (J. Lipid Res. 2006. 47: 2820–2824).

I also can never accept using a TZD instead of a fibrate for treatment of lipids/lipoproteins or for macrovascular benefit. We have lots of trial data supporting fibrates in lipid management resulting in better outcomes and none with TZDs. They have very different mechanisms of actions than do TZDs. I do not object to pioglitazone use in this man because his extremely poor glycemic control demands it, but let's leave lipoprotein/CVD management to proven meds. However if one achieves glycemic control with glucose modulating medications (insulin, TZDs, Byetta, etc) then there may be less need for TG-modulating medication. Also remember that once TG are < 500 mg/dL, ultimately it is the LDL-P, not the TG that is the goal of therapy (unless Type III is present – then apoB is the goal). This man responded acutely to the avoidance of fat calories, glycemic control and then primarily the Lovaza and ultimately (chronically) by the Niaspan and statin. We do need so see a repeat NMR and apoB. If this man truly follows proper lifestyle he may be able to stop many of the above meds. If lifestyle is not adhered to, he will need the meds forever.